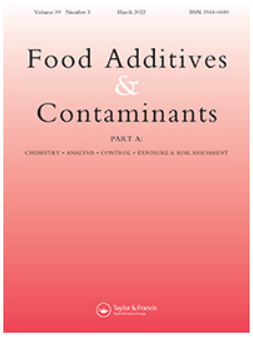

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REVIEW

Guidance in selecting analytical techniques for identification and quantification of non-intentionally added substances (NIAS) in food contact materials (FCMS)

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ABSTRACT

There are numerous approaches and methodologies for assessing the identity and quantities of non-intentionally added substances (NIAS) in food contact materials (FCMs). They can give different results and it can be difficult to make meaningful comparisons. The initial approach was to attempt to prepare a prescriptive methodology but as this proved impossible; this paper develops guidelines that need to be taken into consideration when assessing NIAS. Different approaches to analysing NIAS in FCMs are reviewed and compared. The approaches for preparing the sample for analysis, recommended procedures for screening, identification, and quantification of NIAS as well as the reporting requirements are outlined. Different analytical equipment and procedures are compared. Limitations of today's capabilities are raised along with some research needs.

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Food contact materials; migration; food packaging; plastics; non-intentionally added substances; NIAS; chromatographic methods

Introduction and scope

Food contact materials (FCMs) contain substances with the potential to migrate into foodstuffs. Until recently, the evaluation of the safety of FCMs was limited to the intentionally added substances (IAS) like monomers or pre-monomers used for the construction of the material, or additives used to improve the characteristics of the final article like antioxidants, plasticisers, UV-absorbers, etc. In addition to substances of known origin, the FCMs may contain non-intentionally added substances (NIAS). Examples are impurities present in the IAS or degradation and reaction products created during the manufacturing of the material. The evaluation of NIAS has become of interest since they were specifically mentioned in the European legislation on plastic materials and articles intended to come into contact with food (EU Regulation 10/2011) with the following definition:

> a 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.

According to this legislation, the presence of NIAS in the final plastic article is permitted but should be assessed by the manufacturer in accordance with international recognised scientific principles on risk assessment (Art. 19, EU Regulation 10/2011). Guidance on how NIAS should be analysed and assessed is however missing. Previous publications and guidance have been proposed in an attempt to fill this gap (Koster et al. 2015; Schilter et al. 2019; Kato and Conte-Junior 2021).

Different approaches commonly applied in the management, production, and handling of FCMs affect the formation of NIAS, such as material processing, chemical pre-treatment, thermal treatment, ionisation, oxidation, environmental interactions, and storage. Both IAS and NIAS may be transferred to food during production, preparation, packaging, and storage. According to Article 3 of the Framework Regulation (EU) No. 1935/2004 it needs to be assured that these transfers of substances to the food will not endanger human health. The migration of substances from FCMs into food is traditionally studied using single laboratory

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validated methodologies for the analytes of interest, but for NIAS other issues arise. It is generally accepted that those NIAS, as with any other migrating substance, with a molecular weight below 1000 Dalton (Da), are the migrants of potentially toxicological concern. Components with a molecular mass above 1,000 Da are unlikely to be absorbed by the gastrointestinal tract (or only to a minor extent) and thus are not considered to present a toxicological risk (EFSA CEF Panel 2008), unless they hydrolyse or breakdown in the gastro-intestinal tract to substances <1000 Da. Some question this 1000 Da cut off (Groh et al. 2017). Perfluoro compounds are exempt from this rule as they can be absorbed at higher molecular weights because of their lower relative molecular volumes. Therefore, the threshold of no absorption is shifted to 1500 Da for perfluoro compounds (EFSA CEF Panel 2016).

The study and identification of NIAS in FCMs and their migration is very challenging since not all NIAS are predictable. Migrating substances from FCMs can globally be subdivided into (1) IAS, (2) known or expected/predictable NIAS and, (3) unknown NIAS. Although dedicated analytical techniques are already partially available and are in some cases standardised for IAS and known/predictable NIAS, no standardised methodology is available for non-target screenings and quantification of unknown/unpredictable NIAS in FCMs. FCMs can have very complex structures with many different layers from different materials, either coextruded or laminated, manufactured using different adhesives and different polymers as substrates, even paper or aluminium, which can also be coated by adhesives, varnishes, and printing inks. Each component of FCMs can be a source of NIAS. Figure 1 gives an overview for NIAS (Geueke 2018). Furthermore, NIAS may also be generated from IAS that are used upstream in the supply chain, but that are not known by everyone downstream. All packaging materials can transfer NIAS. Thus, the guidance presented here can be applied to any kind of FCMs, including recycled materials. It aims to provide a harmonised understanding of procedures to determine the identity and level of unknown/unpredictable migrants .

As plastics are the predominant material used in FCMs (Bouma et al. 2003; Poças et al. 2009; Simoneau et al. 2016), there has been a larger focus on NIAS from plastics. However, other types of FCMs, such as paper and board, adhesives, coatings, biopolymers, and natural materials (wood, palm leaves, etc.) also contain NIAS and arguably these present a greater challenge to identify and quantify. Although this document will focus on NIAS originating from the use of organic materials, the techniques to analyse exposed food simulants are also applicable for NIAS from other FCMs. Of the major FCMs, polymers are mainly found in plastics, coatings, adhesives, varnishes, and inks. Paper and board are produced using various resins such as production aids like sizing agents, precipitating/fixing agents, retention agents, dewatering accelerators, dispersion/floatation agents, wet-strength agents, and surface refining agents (BfR 2021b). Recycled paper and board may additionally contain substances from polymers and additives due to plastic multilayers on paper and board, adhesives, inks and – if originated from post-consumer waste – unpredictable NIAS introduced from circular usage. Some breakdown products of catalysts that could be present in trace amounts are organometallic in nature and need specialist knowledge and equipment for detection (BfR 2021a). A review of where NIAS can occur and

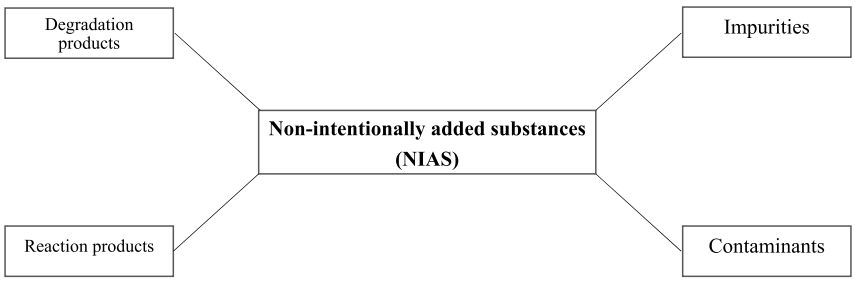

Figure 1. Classification of NIAS, adapted from Geueke (2013). A more detailed description of potential sources of NIAS is described in (Koster et al. 2015).

examples of how they can be detected is the subject of a recent publication mainly focussing on plastics (Kato and Conte-Junior 2021).

The analytical strategy depends highly on the available information about the composition of the material. At each step in the supply chain the amount of this information and consequently the analytical requirements are different. For example, a manufacturer of intermediates knows the composition and possible side reaction products and can perform a targeted analysis, whereas the producer of the final article needs first to find out the composition. The EU Commission intends to improve this information flow in the supply chain via the declarations of compliance in the regulated areas (e.g. plastic materials) or adequate information for other materials or components, respectively. This is explained in the EU Guidance regarding information in the supply chain (European Commission 2013).

Many laboratories from industry, contract research, and academia are performing non-targeted screening tests to identify and quantify potential migrating substances in FCMs, where results are often semi-quantitative in nature. A 10 μg/kg (ppb) limit (10 μg/6 dm^2) was set as the limit for migration from behind a functional barrier in Commission Regulation (EU) 10/2011, with exclusions of substances that are classified as carcinogenic, mutagenic, toxic to reproduction, or nanomaterials. The 10 μg/kg limit was pragmatically based on what could be reasonably achieved by available methods and what would be a meaningful limit from a risk management perspective. For 'unknowns', quantification is difficult or impossible with this 10 μg/kg limit, but it is typically the level currently used for screening NIAS. This NIAS screening approach with the 10 μg/kg migration limit is acknowledged in recital (28) of the 15th amendment of the Plastics Regulation, but substances for which genotoxicity cannot be ruled out are excluded. (European Commission 2011, 2020). For those substances, the limit of 0.15 μg/kg for genotoxic substances according to the threshold of toxicological concern (TTC) concept has to be applied (EFSA Scientific Committee 2019). This low limit will exceed the analytical possibilities in many cases, especially for non-targeted approaches. The Commission therefore included an obligation of transfer of information of those known substances to others in the supply chain (new point 6 of Annexe IV in Commission Regulation (EU) 10/2011 (European Commission 2020). If NIAS are classified as substances of very high concern according to the European Chemical Agency (ECHA), these substances require a thorough study to guarantee their safety in use of the FCMs, even at low concentrations.

It is recognised that by introducing generic screening approaches, not all migrating NIAS will be detected. Experience shows that there is a large diversity of tests and the outcome of those tests varies depending on the methodology used. Furthermore, the results from these tests can/may lead to false alerts because of misidentification or incorrect quantification (e.g. overestimates due to exaggerated test conditions or inappropriate standards for quantification). False reassurances also need consideration, where a FCM is given a 'clean bill of health' due to inadequate or inappropriate methodology. Different protocols involving different sample preparation techniques may lead to different analytical results, which may or may not give rise to concern.

This paper aims to provide a harmonised understanding of procedures to determine the identity and level of unknown/unpredictable migrants and provide background information as to why different approaches may lead to different results. Various analytical techniques are described which could be used, and are presented along with their weaknesses and strengths, including how to compare results from different analytical techniques. The intention is that different laboratories acting throughout the supply chain can generate similar results or, if not, can explain any differences. This paper does not provide any specific migration testing conditions, as these are typically found elsewhere (e.g. Commission Regulation (EU) No 10/2011), or any guidance on how risk assessment should be performed. This paper gives a global overview of methodologies used to screen for NIAS in an untargeted way. It is not proposed to apply all these technologies in parallel to a FCM as this is expensive/not very practical and may not be needed. Therefore, a selection of sample preparation approaches and

analytical techniques is proposed which typically will cover a wide range of NIAS. Highly sophisticated analytical technologies such as on-line LC-GC and GC x GC-MS are not widely available in laboratories yet, but their advantages and disadvantages are nevertheless discussed. Finally, guidance on the understanding and interpretation of the results should enable the user to better understand the reports including the limitations of the analytical approach.

To be able to achieve harmonised methodology, different aspects need to be considered:

(1) Characteristics of FCMs and likely migrants
(2) Extraction and migration
(3) Strengths and weaknesses of analytical techniques
(4) Recommended approaches and best practices
(5) Using the results for risk assessment and risk management
(6) Conclusions

Characteristics of materials and migrants

Chemical and physical properties of polymers used in FCMs

Most FCMs contain polymers (or resins), either synthetic or natural and they vary widely in their chemical and physical properties. This fact influences the choice of conditions for extraction or migration and quantification of substances in the polymers as well as the suitability of sample preparation and test conditions.

Regarding stability of the polymer, the chemical bonding between the monomers needs to be considered. Polyolefins or styrenics have a C-C backbone formed by polymerisation of the double bonds of their monomers. This polymer backbone is stable against most solvents but can be degraded at high temperatures. Polycondensates like polyesters, polyamides, or polyurethanes might be degraded by the attack of polar solvents like water or ethanol. Too severe extraction or migration test conditions may cause artificially high amounts of monomers, oligomers or degradation products formed by hydrolysis, ethanolysis, or transesterification reactions (Ubeda et al. 2019).

Furthermore, the intrinsic diffusivity of the polymers should be considered in planning of the design of a migration study. Highly diffusive polymers like LDPE or elastomers may release components up to and above 1000 Da into simulants during migration testing. In contrast, for low diffusivity polymers like polystyrene or polyethylene terephthalate, the diffusion coefficients of larger molecules are so small that these non-volatile components will only migrate in small amounts at room temperature, with or without short hot fill contact and long-term storage. However, for high temperature applications of low diffusivity food contact polymers, larger molecules of very low volatility need to be considered as potential migrants, as well as the possible formation of NIAS. These considerations can be used in the planning of experiments.

Characteristics of migrants

Not only the physico-chemical properties of the FCMs need to be considered for the selection of appropriate methods, but also those of the expected NIAS. For the unexpected and unknown NIAS it is, of course, not possible to consider their physico-chemical properties, but consideration of the matrix of the FCMs where they are present is important in selecting appropriate testing conditions.

Volatile, semi-volatile and non-volatile substances can be analysed according to the methods listed below. The application ranges of these methods overlap but may differ in sensitivity. Some substance groups (e.g. primary aromatic amines from polyurethane adhesives or pigments, polyaromatic hydrocarbons) require dedicated methods as the concentration level of interest is so low that general non-target screening methods cannot detect them. The analysis of mineral oil, a common NIAS in many samples of paper, board, and polymers, both virgin and recycled materials, requires specific procedures and still represents a considerable analytical challenge (Hochegger et al. 2021).

Solubility is another important parameter. The expected NIAS needs to be soluble enough in the chosen extraction solvent or food simulant

Some components react with ethanol and form artefacts by transesterification. Isocyanates react with ethanol in ethanol-water mixtures to generate

ethyl urethanes. Therefore, migration of primary aromatic amines from polyurethanes is investigated in 3% acetic acid or water instead of aqueous ethanolic simulants. Artefacts can also be formed in hot injectors (e.g. a split-splitless injector of a gas chromatograph). An example is the formation of carcinogenic dichlorobenzidine from traces of diaryl pigments in extracts at temperatures above 200°C. Another example is the re-formation of isocyanates from polyurethane oligomers in the injector (Tinnerberg et al. 1996). These effects need to be considered for the evaluation or the presence verified by another technique (GC with on-column injection or HPLC).

Exhaustive extraction and migration

For many reasons testing in food is not the preferred option to screen for unknown migrants, as the food matrix impedes the extraction and quantification of known migrants and makes the identification of unexpected migrants nearly impossible due to the large number of interfering substances in food. Alternatively, extractants or food simulants can be used for the evaluation. In this context, extraction means the determination of the content in the material whereas simulants are used to determine the migration transfer out of the material. Solvents can act either as a simulant or extractant depending on the conditions used. Concentrations in the material can be used to calculate/mathematically model the expected concentration in food. This gives a value for a worst-case estimate to exposure from the NIAS.

Migration into food and food simulants

Food simulants are intended to simulate the interactions between the FCM and food and are used in migration experiments to simplify the analysis. They are selected to represent the foodstuffs which will be in contact with the FCMs and are supposed to slightly overestimate any transfer into real food (Otoukesh et al. 2020; Canellas et al. 2021) and for oligomers from can coatings this can be greatly over-estimated (Driffield et al. 2018). Simulants should be selected as worse-case according to the food to be packaged. Ideally, they should not cause swelling of the FCM or any other physical change of the FCM that does not occur in contact with the intended foods. Some NIAS may also be lost through sample preparation. Furthermore, artefacts can be formed when aqueous or ethanolic simulants lead to hydrolysis and ethanolysis products, respectively. However, if migrants are identified and the amounts migrating into simulants are larger than anticipated, then the results of the analysis of the respective migrant in the actual food prevails over any simulant results (Art 18(6) of Commission Regulation (EU) No 10/2011) except if the substances react with the food.

Some FCMs are subjected to EU-harmonised legislation, but many are not. For plastic FCMs, rules covering simulants, temperatures, and times for testing are defined in Commission Regulation (EU) No. 10/2011. If the testing conditions representative for the worst foreseeable conditions of intended use of the material or article, are not technically feasible in food simulant D2 (vegetable oil), migration tests can be done with alternative simulants and conditions (Jakubowska et al. 2020) but these might also be too exaggerated related to real food applications (Schmidt et al. 2011; Driffield et al. 2018; Gehring and Welle 2018; Stärker and Welle 2019; Guazzotti et al. 2021). For the other FCMs, (paper & board, coatings, adhesives, printing inks, silicones, elastomers/rubbers, wood, cork, textiles, glass . . .) often referred to as non-harmonised FCMs, the specifications of Commission Regulation (EU) No 10/2011 are used, sometimes inappropriately with unexpected issues arising. In other cases, industry guidelines are available, but are not necessarily recognised by authorities. For paper and board, simulation conditions are described depending on the contact conditions. Cold water (EN 645 1997), hot water extract (EN 647 1997) and substitute simulants (iso-octane/95% ethanol, (EN 15519 2007)) are more or less extractive for hydrophilic and lipophilic components respectively. Modified polyphenylene oxide (Tenax®) (EN 14338 2003) is the most suitable simulant for contact with dry food with paper and board but also for other FCMs.

Vegetable oil is mostly not suitable for non-targeted analysis due to the complexity of the matrix except for highly volatile migrants. For plastics, 95% ethanol and isooctane are recommended as substitute simulants for vegetable oil. These two simulants span the polarity range of migrants from

the plastics encountered in practice. It might be necessary to use both simulants to cover all migrants due to their different solubilities in the solvents. But it needs to be considered, as mentioned, that swelling of the FCMs can lead to overestimation of the migration. An approach to minimise the swelling effect is to adjust the time and temperature conditions.

In general, screening with 95% ethanol is suitable for most of the polyolefin-based FCMs showing only little interaction with the polymer (swelling). 95 % ethanol would cover most of the food categories. FCMs containing acid-soluble components (e.g. primary aromatic amines) should be tested with 3% acetic acid as a worst case, except for materials which are not suitable for acidic foods or those where the substrate would corrode during testing, which would not be the case in practice.

For polymers (resin), there are three types that must be considered: non-polar polymers (e.g. polyolefins), medium polar (e.g. polystyrene), and polar polymers (e.g. polyamides, polyesters, and copolymers). The usual alternative fat simulants, 95% ethanol and isooctane, have different polarities so that the non-polar polyolefins are swollen by non-polar solvents (isooctane) but have only little interaction with polar solvents (95% ethanol). With polar polymers the situation is reversed. Polystyrene, a medium polar polymer, is swollen with both alternative fat simulants 95% ethanol and isooctane. The standard EN 1186–15 uses these effects for accelerated migration testing (EN 1186-15 2002). On the other hand, non-swelling polymer-solvent combinations can be used for diffusion-controlled migration testing under the time-temperature conditions up to 60°C in Annexe V of Commission Regulation (EU) 10/2011. Highly polar polymers like the polyamide polycaprolactam (PA 6) are swollen by water and their polar components are largely extracted in a migration test using water and other aqueous simulants or media.

Exhaustive extraction

Extraction experiments are alternatives to migration tests with food simulants. The aim is to determine the concentration of possible migrants in the FCM. Thus, it requires a complete extraction. The target is to extract and analyse all potentially migrating substances with a molecular mass below 1000 Da. Afterwards, the migration can be calculated based on the packaging data (surface-to-volume ratio). The worst case is assuming 100% migration. Alternatively, the concentration in the material can be used for a more realistic theoretical estimation of migration by mathematical modelling.

A complete/exhaustive extraction can be obtained by:

- Headspace (HS), thermal desorption (TD), Purge & Trap (P&T) of volatile components
- Solvent extraction
- Dissolving the FCM and precipitating the polymer.

Validation for completeness (or near completeness) with multiple extractions/multiple dissolutions and precipitation or by using representative standards of the target analytes is required. In case the polymer is not strongly swollen or dissolved by the solvent, the surface area of the sample should be increased by milling (cold or cryogenic milling) in order to increase extraction efficiency. But this must be done with caution to avoid contamination, degradation and/or losses of substances. The selection of extraction solvent depends on the FCM and on the components to be extracted. For dissolution/precipitation the first solvent should dissolve the FCM whilst the polymer precipitating solvent should not co-precipitate substances < 1000 Da. Using the extraction approach, conditions have to be chosen that ideally swell the polymer, without dissolving the polymeric matter, and almost completely extract the substances < 1000 Da.

Some examples of solvents for extraction of organic components are given in Table 1. It should be considered that there might be interferences with a solvent and that not all substances can be detected with one extraction procedure.

Estimation of migration by mathematical modelling

Starting from the concentration in the material, estimation of migration in food or food simulant not only by 100% transfer assumption but also by mathematical modelling is an acknowledged

Table 1. Examples of extraction for food contact materials (FCM). Solubility of the substance should also be considered when choosing an extraction solvent.

	Extraction solvent	
FCM	Extraction	Dissolution/Precipitation
Polyolefin	Dichloromethane, isooctane	Hot xylene/methanol
Polystyrene	95% ethanol	Dichloromethane /methanol Dimethylacetamide (for headspace analysis)
Polyester (PET) PEN	Acetonitrile/ Dichloromethane	Hexafluorisopropanol or trifluoroethanol or Dichloracetic acid/Methanol
Polyamide	Acetonitrile/ Dichloromethane, 95 % ethanol,	Hexafluorisopropanol or trifluoroethanol or Dichloracetic acid/Methanol
Multilayer films	Depending on material of food contact side	
Paper	Water, ethanol, acidic medium	
PVC	Acetonitrile/ Dichloromethane	Tetrahydrofurane/methanol

alternative to experimental migration testing (Recital 32 and Article 18 of Commission Regulation (EU) No 10/2011).

The level extracted is assigned as initial migrant concentration, Cp_0. By modelling software, migration is calculated for a specific application (time, temperature, size of package, type of foodstuffs to be packed). Prerequisites for the applicability of modelling are described in the JRC *Practical guidelines on the application of migration modelling for the estimation of specific migration* (Hoekstra et al. 2015). The migrants need to be identified (even tentatively) or at least characterised in terms of molecular mass and polarity.

The approach to estimate diffusion coefficients in the modelling guidelines (via A_P values of polymers) is largely overestimating migration especially for low diffusive polymers and higher molecular weight substances. New equations for more realistic estimates of diffusion coefficients have been developed in the last years (Welle 2013; Fang and Vitrac 2017; Mercea et al. 2018). The parameters of the Welle equation, initially developed for PET, have been published for a range of polymers (Ewender and Welle 2016, 2019; Welle 2021). For polyolefins, migration modelling using the A_P equation is still a useful approach (Begley et al. 2005; Hoekstra et al. 2015).

As the diffusion coefficient in a polymer is mainly defined by the molecular mass or volume of the migrating substance, master curves can be established by modelling showing the maximum allowable concentration of a migrant in the packaging material versus the molecular mass or volume of the migrant and be used directly for evaluation. Such an approach is outlined in (Welle 2016). Mathematical modelling with realistic, slightly overestimating parameters is a useful option to overcome the problem with the medium polar polymers that water-ethanol mixtures and the alternative fat simulants 95% ethanol and, in case of styrenics also isooctane, swell the polymer under the migration test conditions and resulting in large overestimation of migration into real foods (Guazzotti et al. 2021).

Strengths and weaknesses of current analytical techniques for analysing migrants from FCMs

This section aims at summarising the strengths and weaknesses of available techniques. Ensuring that as many of the substances migrating are detected is a major challenge as there will most likely be some non-detected substances remaining in the migrate.

Investigation of potential migrants into foodstuffs involves performing complex analyses usually applying a wide range of analytical methods. Advances in NIAS analysis and migration studies are mostly based on gas chromatography (GC) and high-performance liquid chromatography (HPLC) coupled to mass spectrometry (MS) for identification and quantification. Many NIAS can be detected when using highly sensitive advanced analytical techniques, e.g. high-resolution mass spectrometry (HRMS) is a key analytical technology for detecting and identifying NIAS (Canellas et al. 2010; Nerín et al. 2013; Omer et al. 2018; Martínez-Bueno et al. 2019). However, the proper identification requires a deep study in which success is not always guaranteed. It should be highlighted that the analytical methods required for the screening of NIAS will closely depend on both the food simulant used and the type of migrant. Some, especially predictable NIAS, need specific methods to reach the required sensitivity. This means that a good knowledge about the FCM is required, hence the need for good communication within the supply chain.

As with any analytical procedure, two main steps are involved: sample preparation and instrumental analysis. Figure 2 gives an overview of sample preparation and analytical techniques of NIAS in

polymers and Figure 3 gives an overview of analytical techniques in migration testing that are described later in this section. Figure 4 illustrates an analytical approach .

Sample preparation/treatment

Before analysis, sample preparation/treatment is usually required to separate the substances from the matrix (FCM, food simulant or extraction solvent) and to enhance their concentration. Without the appropriate procedures and techniques, there is a risk of missing NIAS partially or completely. Isolation and/or concentration of migrants can be done using different options such as

- Static Headspace over the material (direct analysis) or over the food simulants for the most volatile compounds.
- Dynamic Headspace (P&T) for the most volatile compounds present in food simulants (Nerín et al. 1995, 1998; García Ibarra et al. 2019).
- Direct thermo-desorption from the material such as the one described in (German Association of the Automotive Industry (VDA) 2016; Ouchi et al. 2019) can also be used.
- Extraction or microextraction (liquid–liquid microextraction, LLME (Pezo et al. 2007; Osorio et al. 2018)) with solvent. In case concentration of the migrant solution is required

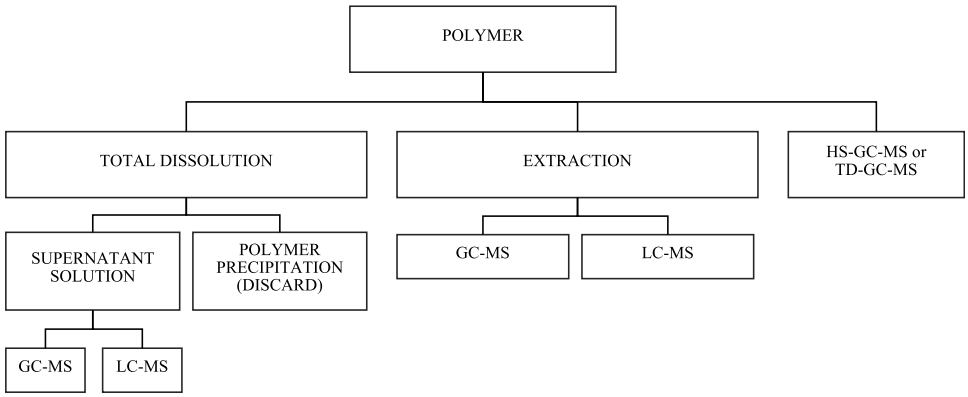

Figure 2. Screening procedure for sample preparation and analytical techniques for identification of NIAS in polymers. GC: gas chromatography; MS: mass spectroscopy; LC: liquid chromatography; HS: headspace; TD: thermal desorption.

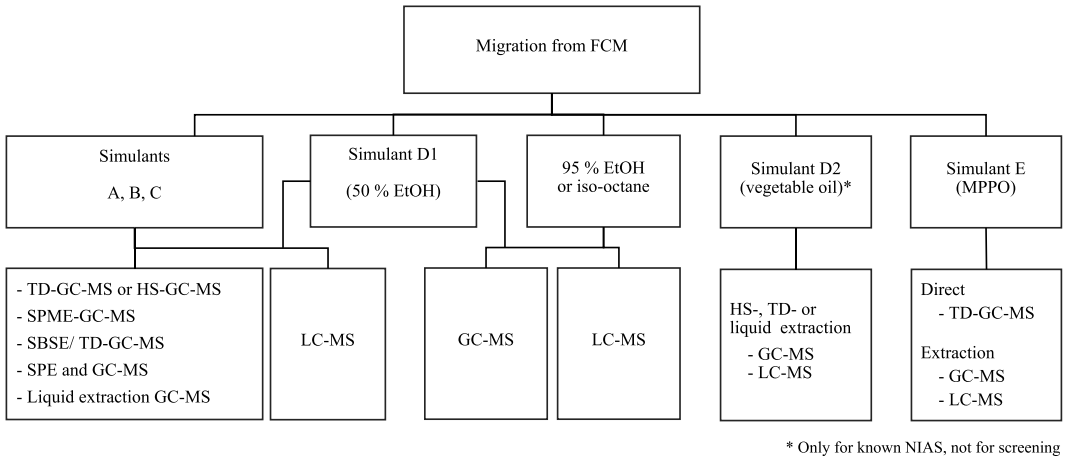

Figure 3. Screening procedure for identification of NIAS in simulants. HS: headspace; TD: thermal desorption from FCM or adsorbent (e.g. MPPO), purge and trap or dynamic headspace; SBSE: stir bar sorptive extraction; SPME: solid-phase microextraction.

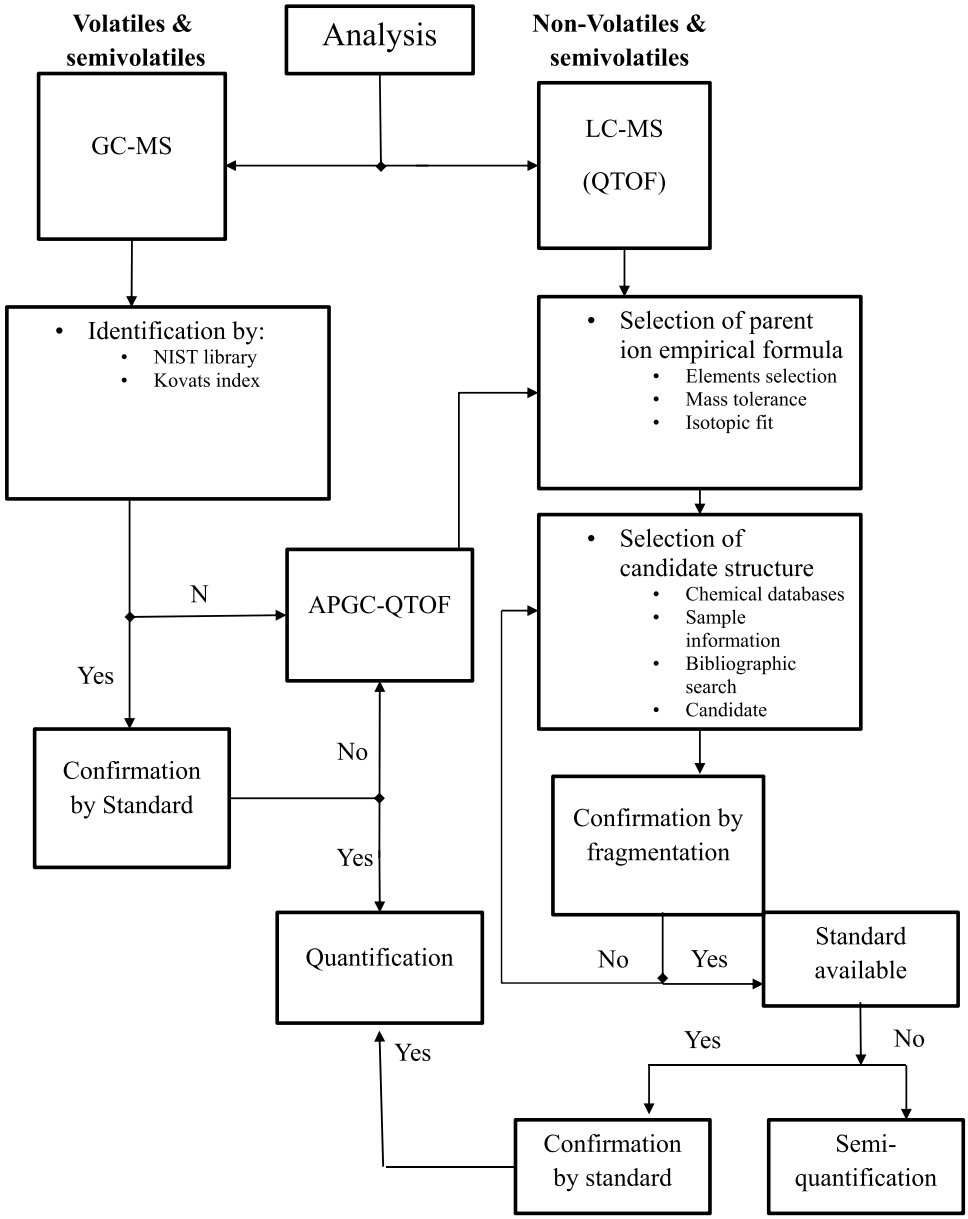

Figure 4. Schematic for analytical approaches for analysing NIAS.

the solvent can be evaporated with special care to avoid losses during the process (e.g. by addition of keeper solvents)

- Solid phase microextraction (SPME) either in total immersion mode, where the SPME fibre is immersed into the food simulant after the exposure, or by headspace, where the SPME fibre extracts the volatile migrants from the headspace over the simulants after the exposure (Song et al. 2019; Su et al. 2020).
- SPE (solid-phase extraction using the cartridges or dispersive-SPE, either partition with C18 or modified silica, ionic exchange, adsorption, etc.).
- Concentration and fractionation can be also done by QuEChERS methods, mainly applied to food (Fasano et al. 2015; Tuzimski and Szubartowski 2019).

Moreover, it is possible to couple a solid phase microextraction sampler (SPME), a thermodesorption unit or a static headspace either to GC-MS or to APGC-MS-QTOF (Atmospheric Pressure Gas Chromatography Mass Spectrometry). All of them are solvent-free sample preparation technologies, fast, economical, and versatile. Using SPME, concentration factors are usually quite high and

some interfering compounds from the sample can be avoided. However, care must be taken to avoid contamination.

LLME, SPME (and stir bar sorptive extraction, SBSE), and static headspace are non-exhaustive extraction methods. The partition coefficient between the phases has to be considered. This is a challenge, especially for the properties of unexpected NIAS (concerning polarity of substances which are not captured e.g. estimated on the basis of octanol-water partition coefficients). In the absence of reference standards, those methods are qualitative only. Thermal desorption and dynamic headspace are exhaustive extraction procedures. However, the adsorbent must be chosen with respect to the analytes that should be covered.

Identification of migrants

After sample preparation, the migrants must be identified and quantified. An overview of the different analytical techniques with their strengths and weaknesses is provided in Table 2. Typically, the analytical approach for NIAS would start with an untargeted analytical screening that should result in a global picture of the molecules that migrated or were extracted. These substances will be known IAS, known/predictable NIAS and unknown/unpredictable NIAS. Without a doubt, the identification and quantification of unknowns is the most difficult task in migrant analysis.

NIAS can be divided into volatile, semi-volatile and non-volatile substances, where each one needs different requirements for analytical techniques. The classification is not unambiguous. There is an overlapping of substances covered by the different analytical techniques.

- Volatile migrants: GC with thermal extraction and MS detection.
- Semi-volatile migrants: GC with MS detection.
- Non-volatile migrants: LC with MS detection.

Figure 2 shows a Decision Tree for the analytical procedure in NIAS identification. GC-MS can be used for volatile and semi-volatile species, typically with a molecular weight below 800 Da, which require solvent or thermal extraction, applied either on the FCM or on food simulants or foodstuffs (Garcia Ibarra et al. 2018). The selection of GC columns depends on the nature of the FCMs. For screening, it is recommended to check the unknowns using both non-polar and polar columns, in order to get as much as possible of potential NIAS. A pragmatic solution here would be to run the samples using a column with 5% phenyl/95% methyl-polysiloxane as a stationary phase, considered the most universal GC column. An example for broad applicability of this column phase is the simultaneous analysis of 84 IAS from plastic materials (Tsochatzis et al. 2020a) as well as of NIAS from polyurethanes and polystyrenes (Tsochatzis et al. 2020b) or from recycled polyolefins as untargeted analysis (Su et al. 2021a, 2021b). Polar substances have a poor peak shape on non-polar or medium polar GC columns that makes identification and quantification difficult. They need a polar column or an LC technique for better analysis. The detection is typically done by MS with electron ionisation (EI) that provides a full fragmentation of the substance and allows comparisons with MS libraries containing tens of thousands of spectra. The similarity between the found spectra and that from a library is commonly used for identification, whereby the match factor (percentage of similarity) gives an indication of the level of confidence. Additionally, the retention time normalised as a Kovats Index can be used for increasing the confidence of the identification. As the EI applies high energy a molecular ion is not in all cases present in the mass spectrum. Without clear information about the molecular ion, the assignment of structures gets difficult. Alternative approaches are soft ionisation tools (e.g. chemical ionisation) combined with MS, which can provide molecular ions and specific fragments which are useful for identification. Another appropriate technique is APGC-HRMS (atmospheric pressure (AP) ionisation combined with HRMS such as APGC-QTOF-MS), that provides accurate mass and facilitates identification (Canellas et al. 2012; Su et al. 2019). As hydrocarbons are not ionised in APGC ionisation mode, they do not overlap with other migrants that could be present, as happens in GC-MS with electron ionisation. An example of this is identification of nine isomers of 2-(dicyclohexylphosphino)-N-methylethanamine and their derivatives in a pressure sensitive adhesive used for food packaging (Canellas et al. 2014). These isomers were detected but could not be identified by EI-GC-MS

Table 2. Overview of strengths and Limitations of different analytical techniques for analysing migrants either in FCMs or in simulants after migration tests, as well as approaches for sample preparation.

Method	Strengthts	Limitations
Static headspace (HS)	Equilibrium conditions needed for reproducibility. Direct analysis for solid samples. Good for the most volatile compounds. Clean chromatograms without solvent delay in MS.	Sensitivity decreases with increasing boiling point. Dependence of partitioning equilibrium on substance and matrix (reference substances needed for quantification). Solution: Multiple headspace extraction allows extrapolation to quantitative transfer into the gas phase under the applied equilibrium conditions
Dynamic headspace (Purge & Trap)	For the most volatile compounds. Very sensitive. Clean chromatograms without solvent delay in MS.	Many interferences. Only suitable for volatiles. Requires specific instrument. Care is required with the moisture content of the sample. The adsorbent must be chosen with respect to the analytes that should be covered. Many parameters (time and temperature of purge, trap, temperature and desorption time) to optimize.
Liquid-liquid microextraction	High concentration rate.	Difficult handling unless automatic device is available. Careful selection of extraction solvent is required. Cannot cover all substances with one solvent
Solvent extraction either from solid FCM or from food simulant, including Tenax, Accelerated Solvent extraction (ASE), Microwave-assisted extraction (MAE) and ultrasonic extraction (USE).	Versatile. High concentration rate is possible.	Compatibility with the subsequent analytical technique is required. Optimization of solvent, volume and conditions are required. Solvent delay required in MS. (some substances will be not detected.
Thermal desorption	High concentration rate. High sensitivity; either direct from the material or from a solid sorbent such as the simulant Tenax®	Requires specific injection port in GC and device for automatic analysis (desorption). In case a sorbent is used it must be chosen with respect to the analytes that should be covered.
SPME/HS or immersion mode	High concentration of analytes. Clean chromatograms without solvent delay in MS. Automatic or manual. Very sensitive. Available for volatile and semi-volatile compounds. Can be applied to aqueous and solid samples.	Requires careful optimization (fibre, time, temperature) as there are several SPME fibres. Important to work under equilibrium conditions for reproducibility. Reference substances needed for quantification. Maximum concentration of organic solvents in aqueous solutions is 10%.
SBSE	High concentration of analytes. Clean chromatograms without solvent delay in MS. Automatic or manual. Very sensitive. Available for volatile and semi-volatile compounds.	Requires special equipment for automatic thermal desorption. Cannot cover all substances with one SBSE phase. SBSE is only useful for extraction of components, when the partitioning between SBSE and FCM/or food simulant allows it.
Low polarity GC column (DB5 or similar)	Quite universal for many low polar volatile and semivolatile organic substances Kovats Indices available in NIST database to support identification	Size and thickness of stationary phase of the GC column need to be selected according to the analytes
Polar GC column (carbowax, polyethylenglycol or similar)	For polar and volatile substances (ketones, aldehydes, etc.) Kovats Indices available in NIST database to support identification	Size and thickness of stationary phase of the GC column need to be selected according to the analytes Restricted temperature resistance of the columns compared to others.
RP-LC (C18 and modified phases) for non-volatile and low polarity substances,	Quite universal. There are more specific modified phases for groups of substances. Different size and thickness available	No suitable for very polar substances. No compatible with organic solvents
HILIC-LC (non-volatile and very polar substances)	Good separation for very polar and/or ionic substances	Careful optimization of mobile phase is required
GC-FID	Can be used for quantification, suitable for volatile and semi-volatile substances Mol wt upper limit ~ 800 Daltons applicable for a wide range of substances.	Non-specific detector, not applicable for identification unless pure standards were used. The response depends on the number of carbons and the chemical structure.
GC-MS (direct injection) Several injection modes are available: on-column, split/split-less, PTV. . .	Libraries available to assist identification. Suitable for volatile and semi-volatile substances Mol Wt upper limit ~ 800 Daltons.	Solvent delay prevents the analysis of the most volatile components. Special care should be taken to avoid new NIAS produced in the injection port
GCxGC-MS or GCxGC-FID	2D separation of overlapped compounds in the first GC.	Expensive equipment that requires specific training. No common in many labs.
LC-MS-triple Quad or ion trap (MS-MS).	Very good for target analysis and for quantification. Widely available. Very sensitive (if the substances are ionisable) for quantification of non-volatiles. Wide range of substances depending on the LC column used and ionisation source.	Limited accuracy of masses of substances. Limited identification. It requires confirmation by pure standards. Targeted analysis.

(*Continued*)

Table 2. (Continued).

Method	Strengthts	Limitations
LC-HRMS various techniques	Very good for untargeted analysis and screening, providing the compounds are ionisable. Accurate molecular mass and mass fragments, essential for identification. Quantification is possible.	No wide libraries commercially available yet, as the spectrum depends on experimental conditions used. Adducts formed, which make identification more difficult. Software required to help with identification. Ionisation and therefore detection depend on the substance, the ionisation technique, solvents, and apparatus settings
LC-IM-HRMS	Accurate molecular mass and mass fragments. Additional separation based on IM that provide CCS values for identification. Values of CCS from IM do not depend on chromatography. Isomers can be separated Quantification is possible.	No commercial libraries are available yet. Some are in process.
NMR	Useful for elucidation of the chemical structure and purity of a reference substance Quantitative NMR can be used to determine the amount of certain functional groups in a migrate (e.g. oxirane moieties) or even the amount of certain substance group (dimethylsiloxane in food; Helling et al. 2010).	Limited sensitivity, need for isolated compounds and not being readily coupled to LC. Not readily available to many companies or laboratories.
UV/DAD/fluorescence (coupled to LC)	Needs a suitable chromophore (selectivity). Very sensitive depending on the chromophore (fluorescence) Very specific (fluorescence)	Reference standard is needed. DAD is not substance specific but tentative identification of the chromophore by UV-spectra (DAD) can be achieved.
HPLCxGC	Provides the separation of one or more pre-separated fractions (2D). Can be also applied off-line	Specific devices for coupling both equipments (LC and GC) is required. Experience required for processing the data and interpreting the results
TGA-GC-MS	-Analysis of decomposition products at high temperature conditions-compositional analysis of polymer blends	Not available in most of the labs

(quadrupole), whilst they were identified by APGC-MS-QTOF due to the presence of molecular ions and the accurate mass.

For some samples, MS detection for identification is not sufficient due to interferences with largely co-eluting substances, which hampers identification. In such cases either a pre-separation of substance groups by other chromatographic techniques like SPE is necessary (BfR 2011) or the use of multi-dimensional chromatographic techniques (GC x GC, 2D HPLC, HPLC-GC) to improve separation. A better description of the multi-dimensional GC x GC applied to migration from FCMs can be found in (Biedermann and Grob 2019). Separation of substances can also be achieved by HPLC-GC x GC prior to MS detection. Examples are the elucidation of oxidised trace compounds in polyethylene (Wolf et al. 2021), the comprehensive analysis of potential migrants in PE, PP, and phenolic resins (Biedermann and Grob 2019), the analysis of saturated and aromatic hydrocarbons migrating from polyolefin-based hot-melt adhesives into food (Lommatzsch et al. 2016), and the analysis of mineral oil hydrocarbons in paper food packaging (Biedermann et al. 2013) and in foods and cosmetics (Biedermann et al. 2017).

For non-volatile migrants, LC-MS is an excellent technique to determine trace levels of non-volatile compounds. LC-MS can be equipped with several mass analysers, each one providing unique features capable of identifying, quantifying, and resolving ambiguities by selecting appropriate ionisation and acquisition parameters. There is no universal ion source, which can be used for ionisation with different structural compounds. The general drawback of LC-MS compared to GC-EI-MS is the lack of a universal MS spectra database for the identification of the substances. LC-MS mass spectra depend on the type of interface used for ionisation, the selected MS settings, and the eluents used: For polar analytes mostly electrospray ionisation (ESI) is successful, while for non-polar analytes atmospheric pressure chemical ionisation (APCI) or atmospheric pressure photoionisation (APPI) are

recommended. Substances are detected either in positive or negative ionisation modes (or in both) and the response strongly depends on the ionisation yield in the interface and therefore from the factors mentioned above. From the factors mentioned above various adducts (H^+, Na^+, NH_4^+, etc.) might be formed, depending on the composition of the LC eluent and the ionisation source. This fact complicates the identification, as the kind of adduct is hard to predict. Some of them, such as sodium adducts, inhibit further fragmentation of the molecular ion, which means that the fragmentation profiles are unavailable to help with identification.

Low-resolution LC-MS is routinely used in many laboratories with triple quadrupole (QqQ) or ion trap (IT) mass analysers. They can be applied for identifying predictable NIAS based on their molecular mass, the isotope pattern and typical fragmentation for certain substance groups. However, identification of unknowns and unpredictable NIAS need additional tools, such as NMR (Hoppe et al. 2016) or others, as the number of potential candidates usually found for each mass fragment in low resolution LC-MS can be very high. An ion trap device provides a higher sensitivity and information about multistage fragmentation compared to QqQ-MSD.

LC combined with HRMS such as time-of-flight (TOF), quadrupole -TOF(QTOF) or Orbitrap™ (ion trap)) provides accurate masses isotopic patterns and intensities, which can lead to theoretical information about composition of fragments (Peters et al. 2019) and opens the possibility of identifying unknown and unpredicted NIAS.

HRMS enhances the selectivity compared to low-resolution MS and therefore the 'confidence of identification' (see below). Knowing the molecular formula, different databases such as ChemSpider® or SciFinder can be used to elucidate the chemical structure and identity of the unknown substance. Fragmentation using a Q-TOF or multi-stage fragmentation using an Orbitrap device, respectively, will give further indications of structural moieties of the sought substance. Software tools for accurate prediction of molecular fragmentation are of great help and there is much available software for this purpose (Habchi et al. 2018).

Unfortunately, databases do not contain information on oligomers. This needs to be compiled by those with knowledge of the potential oligomers. Some examples of the analysis of oligomers can be found in the literature (Hoppe et al. 2016; Paseiro-Cerrato et al. 2016a, 2016b; Groh et al. 2017; Driffield et al. 2018; Ubeda et al. 2018; Zhang et al. 2018; Eckardt et al. 2020b Tsochatzis et al. 2020b; Brenz et al. 2021).

The advanced technology of ion mobility (IM) linked to LC-HRMS provides additional tools for identification (Canellas et al. 2019, 2020, 2021; Kim et al. 2021). This technique provides separation by means of a travelling wave ion mobility cell, mass accuracy and fragment ion information. The time the ions take to traverse the drift cell is called the ion-mobility "drift time". A collision cross section (CCS) value can be derived from the drift time of each compound. The CCS value is related to the three-dimensional conformation of the chemical structure compound and provides cleaner spectra thanks to the alignment of precursors and fragment ions, thus bringing additional confidence in the identification of unknowns (Vera et al. 2019; Canellas et al. 2021). CCS is a physicochemical and stable parameter, characteristic of the molecule, not influenced by the chromatography, and also independent of instruments and laboratories under different experimental conditions according to recent studies (Hinnenkamp et al. 2018; Zhou et al. 2020). Having a library containing not only the MS fragments and characteristics of the molecules, but also the CCS values can greatly assist in identification.

Combination of techniques

For some samples, MS detection for identification is not sufficient due to interferences with largely co-eluting substances, which hampers identification. In such cases either pre-separation and concentration of substance groups by other chromatographic techniques like SPE is necessary (BfR 2011) or the use of multidimensional chromatographic techniques (GC x GC, 2D HPLC, HPLC-GC) to improve separation. A better description of the multi-dimensional GC x GC applied to migration from FCMs can be found in Biedermann and Grob (2019). Separation of substances can also be achieved by HPLC-GC x GC

prior to MS detection. Examples are the elucidation of oxidised trace compounds in polyethylene (Wolf et al. 2021), the comprehensive analysis of potential migrants in PE, PP and phenolic resins (Biedermann and Grob 2019), the analysis of saturated and aromatic hydrocarbons migrating from polyolefin-based hot-melt adhesives into food (Lommatzsch et al. 2016), and the analysis of mineral oil hydrocarbons in paper food packaging (Biedermann et al. 2013) and in foods and cosmetics (Biedermann et al. 2017).

The use of hybrid instruments aims to unify several advantages in one instrument. A tandem HRMS composed of a quadrupole and time-of-flight (Q-TOF) instrument or an ion trap and TOF (IT-TOF) instrument allows accurate mass determinations of the precursor ion and also of the product ions, providing information about fragmentation patterns. Detection of NIAS by UHPLC®-IMS-Q-TOF with novel mass spectrometry Elevated Energy (MS^E) is the latest technology for comprehensive, reproducible profiling and characterisation, developed by companies working on very specific techniques, and similar tools are provided by different suppliers. It consists of the simultaneous acquisition of low and high-energy data with different energy ramps. In this way, the exact mass precursor ion and the exact mass fragments ions are collected for each detectable compound in the sample in a single analytical run, thus providing structural information of unknown compounds and assuring the correct identification. MS^E detection is quicker than standard MS or tandem mass spectrometry and does not require time-consuming sample preparation (Schulz 2019).

Hybrid linear ion trap-high resolution mass spectrometry, LTQ-Orbitrap®, has also allowed the identification of non-targeted and unknown compounds. It combines a high-resolution mass spectrometer, such as an Orbitrap® analyser, with an external accumulation device such as a linear ion trap, making possible multiple levels of fragmentation (MS^n) for the elucidation of analyte structures (Martinez-Bueno et al. 2017; Omer et al. 2018, 2019). The use of the LTQ Orbitrap® allows high-quality accurate mass and acquisition of MS^n spectra with high sensitivity in full scan and the possibility of determination of accurate mass of product ions (Bignardi et al. 2014, 2017).

But even with the analytical advances in LC-MS, the unequivocal identification of unknowns and NIAS is still challenging, and a high investment in pure standards is required as well as a deep knowledge about potential migrants and fragmentation principles to perform the interpretation of the obtained mass spectra. Spectra libraries more specific in the area of FCMs are on the way and hopefully will be available soon.

Table 2 shows an overview of current available techniques used today for sample preparation and analytical determination. However, no laboratory can be expected to have all the equipment or expertise in applying and interpreting the resulting data. Flow charts of both sample preparation and analytical techniques were shown above in Figures 1 and 2, respectively.

Targeted analysis for predicted or identified migrants

It is worth highlighting that although sophisticated analytical instruments are available nowadays, experience and knowledge in the subject are at least as important as the instrumental equipment. Several migrants cannot be seen in direct screening processes and need special sample treatments to isolate and concentrate them before the final analysis in the instrument. Based on the specific knowledge about known NIAS, target analysis for these analytes should be performed. One example is the analysis of primary aromatic amines (PAAs) which are well-known NIAS, formed from either degradation of azo dyes or from the residual isocyanates from polyurethane, which in contact with humidity form PAAs (Aznar et al. 2009; Trier et al. 2010; Pezo et al. 2012). The sensitivity required of 2 µg/kg of food or food simulant cannot be achieved in a general screening and a dedicated procedure is needed (Mortensen et al. 2005; Simoneau et al. 2011). The same happens with bisphenol A (BPA) when certification of BPA-free in an FCM is requested. Very small molecules (<50 Da) cannot be detected in MS, even if they are very volatile substances, such as formaldehyde or acetaldehyde, and a specific procedure is required. Organotin compounds, which have a very low SML in the EU regulation, are not detected in a general screening and are another example of migrants which need a dedicated procedure.

Level of confidence in identification

Despite the wide spectrum of analytical techniques for identification of NIAS, it is currently not possible to confirm the identification of all unknowns, as the corresponding standards are often not available. Therefore, it is necessary to establish a procedure for assigning the level of confidence in the identification. The IUPAC guidance on identification of organic compounds (Molyneux et al. 2019), indicates levels of confidence in the results, whereas the European Commission decision addresses the performance of analytical methods and interpretation of results, although not specifically addressing NIAS (European Commission 2002).

Schymanski et al. (2014); Schymanski and Williams (2017) and Hollender et al. (2017) proposed a system of five levels depending on the available data in HRMS, giving the maximum confidence level 1 when an exact mass, a referenced mass spectrum after fragmentation, the retention time and reference standard are available (Schymanski et al. 2014; Hollender et al. 2017; Schymanski and Williams 2017). Level 2 is given when reference standard is not available although MS, MS2, RT and experimental data were obtained. Level 3 gives a tentative candidate, which means structure, substituent and class, with only MS, MS2 and experimental data. Level 4 is referred only to unequivocal molecular formula, with MS isotope and adduct and finally level 5 only gives the exact mass of interest. A similar approach has been applied by Su et al. (2019) but giving a percentage to each level of confidence from 60 to 100% and adding more requirements for each level (Su et al. 2019).

Quantification and semi-quantification

To confirm the compliance of FCMs, the quantification of migrants is required. Specific quantification needs reference standards, which in many cases are not available. The synthesis of standards is only possible in a few cases and needs a lot of effort. Therefore, a pragmatic solution should be adopted. An option for semi-quantification is using different substances as standards, but with similar chemical structures, and thus similar fragmentation and behaviour in the MS. Another option is using selected internal standards, provided they have a similar detector response as the majority of the anticipated NIAS: e. g. for screenings of plastic materials in contact with drinking water such an approach is used and laid down in a standard (Löschner et al. 2011; EN 15768 2015). Generally, the variability of response factors from the structure of the analyte in MS is much higher than with other detectors.

Therefore, a flame ionisation detector (FID) is often used for semi-quantification of volatile or semi-volatile substances measured by GC. FID has the advantage that the response factors are more similar for many substances than, e.g. in MS. For HPLC, besides MS detection, there are several other possibilities:

- UV-semi-quantification for substances with similar chromophores (e.g. polyester oligomers)
- Semi-quantification for N-containing substances using a CLND (Nitrogen Chemiluminescence Detector) (Heimrich et al. 2012).
- Semi-quantification of non-/semi-volatiles using a CAD (charged aerosol detector) (Eckardt et al. 2018).
- Derivatisation of certain substances with an agent with unique UV-chromophore/fluorophore/ MS-fragment (e.g. determination of isocyanates)

Recommended approaches and best practices

Despite the wide variety of analytical techniques for sample treatment, identification and quantification, there are several critical criteria that should always be applied to NIAS analysis in FCMs. Extraction tests are arguably more productive than migration tests but may extract more substances than would be found in foodstuffs. The following list emphasises the main issues associated with NIAS:

(1) Examine carefully the FCM before the migration or extraction tests and explore its compatibility with the simulants and experimental conditions to apply, mainly temperature and time. In some cases, ethanol reacts with the migrants and changes the chemical structure of the migrants, e.g. oligomers from PLA, hydrolysis, ethanolysis, transesterification.

(2) After the migration or extraction tests, ensure that the screening applied covers as many as possible of the potential migrants in each simulant. It may be that different analytical techniques are required for different simulants particularly if they migrate at low levels e.g. BPA, BADGE (bisphenol A diglycidyl ether) and its hydrolysis and hydrochlorination products, organotins, hydroxyalkylamines, 3-(2,3-epoxypropoxy)propyl] trimethoxysilane (glymo), PAAs, etc.
(3) Prepare independent replicates (typically in triplicate). This enables migration tests to be checked for repeatability. Prepare sufficient migration solution so that different aliquots can be taken for analysis of volatile, non-volatile substances and specific migrants that require dedicated methods.
(4) Be extremely careful with the selection of the analytical method, avoiding analytical artefacts or producing additional migrants during the process, e.g. isocyanates analysed by GC-MS, benzene from PET, etc.
(5) Special care should be taken with the plastic ware and glassware used in the laboratory as well as in the whole process from sampling to the final result, to avoid cross contamination.
(6) A virgin solvent should be prepared and analysed in a same manner as the exposed solvent. Substances detected in the blank should be named in the test report.
(7) Use chemical databases and references to help in the identification.
(8) Level of confidence or match factor or deviation from Kovats index for each detected substance should be provided in the report as well as the mass spectrum.
(9) Confirm the identification with standards, if available. In the absence of standards corresponding to each substance, use others with the same chemical structure and confirm MS fragmentation and similar behaviour, as the potential NIAS. Note that this is not usually undertaken as it significantly increases costs. Instead, one or more representative standards could be used.
(10) Standards for every analytical technique, mainly chromatographic ones, should be run for every set of samples to confirm the calibration of the instrument. For quantification purposes the standards could be:
    a. external standards – reference standards of known analytes to confirm quantification

Table 3. Information to include in the analysis report

Information about the sample
1. Include the picture of the sample if relevant
2. Add information on the sample (type, sample point, time of sampling)
3. Amount of sample taken
4. End use for product if known

Information about the analysis performed
1. Description of the sample preparation
   - Migration/extraction preparation
   - Migration/extraction conditions (time, temperature, solvent, surface to volume ration, single sided migration versus total immersion Solvent(s) or food simulants used, applied t/T (time/temperature) conditions, experimental surface to volume ratio and rationale for the test conditions selected.
   - Include a picture of the sample before and after the analysis if relevant (e.g. in case of delamination, physical damage or swelling).
2. Description of the measurement techniques used and why they collectively provide adequate coverage for all/any migrants from that FCM
   - Indication of the internal standard(s) used.
   - Performance of the migration/extraction (recovery data obtained by spikes, multiple extractions in a row)
   - Indication of the technique used and the experimental conditions applied, including type of injection (PTV, cold-splitless. . .), injection volume, column used, ionization mode, temperature program, mobile phase solvent, gradient, internal standard(s) used for quantification or semi-quantification. ionization mode, internal standard(s) used for (semi-) quantification.
   - Standards used for calibration plot (quantitative purpose).
   - Limits of detection. Limits of quantification.
   - Confidence level in the identification and quantification
3. Migration modelling
   - If modelling is used rather than analysis, it is necessary to obtain a Cp0. This is normally done by analysis.
   - The techniques used and model used with assumptions should be listed

Results
1. Information about the S/V ratio used for calculation
2. Example of calculation
3. For each technique, summary of all detected substances such as:
- name of the semi-quantified substances
- CAS numbers, if available
- MS spectrum when using MS as a detector
- Residual concentration in mg/kg material or mg/dm^2 material (depending on the technique used)
- concentration in mg/kg food using either 6 dm^2/kg or the actual ratio.
- SML if existing
- Limits of detection
- Limits of quantification
- confidence level in the identification

b. internal standards (for multiple purposes like controlling separation, clean-up losses, injection standards, quantification, etc.), use isotope labelled standards, if appropriate and available

(11) After the analysis, a report should be generated containing the information in Table 3.

Using the results for risk assessment and risk management

Analytical and toxicological data are fundamental requirements for any risk assessment or risk management. Knowledge about the certainty of identity and quantity of the species found is essential. Normally, there will be a mixture of knowns and unknowns so that any resulting output will be a combination of risk assessment and risk management. For 'known NIAS' it is possible to obtain some information about their toxicological profile using tools, such as *in silico*, read across etc. for 'unknowns' it is only possible to manage risk. The use of the Threshold of Toxicological Concern (TTC) is an important tool for risk management of unknowns. Bio-assays may be of benefit, if genotoxicity can be excluded. In case of concentrations which seem too high, the relevance of the food simulants or extraction medium(s) to the usage of the FCM will help assist in deciding if the assessment gives cause for concern. Knowledge of the surface area-to-volume ratio of the resulting FCM is very important for risk assessment or risk management, e.g. a large surface area to a small weight of foodstuff will result in a higher exposure to a given substance than a low surface area for the same weight. More detailed information about this process is available elsewhere (Koster et al. 2015; CEFIC 2020).

Limitations & research needs

The presented approach exhibits some limitations:

- Availability of described analytical techniques, as there are many sophisticated and expensive techniques that are not available in most laboratories. Moreover, there is a need for adequately trained experts that are skilled to use these techniques and interpret the results arising.
- Lack of pure or certified standards for confirmation of identity and quantification of compounds, both volatile and non-volatile.
- Difficulties in identifying all the unknowns, even with today's most powerful techniques.
- The need for prior knowledge about the potential migrants, to guide the selection of appropriate sample treatment and analytical techniques in each case.
- Sensitivity needed for NIAS in screening analysis, to reach down to 0.15 μg/kg, as the analytical techniques used for screening cannot provide sufficient sensitivity for all NIAS. Usually several different techniques are required, as above mentioned, and some predictable NIAS should be searched for using dedicated methods.
- An accepted approach for the analysis of NIAS which can be used in addition to exposure approaches to allow adjustment to reflect actual exposure, packaging use factors, food consumption factors etc.

Without a doubt, the analysis of NIAS is challenging and there are many questions to solve before getting a common and consolidated approach available for most of the players involved in this issue. It is difficult to predict if someday the advances in analytical techniques will allow the total identification and quantification of unknowns at low enough migration/exposure levels. However, concerning the safety in use of FCMs, probably what is more important is to be able to perform a risk assessment for any FCM. Currently, the best way is to identify and quantify the migrants as much as possible and then apply the risk assessment based on these data. If toxicity tests applied to mixtures of migrants are developed at sufficient sensitivity, the application of an appropriate risk assessment is expected to be much easier and faster. Thus, main areas of research can be highlighted here:

- Analytical research trying to improve the identification and quantification of as many compounds as possible using widely available equipment. Quantification of unknown migrants is a major hurdle in determining which migrants should be further considered for risk assessment. Both over- and under-estimation can cause

problems – creating an issue where there is none and overlooking a migrant when it is actually present at higher levels than determined.
- Development and agreement on standardised analytical protocols, would have a significant impact.
- The development of comprehensive database-(s) containing all compounds found in migration from different FCMs is essential. It must also contain substances other than oligomers. This must be publicly available and include typical oligomers from different types of polymers and other common NIAS coming from FCMs.

Once tentative structures could be proposed for NIAS then structural alerts would help in risk assessment and if levels could be estimated then it might be possible to apply TTC

- In case of complex mixtures, methods for determining the amount of specific molecule moieties as indicated by Structure Activity Alerts, could be helpful (e.g. amount of phenolic groups in a migrate of phenol-containing coatings, (Eckardt et al. 2020a, 2020b). This could follow the TTC decision tree approach (Barlow 2005).
- The development of suitable alternative simulants and migration test conditions is needed for specific polymers, e.g. (thermoplastic) elastomers, medium-polar polymers, for which the usual screening simulants ethanol and isooctane overestimate migration into real foods and for which increased contact with ethanol/isooctane form artefacts.
- The development of alternative simulants for high-temperature applications in cases where MPPO is inappropriate to absorb the relevant substances.
- Further investigation and techniques for testing a wide range of FCMs and possible development of SOPs is highly desirable.
- Correlation between migration of oligomers into food and simulants, particularly for higher molecular weight oligomers (500–1000 Da) needs to be examined considering the findings in which simulant results seem to substantially overestimate actual measurements into canned foodstuffs for oligomers (Driffield et al. 2018).
- Correlations between analytical results and those from bioassays would greatly assist risk assessors, risk managers and authorities.

Conclusion

Today a comprehensive analysis of migrants from FCMs is not achievable for even the most sophisticated laboratories. Not all migrants can be detected using today's wide range of available analytical techniques. Therefore, compromises are necessary like screening procedures and semi-quantitative estimation of concentrations when appropriate quantification is not possible. Combining this with the fact that different analytical equipment may give different results, particularly if a representative standard is not used, places the emphasis on the persons undertaking the analysis and interpreting the results, along with their procedures for sample preparation. With today's knowledge and available equipment, it is not possible to give an accurate picture of all migrants from FCMs, particularly those migrating below the level of detection or quantification. This means that analysis alone will not result in identifying 100% of all migrants from FCMs. However, this cannot replace communication in the supply chain and the diligent choice of suitable raw materials for the intended purpose. The strengths and weakness of each technique used must be recognised, both by industry, authorities, and regulatory bodies.

Finally, the goal of NIAS determination is to assist the risk assessment and risk management of FCMs. Other techniques such as bioassays are desirable to supplement the analytical results, especially when numerous, unknown peaks are detected on a chromatogram at low levels.

Glossary

NIAS	Non-intentionally added substances
APCI	Atmospheric pressure chemical ionization
APGC	Atmospheric pressure gas chromatography
APPI	Atmospheric pressure photoionization
BADGE	Bisphenol A diglycidyl ether
BPA	Bisphenol A
CAD	Charged aerosol detector
CLND	Chemiluminescent nitrogen detector
CSS	Collision cross section
EI	Electron ionization

(*Continued*)

NIAS	Non-intentionally added substances
APCI	Atmospheric pressure chemical ionization
APGC	Atmospheric pressure gas chromatography
APPI	Atmospheric pressure photoionization
BADGE	Bisphenol A diglycidyl ether
BPA	Bisphenol A
CAD	Charged aerosol detector
CLND	Chemiluminescent nitrogen detector
CSS	Collision cross section
EI	Electron ionization
ESI	Electrospray ionization
FCMs	Food contact materials
FID	Flame ionization detector
GC	Gas chromatography
GC x GC	Multidimensional gas chromatography
GC-MS	Gas chromatography–mass spectrometry
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectroscopy
HS	Headspace
IAS	Intentionally added substances
IM	Ion mobility
IT	Ion trap
LC	Liquid chromatography
LC-MS	Liquid chromatography–mass spectrometry
LDPE	Low density polyethylene
LLME	Liquid-liquid microextraction
MPPO	Poly(2,6-diphenyl-*p*-phenylene oxide) Tenax®
MS	Mass spectroscopy
MS^n	Multi-stage mass spectroscopy
NMR	Nuclear magnetic resonance
P&T	Purge and trap
PAAs	Primary aromatic amines
PET	Polyethylene terephthalate
QqQ	Triple-quadrupole mass spectrometer
QTOF	Quadrupole time of flight
QuEChERS	Quick, Easy, Cheap, Effective, Rugged & Safe
RT	Retention time
SBSE	Stir bar sorptive extraction
SML	Specific migration limit
SOP	Standard operating procedure
SPE	Solid phase extraction
SPME	Solid phase microextraction
TD	Thermal desorption
TTC	Threshold of toxicological concern

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