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Food Packaging Forum

Dossier – Non-intentionally added substances (NIAS)

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Birgit Geueke

1 Definition of NIAS

Non-intentionally added substances (NIAS) are chemical compounds that are present in food contact materials (FCMs) and could therefore migrate into food, but they are not added for a technical reason during the production process. Often their presence is not known by the consumer and not even by the producer. The phenomenon of NIAS is not new, but the awareness towards this topic only rose within the last few years due to increasing sensitivity in chemical analysis.

NIAS originate from different sources and include break-down products of food contact materials (FCMs), impurities of starting materials, unwanted side-products and various contaminants from recycling processes (Figure 1). The break-down products can be separated into degradation products from polymers, processing aids and additives. Side-products can originate from the production process and also from chemical reactions between food and its packaging. NIAS can enter the value chain of FCMs at any level, e.g. during the chemical synthesis of raw materials and the production of the final containers and materials. The properties of certain food types can also initiate the formation of NIAS from the respective FCMs, e.g. the hydrolysis of BADGE to BADGE·2H_2O in the food [1]. Generally, it is accepted that only compounds <1000 Da are considered as NIAS, because substances with a higher molecular weight are regarded as inert towards migration (EC 10/2011, preamble paragraph 8). Therefore, compounds >1000 Da are not further identified during the analysis of NIAS.

When investigating the NIAS of a FCM, usually not all compounds of interest can be detected with state-of-the-art analytical techniques (Figure 1). Those chemicals that are detected can be further divided into identified and unknown compounds. The known substances are either approved for food packaging or not. It is in accordance with the current European legislation that also non-authorized substances are present in FCMs when they are non-intentionally added, but the FCM manufacturer is obliged to ensure NIAS safety, according to article 3 of the Framework Regulation EC 1935/2004.

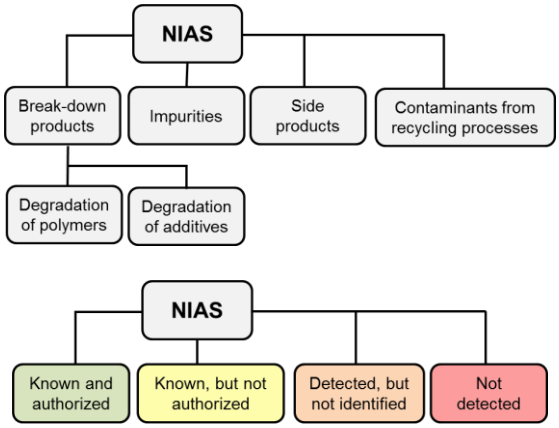

Figure 1. Sources and categories of non-intentionally added substances.

2 Sources of NIAS

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

2.1 Break-down products

FCMs undergo break-down processes. Both the polymers and the additives can be degraded during manufacturing, processing, and storage or in contact with the food itself. Reasons for degradation of FCMs are manifold and include heat treatment, irradiation, and contact with oxygen and/or acid. The break-down products are a major part of NIAS, but it has to be pointed out that NIAS do not include those break-down products that lead to the original monomer (e.g. degradation of polycarbonate to bisphenol A does not result in the formation of NIAS, because bisphenol A is the starting substance). In general, break-down products have a lower molecular weight than their parent compounds leading to higher diffusion coefficients and migration potential. The break-down products often fall into the category of unknown NIAS. A special case of break-down products are antioxidants, because they are even added with the purpose to be oxidized earlier than the material itself.

2.2 Impurities

Raw materials and additives that are used to produce FCMs often contain impurities. Starting substances do not need to reach defined purity levels (e.g. 99%), but the supplier has to guarantee their safety (Framework Regulation EC 1935/2004, Art. 3). The quality of starting materials can vary from batch to batch. Main impurities are generally known by the producer, whereas minor impurities are often unknown [2]. Impurities can persist in the finished FCM. Alternatively, they migrate and/or further react with other substances present in the packaging or the food.

2.3 Side products

FCMs are often produced in several steps and they usually contain additives such as antioxidants, UV protectors, adhesives and dyes. Side-reactions occur during the production of the starting substances, materials and additives. Besides the main chemical reaction pathways, many other reactions and transformations are possible, but difficult to predict. These reactions form a variety of novel products. Additionally, the close contact between the single materials can also lead to the formation of unwanted reaction products, which are often not known.

2.4 Contaminants from recycling processes

FCMs made out of recycled materials are a special source of NIAS, because the contaminants originate from the recycled material, the previously packaged food, and/or misuse of the packaging before recycling [3, 4].

Materials intended for recycling, such as paper and board, PET and polyolefins [5, 6], often contain intrinsic contaminants such as additives, dyes, and degradation products. The mixtures of chemicals that are present during the recycling processes can react and form

new unwanted compounds that add to the list of NIAS. Furthermore, accumulation of chemicals might play a role when materials are recycled several times. The identification and management of NIAS in recycled materials is a particular challenge because of the difficulty in tracing their origin.

3 Comprehensive study on six different plastics

In 2007, Bradley and Coulier systematically investigated the NIAS from six different plastics typically used as FCMs (polypropylene, high density polyethylene, polystyrene, PET, polyvinyl chloride, and polyamide) [2]. In their report the authors give an overview of the chemical composition of the major food contact polymers. They combined a thorough literature search with theoretical predictions and detailed analytical studies. The two involved teams applied thermodesorption GC-MS, GC-MS, GCxGC-TOF-MS, LC-MS, LC-FT-MS, LC-TOF-MS and NMR to analyze the different materials. They showed that GC-MS was the technique that resulted in the highest number of detected compounds. Although the authors proposed identities for newly detected compounds, many of the peaks were not assigned to any structure.

4 Analytical techniques

Advances in analytical methods enable the detection of increasing numbers of NIAS from FCMs. An overview of the current techniques and open questions is given in this paragraph. To identify possible NIAS, the FCM itself or migration into a food simulant (solid or liquid) can be analyzed. The measured concentrations are higher, if the polymer is studied directly, but this technique does not provide additional information about the migration behavior of NIAS. One has to be aware that the sample preparation is crucial for the comprehensive analysis of a FCM. Incomplete transfer of NIAS results in a high number of compounds that cannot be detected and identified (Figure 1, red box). Polymers and solid food simulants can be analyzed by direct thermal desorption techniques, such as atmospheric solids analysis probe (ASAP) MS [7], direct analysis in-real-time (DART) MS [8] and desorption electrospray ionization (DESI) MS [9]. These methods do not include any separation steps, but the extraction steps can be avoided. As a consequence, 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 step that transfers as many compounds as possible into the liquid or gaseous phase. The polymers and solid food simulants such as Tenax can be extracted by solid-liquid extraction and separated by chromatographic steps. Further options for polymer analyses are thermodesorption of very volatile substances followed by 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 the sample, but might result in some loss of material due to incomplete transfer.

In general, the extracts are analyzed by GC, LC and/or NMR. Combination of different methods should be performed 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 [3]. The most powerful detection techniques are all based on mass spectrometry. Different mass analyzers, such as quadrupole, ion trap, time of flight and Orbitrap, 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 to facilitate any non-targeted analysis [3].

Once a mass spectrum or a fragmentation pattern is obtained, it is compared with spectral libraries (e.g. NIST library). For GC measurements, the retention index (Kovats index) further helps to identify a compound. High-resolution MS gives accurate masses that can provide the elemental composition of the unknown substance after GC and LC measurements. Combining all available information (spectra, retention index, elemental composition, isotopic pattern, software tools for structure assignments, database searches, and sample information) helps to assign a structure to many measured compounds.

For risk assessment purposes, the concentrations of NIAS in the migrate should be known. Often analytical standards are missing and the concentrations are determined by comparing the peak areas with a defined internal standard. Depending on the detector used the response signals can differ significantly. In 2012, Koster showed that detectors that are proven for ‘uniform’ responses differ by a factor of 6 [10].

Almost every study investigating NIAS reports non-identified substances (Figure 2, orange box) [11-13] and experts agree that not all substances can be detected by current analytical techniques. The analysis of recycled materials is even more demanding, because even the manufacturer cannot easily assure the safety of the raw material as has been shown for paperboard [14]. Bradley and Coulier demand the cooperation of the chemical and plastics industry to provide more information on the starting substances, impurities, the production processes and possible side-reactions [2].

5 Regulations

5.1 European Union

Article 3 of the EU Framework Regulation EC 1935/2004 states that

> *“1. 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.”*

Consequently, the safety of NIAS has to be assessed. To reach this aim, theoretically all NIAS have to be identified, quantified and toxicologically evaluated. Practically this is not possible, as several studies have shown [2, 11, 12, 14].

In 2011, the European Commission defined NIAS in their regulation on plastics (EC 10/2011) as:

> *“(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.”*

Table 1. Examples of NIAS detected in food contact materials.

Packaging / Material	NIAS: - Name (CAS)	EU: Listed by DG SANCO	FDA: Listed as Indirect Food Additive	Origin of NIAS	References
Polyethylene terephthalate (PET)	- formaldehyde (50-00-0)	yes	no	break-down product	[15, 16]
	- acetaldehyde (75-07-0)	yes	no	break-down product	
	- propanal (123-38-6)	yes	no	break-down product	
	- butanal (123-72-8)	yes	no	break-down product	
	- nonanal (124-19-6)	no	no	break-down product	
	- glyoxal (107-22-2)	no	yes	break-down product	
	- methylglyoxal (78-98-8)	no	no	break-down product	
	- acetone (67-64-1)	yes	no	break-down product	
	- phthalates (131-11-3, 84-66-2, 84-74-2, 84-69-5, 85-68-7, 117-81-7)	yes/no	yes	not clear	
Recycled PET	- PET dimer and trimer	n.c.	n.c.	side / break-down products	[13]
	- AOX-24 (93-46-9), AOX-27 (90-66-4), AOX-26 (96-69-5), HALS-3 (71878-19-8)	no/yes	yes/no	contaminants from recycling processes (antioxidant from PVC)	
	- diethylene glycol dibenzoate (120-55-8)	yes	yes	contaminants from recycling processes (plasticizer from PVC)	
Epoxy-based lacquers	- BADGE·H_2O, BADGE·$2H_2O$	no[1]	no[1]	reaction products of bisphenol A diglycidyl ether (BADGE, 1675-54-3)	[17-21]
	- BADGE·HCl, BADGE·2HCl	no[1]	no[1]		
	- BAMGE·H_2O	no	no		
Epoxidized soy-bean oil (ESBO) (stabilizer of PVC)	- chlorohydrins	n.c.	n.c.	reaction products of HCl released from PVC and ESBO	[22]
Irganox 1010 and Irgafos 168 (antioxidants)	- 2,4-DTB (96-76-4)	no	no	break-down product	[23-25]
	- 2,6-DTBQ (719-22-2)	no	no	break-down product	
	- 2,6-ditertbutyl-4-methoxyphenol (489-01-0)	no	no	break-down product	
	- 3,5-ditertbutyl-4-hydroxybenzoic acid (1421-49-4)	no	no	break-down product	
	- triphenyl phosphate (115-86-6)	no	yes	break-down product	
	- tri-*o*-tolyl phosphate (78-30-8)	no	no	break-down product	
	- diphenyl phosphate (838-85-7)	no	no	break-down product	
	- 3-(3,5-di-tert-butyl-4-hydroxybenzyl) propionic acid (20170-32-5)	no	no	break-down product	

Packaging / Material	NIAS: - Name (CAS)	EU: Listed by DG SANCO	FDA: Listed as Indirect Food Additive	Origin of NIAS	References
Tris(nonylphenyl)phosphite (TNPP) (antioxidant)	- nonylphenol (104-40-5)	no	yes	break-down product	[26-28]
Ethyl lauroyl arginate (LAE) (antimicrobial)	- LAS (42492-22-8)	no	no	LAE impurities	[11]
	- not identified, $C_{16}H_{32}N_4O_3$	n.c.	n.c.	unknown	
	- N-dodecanoyl-L-tyrosine ($C_{21}H_{33}NO_4$)	n.c.	n.c.	unknown	
	- not identified, $C_{19}H_{38}N_4O_3$	n.c.	n.c.	unknown	
Polyurethane (PU) adhesives	- 1,4,7-trioxacyclotridecane-8-13-dione	n.c.	n.c.	reaction product from adipate plasticizer/adipate acid	[12]
PU adhesives	- *m*-phenyolenediamine (108-45-2)	yes	yes	reaction products from residual isocyanates with moisture: primary aromatic amines	[29]
	- 2,6-toluenediamine (823-40-5)	no	no		
	- 2,4-toluenediamine (95-80-7)	no	yes		
	- 4,4-diaminodiphenylether (101-80-4)	no	no		
	- 4,4-methylenedianiline (101-77-9)	no	yes		
	- 2-naphtylamine (91-59-8)	no	no		
	- 4-aminobiphenyl (92-67-1)	no	no		
Azodicarbonamide[2] (blowing agent)	- semicarbazide (57-56-7)	no	no	thermal break-down product	[30]
Di-(2-ethylhexyl) sulfosuccinate (DEHSS) (varnish)	- di-(2-ethylhexyl) maleate (DEHM) (142-16-5)	no	yes	impurity of varnish (DEHM is remaining starting substance)	[31]

n.c. – Presence on the lists could **n**ot be **c**onfirmed due to missing CAS numbers.

[1] The sum of the migration of these substances is regulated in Commission Regulation EC 1895/2005, but they are not listed on the DG SANCO list.

[2] Since 2005, the use of azodicarbonamide as FCM is forbidden in the European Union.

*"(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."*

At the moment, no levels of migration or exposure are set for which compliance with this requirement 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 does not pose a threat to human health. Hence, self-regulation by industry is expected at the moment. Practically, a threshold of 10 μg/kg (10 ppb) in food is often recommended by testing laboratories and used by manufacturers. This level is actually specified in EC 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 CMRs or have nanomaterial properties may not be used accordingly

5.2 United States

In the US, a threshold of regulation for substances used in food-contact articles is defined in the legislation (21 C.F.R § 170.39):

"(a) A substance used in a food-contact article (e.g., food-packaging or food-processing equipment) that migrates, or that may be expected to migrate, into food will be exempted from regulation as a food additive because it becomes a component of food at levels that are below the threshold of regulation if:

(1) The substance has not been shown to be a carcinogen in humans or animals, and there is no reason, based on the chemical structure of the substance, to suspect that the substance is a carcinogen. (…)

(2) The substance presents no other health or safety concerns because:

(i) The use in question has been shown to result in or may be expected to result in dietary concentrations at or below 0.5 parts per billion, corresponding to dietary exposure levels at or below 1.5 micrograms/person/day (based on a diet of 1,500 grams of solid food and 1,500 grams of liquid food per person per day)"

Theoretically, NIAS could be regulated accordingly, but their presence, concentrations and some basic information on the structure and toxicity have to be provided to fulfill these requirements.

6 Risk assessment

Although the European Commission mentioned NIAS in the Framework Regulation EC 1935/2004 and in the plastics regulation EC 10/2011 (see Regulations), no clear advice is given how to handle the complex issue of its risk assessment. Different approaches are discussed among experts. It is also possible to combine the following approaches or to develop a tiered-approach that uses aspects of the different methods. With a combination of bioanalytical and analytical techniques, a detailed understanding of the human exposure to chemicals from FCM would be facilitated.

6.1 The classical approach

Migrates are screened, substances are identified by different analytical procedures and toxicologically tested. The advantage of this approach is its sensitivity and specificity. On the other hand, not all NIAS can be measured and identified with the current analytical techniques and the toxicological evaluation is very complex and expensive. Thus, non-identified substances have to be omitted from risk assessment and the question arises how these compounds shall be assessed.

6.2 Bioassays of the whole migrate

In contrast to the classical approach, bioassays with the whole migrate are quick and cost efficient, but they do not generate any information about specific substances and might even not cover the relevant toxicological endpoints. Nevertheless changes in the composition of a material can occur from batch to batch and are difficult to measure with these techniques. Very careful choice of the bioassays is a prerequisite for successful risk assessment using this approach. Wagner and Oehlmann showed that also the sample preparation has a strong impact on the sensitivity of the test, especially when unknown mixtures of bioactive compounds were tested [32]. As an alternative they suggest studies where sample preparations can be avoided [33].

6.3 Threshold of toxicological concern (TTC) approach, adapted to NIAS

The TTC approach was first developed to establish a generic human exposure threshold value for substances that allows the determination of safe levels of exposure. In 2004, it was applied for substances found in the diet [34]. Some years later, Koster et al. proposed the application of the TTC approach to unknown substances found in food [35]. This pragmatic, step-wise risk assessment is based on the TTC concept and illustrated in Figure 2. The most important aspects, which have to be considered, are listed below:

- As many substances as possible have to be detected by applying several analytical techniques.
- Compounds >1000 Da are not analyzed further, because they usually cannot be absorbed in the body and are regarded as inert.
- Chemicals that can be identified in the sample are classified according to the Cramer rules. They are sorted into three classes and a maximum intake level is applied for each class (class I – 1.8 mg/person/day; class II – 0.54 mg/person/day; class III – 0.09 mg/person/day).
- Substances that lead to exposure of less than 0.09 mg/person/day and belong to Cramer classes I-III are regarded as safe. In this step, the estimate of exposure plays a very important role, because it determines whether or not the TTC is exceeded (Figure 2, steps 4 and 5). By applying this approach, the analytical screening can be increased from 10 μg/kg food to 0.09 mg/person/day.
- Substances that are carcinogenic, mutagenic or reprotoxic (CMR), substances that accumulate (K_{OW}>3, [36]) and proteins are completely excluded from this classification. To be sure to get hold of all high-risk compounds (irrespective of their concentrations), they have to be identified even at low concentrations. In 2011, Koster et al. published a detailed protocol that helps to detect these chemicals and includes analytical methods for structural alerts and bioassays [35]. Especially the correct choice of suitable chromatographic techniques, sample preparation and/or detection methods are considered as very important to (partial) identify the unknown compounds (Figure 2, step 2). In case these approaches do not

rule out the presence of toxic compounds, specific screening methods and targeted analyses have to be performed (Figure 2, step 3).

Although analytics are steadily improving, certain compounds might not be assigned to the proper risk class or even not detected at all. Furthermore, cumulative effects of mixtures are not covered by the TTC approach. A solution could be the combination of the TTC with bioassays to increase the safety of FCMs.

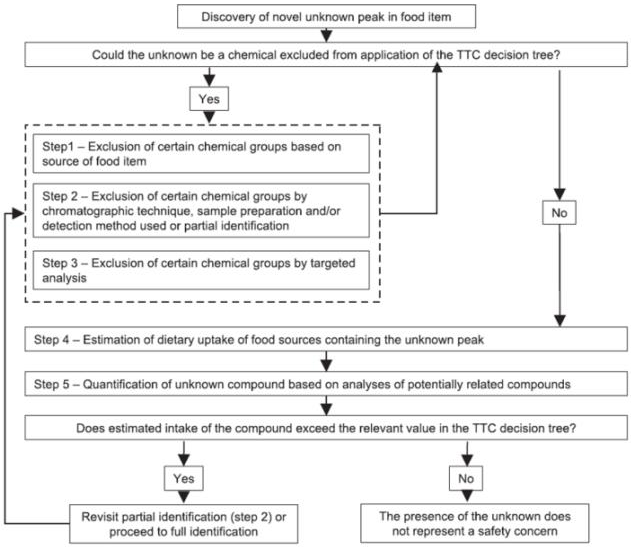

Figure 2. Overview of the approach to the application of the TTC concept to unknown peaks (copied from Koster et al. [35]).

7 Conclusions and future challenges

Due to the increasing complexity of FCMs, NIAS will stay an important topic in the coming years. Their detection and identification will become easier due to advances in analytical techniques and growing databases. European authorities recognized the importance of a proper risk assessment for NIAS, but no guidance exists so far. At the moment it means that industry is expected to assure the safety of their products without having proper guidelines to follow.

The development of suitable guidelines that guarantee the safety of FCMs including their NIAS is intensively discussed at the moment and many open questions have to be answered: Is it necessary to perform the classical approach including full identification and toxicological tests of all detected substances? Should the TTC concept be adopted to evaluate the safety on NIAS? Are bioassays with the migrates necessary to cover possibly hazardous substances that are either not detected at all or lie below the threshold and do not give a structural alert? Should intermediate and/or tiered approaches be developed?

For all concepts, a better information transfer through the whole value chain would largely facilitate the identification of unknown compounds. Proper toxicological assessments have to be defined. It has to be clarified whether the whole migrate or single compounds have to be evaluated. If the whole migrate is analyzed, one has to be aware that the NIAS can strongly vary depending on the chemical synthesis route and starting substances. The TTC approach needs solid and realistic exposure models and sensitive methods to identify CMR and further toxic substances. Last, but not least, a common acceptance by the involved parties is necessary for any new risk assessment approach.

Some challenges will remain that are strongly, but not only linked to NIAS: What about the toxicity of mixtures? Will they increase the toxicity of the FCM? Does bioaccumulation play a role due to the permanent exposure towards FCMs? Can the general thresholds for single substances (i.e. 10 ppb in Europe/0.5 ppb in the US) be considered safe when constant exposure to all population groups occurs below these levels? How can we know if a NIAS is unique or if it could arise from several sources?

Abbreviations

ASAP	Atmospheric Solids Analysis Probe
BADGE	Bisphenol A diglycidyl ether
DART	Direct Analysis in Real-Time
DESI	Desorption Electrospray Ionization
FCM	Food Contact Material
GC	Gas Chromatography
LC	Liquid Chromatography
MS	Mass Spectrometry
NIAS	Non-intentionally Added Substances
NMR	Nuclear Magnetic Resonance Spectroscopy
TTC	Threshold of Toxicological Concern

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