Food
Packaging
Forum

Dossier –
Non-intentionally added substances (NIAS)

June 2018, 2ⁿᵈ edition   **Birgit Geueke**

1   What are NIAS?

Food contact materials (FCMs) and food contact articles (FCAs) may contain non-intentionally added substances (NIAS) which can potentially migrate into food. NIAS comprise all substances that have not been added for a technical reason during manufacturing of FCMs and FCAs. They have various sources and can be grouped into side products, breakdown products, and contaminants (Figure 1A). NIAS can enter the supply chain of FCMs/FCAs at any level, e.g., during chemical syntheses of raw materials as well as manufacture, transport, and recycling. The awareness of NIAS as an issue of concern for food safety has grown during the last years due to increasing sensitivity in chemical analysis and the random identification of potentially hazardous chemicals migrating from FCMs and FCAs [1-3].

Since many FCMs and FCAs have a high chemical complexity, a complete characterization of all NIAS is currently unrealistic [4]. It has been estimated that tens of thousands of substances migrate from FCMs and FCAs [5]; thus it is a challenge to identify those NIAS that may be of concern. While more and more NIAS are being identified over time, not all these known substances have been risk assessed so far (Figure 1B). Other NIAS may have been detected by chemical analysis but their structures remain unknown; thus, conclusions on the safety cannot be drawn. The last group of NIAS are those substances which completely stay under the radar, because they are not detected by any of the applied analytical methods.

NIAS may be predicted based on the knowledge of chemical processes, manufacturer's experience, and conditions of use. Such substances may then be identified and quantified rather easily by targeted chemical analyses (Figure 1C). However, many other NIAS cannot be predicted at present. They may either be detected by non-targeted screening methods or remain completely unknown.

The term NIAS was introduced for plastic FCMs in Europe in the legal context (Commission Regulation (EU) No 10/2011). However, NIAS do not only occur in plastic, but also in non-plastic FCMs (e.g., paper and board, coatings, adhesives, printing inks, silicones, glass, ceramics).

2   Origins of NIAS

Here, we describe the different sources of NIAS (Figure 1A) and give selected examples that illustrate the current knowledge, but also the difficulties in analyzing these unwanted compounds (Table 1).

2.1 Side products

FCAs are often composed of several types of FCMs that are produced in individual steps and finally combined. Side reactions may already occur during the production of the starting substances, but also during all further manufacturing stages. For many processes, major side products are known (Table 1). Such NIAS can easily be monitored, or their formation may even be reduced by changing the process parameters. However, considering the high number of starting substances used to produce FCMs and the complexity of

manufacturing processes, a comprehensive prediction of all potential side products remaining in the final FCA is currently impossible [6]. Oligomers are typical side products formed during the synthesis of polymers [7]. In terms of quantity, oligomers can strongly contribute to the overall migrate of a plastic FCM [8, 9]. Although their presence is usually known to the manufacturer, the risk assessment of oligomeric mixtures is challenging, because of their complex composition.

2.2 Break-down products

Both the structure-providing constituents of FCMs (e.g., polymers, fibers) as well as additives may undergo chemical reactions during manufacture and use. Such processes can be caused or accelerated by external factors such as heat treatment, irradiation, and contact with food and/or oxygen. Some types of additives form intended reaction products while fulfilling their function during use (e.g., antioxidants). These degradation products are often predictable and well-known [4, 10, 11], but nevertheless they are defined as NIAS. Break-down products of polymers often fall into the category of unknown NIAS [12]. They have a lower molecular weight than their parent compounds, and therefore higher diffusion coefficients and increased migration potential. Whether break-down products of polymers leading to the original starting substances (e.g., bisphenol A formed via degradation of polycarbonate) shall be considered NIAS or intentionally added substances needs further specification (see 4.1).
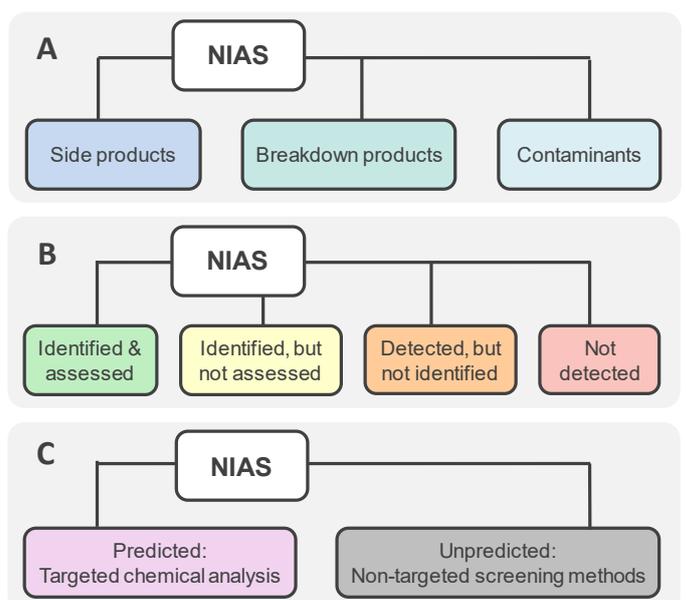

Figure 1. Origins (**A**) and categories (**B**, **C**) of non-intentionally added substances (NIAS).

2.3 Contaminants

Contaminants in FCMs and FCAs have various origins and can be introduced at any stage of production and use.

Impurities and environmental contaminants

Polymer starting substances, additives, and other materials such as solvents that are used for producing FCMs often contain impurities, since they are generally of technical grade. European legislation requires that FCMs are manufactured under good manufacturing practice from starting substances compliant with pre-established specifications (Commission Regulation (EC) No 2023/2006). However, the levels and composition of impurities in starting materials may vary from batch to batch. Main impurities are generally known and controlled by the producer, whereas minor impurities are often unknown [4].

Heavy metals are examples of trace elements and environmental contaminants that may be already present in the raw materials and remain as NIAS in the final FCA. An example is lead in glass containers, which is a geogenic element present in glass' raw material, silica sand.

Process contaminants

Residual cleaning agents and residues from previous batches as well as non-authorized biocides and lubricants are examples of typical process chemicals that may contaminate FCMs and FCAs during their production. In contrast to the other types of contaminants, such NIAS may be rather easily identified and avoided.

Contaminants related to recycling

FCMs consisting of recycled materials are part of the solution to the circular economy, but can be of special concern, because they may be contaminated with NIAS from many different sources. Firstly, recycling streams may contain non-food grade materials introducing unwanted substances into the recycled product [13]. Secondly, recycling processes may be disturbed by incompatible materials that are not sorted out in advance or are difficult to separate (e.g., adhesives, printing inks, coatings) [14, 15]. Thirdly, certain materials (e.g., plastics, paper and board) change their physico-chemical properties and tend to form degradation products during use and recycling [16]. Fourthly, food components sorbed to the FCM as well as residues of process chemicals and/or consumer misuse can additionally introduce NIAS [17, 18].

The resulting, often undefined mixtures of chemicals that are present during recycling can react and form additional substances that extend the list of potential NIAS. Furthermore, accumulation of chemicals might occur when materials are recycled several times. Thus, the prediction, identification, and management of NIAS in recycled materials is a formidable challenge because of the difficulty in tracing their origin.

3 Analytical techniques

Advances in analytical methods enable the detection of increasing numbers of NIAS in FCMs. The FCM itself, a migrate or an extract can be analyzed or screened for predicted or unpredicted NIAS.

Polymers and solid food simulants can be analyzed by direct thermal desorption techniques, such as atmospheric solids analysis probe (ASAP) mass spectrometry (MS) [19], direct analysis in-real-time (DART) MS [20], desorption electrospray ionization (DESI) MS [21], and X-ray fluorescence spectrophotometry [22]. These methods do not require any extraction steps and do not separate the analytes further. Therefore, it is a quick technique, but should be only used to analyze well-known substances due to the complicated fragmentation patterns that are usually obtained.

Any chromatographic analysis of solid samples requires an extraction or migration step that transfers as many compounds as possible into the liquid or gaseous phase or is representative for what may migrate into food. Samples of FCMs and solid food simulants such as Tenax® can be extracted by solid-liquid extraction and then separated by chromatographic steps. Further options for polymer analyses are thermodesorption of very volatile substances followed by gas chromatography (GC)-MS or the dissolution of the complete material followed by any analytical method. Liquid food simulants that are used in migration tests can either be analyzed directly or extracted by solid-phase or liquid-liquid (micro-)extraction steps. Extraction helps to concentrate and prepare a sample for further analysis but might result in some loss of material due to incomplete transfer.

Extracts and migrates are separated by GC or liquid chromatography (LC), connected to, e.g., MS, flame ionization, ultraviolet or fluorescence detectors. Combinations of different methods and complementary approaches help to identify a wider range of substances. GC is suitable for (semi-)volatile substances, whereas LC should be used for compounds that are thermally instable, non- or highly volatile [23]. The most powerful detection techniques are all based on MS. Different mass analyzers, such as quadrupole, ion trap, or time of flight, can be used in LC-MS and GC-MS. They can also be applied as hybrid instruments to unify the advantages of the single detectors in one instrument and facilitate any non-targeted analysis [23]. Such data may be further supported by nuclear magnetic resonance (NMR) spectrometry. With increasing power of analytical tools, data evaluation relies more and more on algorithms. Once a mass spectrum is obtained, it can be searched, often together with the retention index information, in spectral libraries in order to identify the analyzed compound [24]. The elemental composition of an unknown substance can be characterized by high-resolution MS based on the accurate masses it provides. Combining all available information (spectra, retention index, elemental composition, isotopic pattern, structure suggestions by software tools, database searches, and sample information) helps to assign a structure to previously unknown compounds. However, many substances remain unidentified despite strong analytical efforts.

For risk assessment purposes, the concentrations of individual NIAS need to be known. Since analytical standards are often missing, actual levels cannot be measured. The concentrations are then estimated by comparing the peak areas with one or several internal standards. Internal standards can be closely or distantly related to the substance being measured, thus adding to the quantification uncertainty. Depending on the detector used the response signals can vary significantly. Different studies have shown that the prediction error ranges of detectors optimized for 'uniform' responses differ by factors between 3 and 6 [25, 26].

Almost every study investigating NIAS reports non-identified substances (Figure 1B, orange box) [13, 27-30] and experts agree that some NIAS may also be overlooked by current analytical techniques [31].

Table 1. Selected examples of NIAS detected in different types of food contact materials. Sorted according to their origins (**A**) and classifications (**B**,**C**).

A	NIAS	Type of FCM/FCA	Comments	Ref.
Side products	Primary aromatic amines	Multilayer films glued with polyurethane (PU adhesives)	Reaction products from residual isocyanates with moisture.	[32]
	Caprolactam oligomers, (cyclic) polyester oligomers	Flexible multilayer materials; joined by PU adhesives	Caprolactam oligomers derived from polyamide layer; identification of various PU oligomers, depending on the starting substances.	[33]
	Derivatives of bisphenol A diglycidyl ether (BADGE)	Epoxy can coatings	Polymerization side products. The sum of migration of BADGE and some of its derivatives is regulated in Commission Regulation EC 1895/2005.	[34-39]
	Styrene oligomers	Polystyrene food packaging	Mainly dimers and trimers.	[40]
	Cyclic oligoesters	Polyester can coatings	(Tentative) identification of oligomers possible if monomers are known.	[41]
	Unreacted molecules, dehydroxylated bisphenol A derivatives	Polycarbonate tableware	Substances possibly derived from incomplete polymerization.	[7]
Break-down products	Polyolefin oligomeric saturated hydrocarbons (POSH)	Polypropylene (PP) films, without additives	Electron-beam processing increased concentration of POSH tenfold.	[42]
	Dimer and trimer of polycarbonate	Polycarbonate (PC) tableware	Possible hydrolysis products; oligomer levels positively correlated with age of the material.	[7]
	Degradation products of antioxidants	PP films, with additives	Additives reduced degradation of polymer backbone after radiation-energy treatments, but generated degradation products themselves.	[42]
	Several degradation products of photoinitiators and antioxidants	Multilayer-multimaterial printed films	Focus on print transformation products and their set-off capabilities.	[43]
	Carbonyl compounds	PET bottles	Thermo-oxidative and thermo-mechanical degradation of PET.	[44, 45]
	Nonylphenol	Polyvinyl chloride (PVC) films	Tris(nonylphenol) phosphite used as an antioxidant in PVC films is degraded into nonylphenol.	[46]
	Semicarbazide	Foamed PVC seals of metal lids	Thermal break-down product of blowing agent azodicarbonamide. Since 2005, the use of azodicarbonamide as blowing agent is prohibited in the European Union (Commission Directive 2004/1/EC).	[47]
	Mono-, polychlorohydrines; cyclic derivatives	PVC seals of metal lids	Reaction products of hydrochloric acid (released from PVC) and epoxidized soybean oil (plasticizer and stabilizer).	[48]
Contaminants	Various substances found in plastic additives	Plastic polymers (PP, high-density polyethylene (HDPE), polystyrene (PS), PVC, PET, polyamide (PA)) containing representative additives	Additives used for the manufacture of different types of plastic contain many unexpected impurities.	[4]

A	NIAS	Type of FCM/FCA	Comments	Ref.
Contaminants	Di-(2-ethylhexyl) maleate (DEHM)	Printed cardboard boxes	DEHM is unreacted starting material in di(2-ethylhexyl) sulfosuccinate which is used as emulsifier for varnishes.	[49]
	N2-Dodecanoyl-L-arginine (LAS)	Active packaging based on PET film, containing ethyl lauroyl arginate (LAE) as antimicrobial substance	LAS already present in LAE starting material, migration of LAS possible.	[27]
	Phthalates	PET bottles	Unknown origin.	[44]
	Several antioxidants and one plasticizer	Recycled PET pellets/flakes	Contaminants from recycling processes; detected substances are typically used in PVC.	[29]
	Mineral oil hydrocarbons, bisphenols, phthalates, diisopropylnaphthalenes, photoinitiators	Recycled paper and board	Contaminants partially assigned to specific types of paper and board used for recycling.	[13, 30, 50]

B				
Confirmed & assessed	Cylco-diBA	Epoxy can coatings	*In silico* assessment performed, more data needed.	[2, 51, 52]
Confirmed, but not assessed	75 substances tentatively identified	Recycled paperboard	15 out of 75 substances prioritized for further *in vitro* testing, but commercial standards for only 7 substances available.	[53]
Detected, but not identified	?	Plastic polymers (PP, HDPE, PS, PVC, PET, PA) containing commonly used additives	Although comprehensive lists of possible impurities, degradation and reaction products of plastic additives were provided, and substances were confirmed by chemical analyses, many NIAS remained unidentified (especially for PP, HDPE and PVC).	[4]
	?	Multilayer packaging	10 out of more than 60 substances detected in screening tests were not identified.	[28]
Not detected	?	-	Estimates range from 10'000 to 100'000 NIAS in total.	[5]

C				
Predicted: Targeted chemical analysis	See parts **A** and **B**	See parts **A** and **B**	Many of the NIAS shown in parts **A** and **B** of this table are substances that can *now* be predicted based on the demonstrated experience and monitored by targeted chemical analysis.	
Unpredicted: Non-targeted screening	101 substances identified	Paper and board	Identification of substances used in paper pulp processing (e.g., processing aids) and substances originating from printing inks or adhesives (e.g., photoinitiators, plasticizers, solvents), impregnation and coating (e.g., solvents, hydrocarbons).	[54]
	140 substances extracted, 53 substances identified	Silicone rubber teats	Identified substances were grouped into 12 categories: Alkanes, siloxanes, aromatics, aldehydes, trimethylsilanol, butylated hydroxytoluene, *N,N*-dibutylformamide and benzothiazole.	[55]

4 Regulations

4.1 European Union

Article 3 of the European Framework Regulation on FCMs and FCAs states that

"*materials and articles, including active and intelligent materials and articles, shall be manufactured in compliance with good manufacturing practice so that, under normal or foreseeable conditions of use, they do not transfer their constituents to food in quantities which could: (a) endanger human health; or (b) bring about an unacceptable change in the composition of the food; or (c) bring about a deterioration in the organoleptic characteristics thereof.*" (Regulation (EC) No 1935/2004)

NIAS are defined in article 3 of the Plastics Regulation as

"*an impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product.*" (Commission Regulation (EU) No 10/2011)

Further specifications are given in recital (18) and (20):

"*(18) Substances used in the manufacture of plastic materials or articles may contain impurities originating from their manufacturing or extraction process. These impurities are non-intentionally added together with the substance in the manufacture of the plastic material (non-intentionally added substance – NIAS). As far as they are relevant for the risk assessment the main impurities of a substance should be considered and if necessary be included in the specifications of a substance. However it is not possible to list and consider all impurities in the authorisation. Therefore they may be present in the material or article but not included in the Union list.*"

"*(20) During the manufacture and use of plastic materials and articles reaction and degradation products can be formed. These reaction and degradation products are non-intentionally present in the plastic material (NIAS). As far as they are relevant for the risk assessment the main reaction and degradation products of the intended application of a substance should be considered and included in the restrictions of the substance. However it is not possible to list and consider all reaction and degradation products in the authorisation. Therefore they should not be listed as single entries in the Union list. Any potential health risk in the final material or article arising from reaction and degradation products should be assessed by the manufacturer in accordance with internationally recognised scientific principles on risk assessment.*" (Commission Regulation (EU) No 10/2011)

It is in accordance with the current European legislation that NIAS are present in FCMs and FCAs, but the manufacturer is obliged to ensure their safety by assessing all substances that may migrate from the final product. In 2016, the European Parliament emphasized the importance of further scientific research on NIAS to enable their risk assessment [56].

At the moment no levels of migration or exposure are set for which compliance with the safety requirements can be demonstrated. Thus, it is the responsibility of the producer of the food packaging and/or the food packer to conduct a risk assessment and define the level below which migration of NIAS does not pose a threat to human health. Hence, self-regulation by industry is currently expected. Practically, a threshold of 10 µg/kg (10 ppb) in food is often recommended by testing laboratories and used by manufacturers. This level has been specified in the Plastics Regulation (EU) No 10/2011 for migration through a functional barrier: Unauthorized, but intentionally added substances may be used in FCM plastics behind a functional barrier provided they do not migrate at levels above 10 µg/kg food; substances that are known to be carcinogenic, mutagenic or toxic for reproduction (CMR)

or have nanomaterial properties may not be used accordingly. The threshold of 10 µg/kg is a pragmatic limit and not based on current toxicological understanding. Generally, it is accepted that only compounds <1000 Da are considered as NIAS, assuming that substances with a higher molecular weight cannot be absorbed in the body ((EU) No 10/2011, preamble paragraph 8). Therefore, compounds >1000 Da are generally not further dealt with during the analysis of NIAS, although scientific evidence exists that these substances are also taken up in the gut [57].

4.2 United States

Any food contact substance (FCS) that is reasonably expected to migrate into food because of its intended use in an FCA must comply with the legal requirements [58, 59]. An FCS is defined 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 is not intended to have any technical effect in such food*" (21 CFR 170.3(e)). This definition does not cover substances that are non-intentionally added, and the term NIAS is not used in a legal context in the US. However, there are several provisions concerning some types of NIAS. For example, the safety assessment of an FCS shall include also "*any substance formed in or on food because of its use*" (21 CFR 170.3(i)). Under 21 CFR 174.5, any FCS "*shall be of a purity suitable for its intended use*" and, also in the case of polymers, the submission of information on the major impurities and side reactions is recommended [60].

4.3 China

Standard GB 4806.1 provides a definition for NIAS that includes impurities in FCMs originating, e.g., from the raw materials, decomposition products, and residual reaction products. Manufacturers of FCMs shall perform a risk assessment and confirm the safety of NIAS, but explicit approvals are not required under GB 4806.1 [61].

5 Approaches to handling the risk of NIAS

Although NIAS are mentioned in the Framework Regulation ((EC) No 1935/2004) and in the Plastics Regulation ((EU) No 10/2011), no clear advice is given by authorities on how their safety should be assessed. In 2015, ILSI Europe published a guidance document on the risk assessment of NIAS to be based on information collection, chemical analysis, hazard identification and characterization, and exposure assessment [31]. Furthermore, different guidance documents have been released by European industry associations summarizing the efforts of FCM manufacturers to assess NIAS [62, 63].

5.1 Identification of NIAS

A basic requirement to facilitate the identification and subsequent risk assessment of NIAS is the transfer of relevant information through the supply chain. Ideally, good communication and assumption of responsibilities help to avoid knowledge gaps and duplication of work [31]. For specific stages of the production chain, NIAS may be rather easily predicted based on previous experience and/or theoretical chemistry. Since NIAS can further react during the following processing steps or be passed on to the final FCA, it is of high importance to consider any relevant information upstream *and* downstream of the supply chain. Detailed knowledge of the starting substances and processes strongly facilitates the analysis of NIAS in the final product, as has been discussed for, e.g., polyester coatings [64]. Additionally, non-predicted NIAS may be partially identified by non-targeted

screening methods [24]. However, the current analytical techniques do not allow the detection and identification of all NIAS that may be present.

5.2 Hazard identification and tools for priority setting

The identification and assessment of a chemical hazard forms the basis for further risk assessment. For NIAS, hazard assessment is strongly influenced by the available level of information about a certain substance (Figure 1B). Hazards can be identified experimentally or estimated using *in silico* tools. The results of such tests may be simple yes/no answers (e.g., for genotoxicity) or a reference concentration (e.g., the tolerable daily intake (TDI)). All approaches focusing on single substances neglect the potential mixture toxicity of a migrate.

Classical approach

According to the classical approach, any NIAS should undergo a toxicological evaluation requiring the same toxicity data as intentionally added substances. Toxicity data of single substances may be collected from existing scientific information and complemented by further *in vivo*, *in vitro*, and/or *in silico* tests. However, this concept is expensive, time consuming, and only applicable for identified NIAS.

In silico tools and read-across

For all NIAS with a known chemical structure, but no toxicological data, *in silico* tools may provide qualitative or quantitative hazard information. For example, structure-activity relationships (SAR) link mechanistic endpoints to certain structures in a molecule, and quantitative structure-activity relationships (QSAR) allow the quantitative prediction of toxicological endpoints. Such data may be combined to reduce the level of uncertainty. Information from read-across may further help to predict toxicological properties based on tested chemical analogues.

Bioassays

To complement the classical approach consisting of detecting, identifying and assessing single NIAS, the overall migrate or extract of an FCM or FCA can be tested by means of *in vitro* bioassays. In recent years, bioassays have been increasingly used to assess the cytotoxicity, genotoxicity, and endocrine disruption potential of migrates or extracts from different FCMs [65-67]. Such tests may help to detect cumulative effects of (uncharacterized) chemical mixtures for toxicological endpoints that are known to be sensitive towards mixture toxicity. Extracts or migrates generating positive responses in bioassays may subsequently be fractionated and re-analyzed to identify the active substance(s).

However, the array of available assays and sample preparation protocols require further optimization and standardization before bioassays can be used routinely [65, 66, 68, 69]. Hereby, special focus should be placed on their sensitivity and specificity, i.e., aiming at low rates of false negatives and positives, respectively.

Assigning thresholds to known and unknown NIAS

The threshold of toxicological concern (TTC) concept assigns human exposure thresholds to substances with unknown toxicity, but known structure (for more information: [70-73]). By applying the TTC decision tree, chemicals are categorized, mainly on the basis of their two-dimensional chemical structure and expected reactivity, into several classes of concern for which maximum intake levels (thresholds) have been defined. In 2011 it was proposed to extend the application of the TTC concept also to unknown substances in food [74]. However, to meet the exclusion criteria of the TTC concept, all high-risk compounds need to be identified, irrespective of their concentrations (e.g., high-potency carcinogens, substances that bioaccumulate, and metals [72]). A detailed protocol has been developed, including analytical methods for structural alerts and the application of bioassays to exclude

genotoxicity [74], and the approach was demonstrated for carton FCM [75]. If the presence of known hazardous substances cannot be ruled out, the TTC concept cannot be applied for unknown NIAS.

5.3 Exposure

Exposure estimation of NIAS is based on migration and consumption data. Migration data may be obtained by migration testing, worst-case calculations, and migration modelling, whereas consumption data can be retrieved from standardized exposure models, e.g., by applying a surface-to-volume ratio of 6 dm^2 per 1 kg of food ((EU) No 10/2011). Alternatively, specific databases may help to estimate exposure based on actual food consumption data, information on packaging composition and usage, and market shares. Often, these tools comprise data for food packaging, but not for other FCMs.

In Europe, the Flavourings, Additives, and food Contact materials Exposure Tool (FACET) has been developed to estimate exposure to chemicals from food. Although NIAS are not included in the database, FACET may be used to correlate NIAS with a known substance, a particular material or process, or one or more different food groups [31, 76]. However, the success of the method strongly depends on the information that is available for the substance of interest, i.e., the exposure to unpredicted unknown NIAS cannot be estimated at all.

5.4 Risk assessment and management

The risk assessment and management of NIAS strongly depends on the information available on their hazard and exposure. A risk assessment strategy for NIAS has been proposed by ILSI Europe and is referred to in the following paragraphs [31]. Depending on the outcome of such a strategy, possible risk management measures include the reduction or substitution of known NIAS or further investigations of unknown NIAS that are of potential concern.

NIAS with structural information

For any fully or partially identified NIAS, concentrations may be quantified or at least approximated. Ideally, migration and consumption data allow the subsequent estimation of exposure (see 5.3). The hazard of a substance may be assessed by applying one or combining several of the above-mentioned strategies (see 5.2). According to traditional risk assessment approaches, the substance is of no concern if exposure is below a hazard-based reference concentration. However, for certain groups of substances (e.g., genotoxins) no thresholds exist. Thus, their presence should be completely avoided or further assessed, e.g. by applying the margin of exposure (MOE) approach [77].

Detected NIAS with unknown structure

The concentrations of detected substances with unknown structures may, even in the absence of appropriate standards, be roughly quantified and serve as basis for exposure estimates. In addition, bioassays could provide valuable data to identify a hazard in a sample containing unidentified NIAS.

The TTC concept could be another option to assign exposure thresholds to unidentified NIAS [74]. However, a rather high level of knowledge is needed to guarantee that the substance does not belong to a TTC exclusion group and is neither a carbamate/organophosphate nor genotoxic. Only then, a threshold of 90 µg/kg person/day may be applied to exclude a risk. Any substance with exposure estimates above this value would be of concern and require further tests.

Undetected NIAS

Substances that are not detectable by current analytical techniques may nevertheless generate a response in *in vitro* bioassays. In such cases, the search for the active molecule(s) may become an analytical challenge [78]. If the active substance cannot be identified or avoided, it may eventually be necessary to use an alternative FCM.

6 Conclusions and future challenges

With increasing complexity of FCMs and FCAs, NIAS will continue to be an important topic in the coming years. Their detection and identification are steadily getting easier due to advances in analytical techniques and growing databases. However, comprehensive analysis of migrates or extracts from most FCAs is still out of reach.

International authorities recognized the importance of a risk assessment for NIAS, but have not provided official guidance so far, making it difficult to enforce and comply with the legal requirements.

Therefore, strategies for the risk assessment of NIAS have been developed and improved by different stakeholders in the past years. Most approaches focus on the risk assessment of single substances by *in vivo*, *in vitro* or *in silico* methods, but *in vitro* testing of the whole migrate or extract is also recommended. Additionally, robust exposure models and sensitive methods to exclude CMR and further chemicals of concern are needed. Regardless of the applied concept for risk assessment, communication within the whole supply chain is essential to facilitate the prediction, identification, and quantification of NIAS.

Abbreviations

ASAP	Atmospheric solids analysis probe
BADGE	Bisphenol A diglycidyl ether
CMR	Carcinogenic, mutagenic and toxic for reproduction
DART	Direct analysis in real-time
DEHM	Di-(2-ethylhexyl) maleate
DESI	Desorption electrospray ionization
FACET	Flavourings, additives, and food contact materials exposure tool
FCA	Food contact article (*term used in EU legislation*)
FCM	Food contact material (*term used in EU legislation*)
FCS	Food contact substance (*term used in US legislation*)
GC	Gas chromatography
HDPE	High-density polyethylene
LAE	Ethyl lauroyl arginate
LAS	N2-Dodecanoyl-L-arginine
LC	Liquid chromatography
MS	Mass spectrometry
MOE	Margin of exposure
NIAS	Non-intentionally added substances
NMR	Nuclear magnetic resonance
PA	Polyamide
PET	Polyethylene terephthalate
POSH	Polyolefin oligomeric saturated hydrocarbons
PP	Polypropylene
PS	Polystyrene
PVC	Polyvinyl chloride
PU	Polyurethane
QSAR	Quantitative structure-activity relationship
SAR	Structure-activity relationship
TDI	Tolerable daily intake
TTC	Threshold of toxicological concern

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