ILSI Europe
Report Series

An Overview of Approaches for Analysing NIAS from different FCMs

REPORT

Commissioned by the Packaging Materials Task Force

ILSI EUROPE

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AN OVERVIEW OF APPROACHES FOR ANALYSING NIAS FROM DIFFERENT FCMs

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1. INTRODUCTION AND SCOPE

1.1 Scope

This overview is designed to supplement the recent ILSI publication 'Guidance in selecting analytical techniques for identification and quantification of non-intentionally added substances (NIAS) in food contact materials' (Nerín et al., 2022) by providing more background information for those not analysing for NIAS (and Intentionally Added Substances, IAS) every day and to assist with interpreting analytical results and is intended to assist those tasked with risk assessment and risk management. Nerin et al., 2023 provide a more detailed explanation of the different analytical techniques along with the strengths and weaknesses of each with regards to NIAS determination. Furthermore, this overview and the Nerin et al paper complement other recent ILSI publications concerning migrants from Food Contact Materials and Articles (FCM&A)s, hereafter abbreviated to FCMs (Koster et al., 2015, Schilter et al., 2019) and exposure assessments 'Guidance for Exposure Assessment of Substances Migrating from Food Packaging Materials' (ILSI Europe 2007). These publications help to form the basis of risk assessment and/or risk management (RA/RM). In conjunction with the paper ILSI Guidance for Exposure Assessment of Substances Migrating From Food Packaging Materials, 2007, the guidelines and overview are intended to supplement the ILSI flow chart describing different aspects that should be followed to perform a full safety assessment (for both IAS and NIAS) of an FCM migrate (Koster et al., 2015), by critiquing the analytical approaches and potentially different results from different methodologies. It is necessary to combine all aspects of these publications by considering how relevant any data generated are and where could there be false results.

Over the past 26 years ILSI has published several of Black and White Monographs dealing with different FCMs and approaches for demonstrating their safe use. These are listed in Table 1. The reader is recommended to consult these for more comprehensive treatment of different FCMs.

Table 1: List of published ILSI Europe Report Series

Name of the Report Series	Year of publishing
Food Consumption and Packaging Usage Factors	1997
Packaging Materials 1: Polyethylene Terephthalate (PET) for Food Packaging Applications	2002
Packaging Materials 2: Polystyrene for Food Packaging Applications	2002
Packaging Materials 3: Polypropylene as a Packaging for Food and Beverages	2002
Packaging Materials 4: Polyethylene for Food Packaging Applications	2003
Packaging Materials 5: Polyvinyl Chloride (PVC) for Food Packaging Applications	2003
Packaging Materials 6: Paper and Board for Food Packaging Applications	2004
Packaging Materials 7: Metal Packaging for Foodstuffs	2007
Guidance for Exposure Assessment of Substances Migrating From Food Packaging Materials	2007
Packaging Materials 8: Printing Inks for Food Packaging Composition and Properties of Printing Inks	2011
Packaging Materials 9: Multilayer Packaging for Food and Beverages	2011
Guidance on Best Practices on the Risk Assessment of Non Intentionally Added Substances (NIAS) in Food Contact Materials and Articles	2015
Packaging Materials 1: Polyethylene Terephthalate (PET) for Food Packaging Applications	2017
Packaging Materials 2: Polystyrene for Food Packaging Applications. Updated version	2017
Packaging Materials 10: Adhesives for Food Packaging Applications	2018

1.2 Introduction

All FCMs shall be produced in accordance with the Framework Regulation (EC) No. 1935/2004 and must be manufacture using the Good Manufacturing Practice Regulation (EU) No. 2023/2006. Art 3 of EC/1935/2004 states, amongst other things, that any substances migrating must not migrate in quantities which would endanger human health.

Both IAS and NIAS might be transferred to food during production, packaging and storage. NIAS are reaction products generated during manufacture and can come from any IAS used in the process, as well as impurities, contaminants and degradation products. The migration of substances from FCMs into food is traditionally studied using validated (often in-house) methodologies for the analytes of interest (European Commission, 2004). However, standardised validated methodologies do not exist for many migrants, especially NIAS. This is further complicated by the fact that there are few standardised and regulated test protocols for migrants/extractants for non-harmonised FCMs. Furthermore, not everyone in the supply chain will be aware of any or all anticipated NIAS. IAS used in the beginning of the supply chain might be unknown to the end-user but should be considered by all operators, as they can also generate or introduce NIAS. All types of materials, including but not restricted to virgin, recycled, biopolymers as well as natural materials, contain and can transfer NIAS. Therefore, this guidance is applicable to any kind of FCM.

All substances including NIAS migrating from FCMs must be risk assessed. There are two classes of FCM – harmonised and non-harmonised. The harmonised FCMs (such as plastics) are covered by material specific EU legislation. For regulated IAS in plastic FCMs, specific migration limits and rules for testing exist. For new IAS it is necessary to use the EFSA note for guidance [EFSA CEF Panel, 2020] and to apply for an opinion from EFSA for harmonised FCMs, such as plastics. For non-harmonised FCMs, a Member State approval protocol may need to be followed in order to demonstrate compliance with Article 3 of the Framework Regulation.

The study of NIAS in FCMs and their migration can be very challenging. Analytical results, or in some cases results using migration modelling, should form the basis for risk assessment (or management), both from the identification and quantification of the migrating species perspective. Nerin et al., 2022 describe various techniques which could be used along with their strengths and weaknesses to the comparison of results

from those different analytical techniques. In analytical terms NIAS analysis presents the most uncertainty as in most cases they are not known until detected and even then, it may not be possible to identify them, whereas with IAS at least the starting material is available for comparative purposes.

In order to undertake or understand a risk assessment or management process, it is imperative that the uncertainties behind any of the analytical techniques are understood. These uncertainties come from various sources, such as:

1. Sampling
2. Preparation of the samples for analysis by using either extractants or food simulants
3. The analytical techniques used
4. The relevance of the results to the intended applications
5. The standards used for identification and quantification
6. The sensitivity of the selected analytical techniques

The Plastics Regulation, i.e., Regulation (EU) No 10/2011 and its amendments (European Commission, 2011), requires that any substance (IAS or NIAS) that migrates from the FCM into food should undergo a safety assessment. For this, one should know which substances migrate and at what level. In order to identify and quantify, or at least semi-quantify using authentic standards of substances with a similar structure, all substances that could migrate, non-targeted screening methodologies have been developed by various scientific groups. These screening methodologies have a common thread that is, they are operated in a non-targeted manner, as it is not possible to predict all substances which will be present. Today, an official validated methodology to determine the presence and level of all migrating substances is not available. Numerous analytical techniques are available for analysing selected migrants from FCMs, and more are being constantly developed.

To reach a harmonised methodology or consistent approach, the following different aspects should be considered:

1. Selection of suitable extraction solvents or food simulants for the material and the substance(s).
2. Exposure of sample(s) to either extractants or food simulants under appropriate time and temperature conditions

3. Analysis of extracts or migration solutions in order to identity and quantity NIAS
4. Reporting of results with relevant information (e.g., confidence limits etc.)

Experience shows that the diversity of test methods used are large, and the outcome of the test method varies in line with the methodology. It is problematic if results from these test methods lead to false alerts because of misidentification or incorrect quantification (e.g., overestimates due to exaggerated test conditions or inappropriate standards for quantification). Conversely, results which do not detect certain migrants or lead to underestimates of amounts present may result in a belief that there are no issues with the FCM. Whereas the opposite may be true. Industry and other stakeholders are facing the problem that different protocols and sample preparations may/can lead to different analytical results. The reasons for these variations must be understood by risk assessors and managers. It is clear that generic screening approaches will not detect all migrating NIAS dependent on their physio-chemical properties. Part of this gap is typically addressed in supporting documentation which should include information on NIAS generated throughout the supply chain. It should be noted that not all NIAS will necessarily migrate. The pros and cons of different analytical techniques and approaches are discussed in Nerin et al., 2022.

This document describes:

- How to deal with NIAS from different (non-harmonized) FCM
- Sample preparation techniques for NIAS
- An overview of analytical techniques used to identify and quantify NIAS summarising the detailed descriptions in Nerin et al., 2022
- Transfer of information relevant to NIAS along the supply chain

2. REGULATIONS, RECOMMENDATIONS AND INDUSTRY GUIDELINES FOR DIFFERENT TYPES OF FCM

The European Commission (DG Santé) categorises FCMs as either harmonised or non-harmonised, depending upon whether there is an EU regulation for that particular type of FCM (harmonised). Those that do not have such regulation are classified as non-harmonised, and National Regulations, where they exist, apply. All FCMs are covered by the Framework Regulation [1935/2004] Annex 1 and the Good Manufacturing Practice Regulation 2023/2006. For harmonised FCMs the test conditions are specified, but they do not necessarily apply for non-harmonised FCMs. Specific regulations and some non-binding recommendations, including those from professional industry associations, for FCMs are given in Table 2 and they demonstrate that the same test rules for plastics cannot be universally applied to all FCMs. Whilst many conditions (time, temperature, simulant) were developed to demonstrate compliance of IAS with limits, they are equally suited for the analysis of NIAS.

Regulation (EU) 10/2011 is a harmonised regulation for plastics. In the absence of specific Regulations, this Regulation is often applied to other types of FCM, however the conditions (times, temperatures and simulants) listed for testing migrants are not always appropriate for testing non-plastic FCMs. Indeed, in a few cases, they are unsuitable for testing some plastics certainly at elevated temperatures and the regulations permit deviation from those specified if it can be demonstrated that they are inappropriate More details regarding migration testing for plastic FCM, can be found in Regulation (EU) 10/2011.

Table 2: List of FCM materials which are covered by specific measures

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
1. Active and intelligent materials and articles	harmonised	450/2009/EC	
2. Adhesives	non-harmonised	Bedarfsgegenständeverordnung (Germany) Warenwet (The Netherlands) Decreto Ministeriale del 21/03/1973 (Italy) Real Decreto 847-2011 on polymeric materials (Spain) BfR Recommendation XXVIII on 'Cross linked polyurethanes as adhesive layers for Food Packaging Materials' See. ANNEX 7 In: Simoneau, C., B. Raffael, S. Garbin, E. Hoekstra, A. Mieth, J. F. Alberto Lopes and V. Reina (2016). Non-harmonised food contact materials in the EU: Regulatory and market situation: BASELINE STUDY: Final report JRC Science for Policy Report EUR 28357 EN / JRC104198, doi 10.2788/234276	• https://www.feica.eu/our-projects/food-contact Updated FEICA guidance for evaluating the food contact status of adhesives containing mineral oil hydrocarbons (MOHs). (2022) • FEICA recommendation to adhesive suppliers and users on the assessment of PAAs in polyurethane adhesives intended to be used in food packaging (2022) • FEICA Guidance Paper 2016 - Migration testing of adhesives intended for food contact materials.pdf • FEICA Guidance Paper 2015 - Guideline for Good Manufacturing Practice of food packaging adhesives.pdf • FEICA Guidance for a food contact status declaration for adhesives.pdf (2022) • https://www.feica.eu/our-projects/food-contact • FEICA Guidance for evaluating the food contact status of adhesives containing mineral oil hydrocarbons (2022) - *Also available in* French, German, Spanish, Italian *and* Dutch. • FEICA Guidance for a food contact status declaration for adhesives (2022) - *Also available in* French, German, Spanish, Italian *and* Dutch. • FEICA recommendation to adhesive suppliers and users on the assessment of PAAs in polyurethane adhesives intended to be used in food packaging (2022) • Study on oligomeric hydrocarbons from hotmelt adhesives used in cardboard packaging (2021)

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
			• FEICA recommendation to substitute GLYMO by the end of 2020 in applications intended for food contact (2019) • FEICA Guidance on migration testing of adhesives intended for food contact material (2016) - *Also available in* French, German, Spanish *and* Italian. • FEICA guidance for Good Manufacturing Practice - GMP (2015) - *Also available in* French, German, Spanish, Italian *and Dutch (on demand)*.
3. Ceramics	harmonised	84/500/CEE	
4. Cork	non-harmonised	Policy statement concerning cork stoppers and other cork materials and articles intended to come into contact with foodstuffs (https://www.edqm.eu/en/d/164352 CoE Version 2 dated 05.09.2007) Decree No 38/2001 Annex 14: Cork - list of materials for treating products - requirements (Consolidated 2009-05-15)(English) Check Republic	
5. Rubbers	non-harmonised	- BfR Recommendation XXI for commodities based on natural and synthetic rubber - CoE ResAp 2004(4) on rubber - 93/11/CEE nitrosamines in elastomers and rubbers Spain RD847/2011	(Simoneau et al., 2016): • ISO 14285:2014 (ISO/TC 45/SC 4) - Rubber and plastics gloves for food services - Limits for extractable substances • EN 12868:1999 (CEN/TC 252) - Child use and care articles - Methods for determining the release of N-Nitrosamines and N-Nitrosatable substances from elastomer or rubber teats and soothers

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		CoE Framework Resolution Res AP (2004)1 on Coatings Intended to Come Into contact with Foodstuffs - Version 3 (2009-02-12)(English) BfR Rec. 30 [XXX.] Conveyor belts from gutta-percha and balata (1984-07-01)(English) BfR Rec. 211 [XXI/1.] Commodities based on natural and synthetic rubber in contact with food (2021-07-01)(English) BfR Rec. 212 [XXI/2.] Special consumer goods made of natural and synthetic rubber and of latices made of natural and synthetic rubber (formerly special category) (2021-07-01)(English)	• EN 12873-4:2006-06 (CEN/TC 164) - Influence of materials on water intended for human consumption - Influence due to migration • EN 15768:2015 (CEN/TC 164) - Influence of materials on water intended for human consumption. GC-MS identification of water leachable organic substances • DIN 11861 (1976) - Drink- and dairy fittings; sealing rings made of elastomeric materials, requirements testing • DIN 5080 (1978) - Preserving Jars And Bottles For Domestic Purposes; Rubber Seal Rings • DIN 7750:1979-01 - Rubber sealing rings for lever stoppers of bottles • PN C-94150:1997 PKN (PL) TC 186 - Rubber Seals For Weck Type Jars
6. Glass	non-harmonised		
7. Ion-exchange resins	non-harmonised	Spain RD847/2011	
8. Metals and alloys	non-harmonised	Resolution CM/Res(2020)9, Metals and alloys used in food contact materials and articles A practical guide for manufacturers and regulators Resolution CM/Res(2013)9 Resolution AP(2004)/1 Resolution AP(92)2	
9. Paper and board	non-harmonised	Guidelines from EDQM: EDQM Freepub	Food Contact Guidelines for the compliance of paper & board materials and articles – the guidelines are developed by the paper & board value chain to support the industry compliance

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		technical guide 'Paper and board used in food contact materials and articles.' This publication consists of two parts: • Part I. Council of Europe Resolution CM/Res (2020) 9 on the safety and quality of materials and articles for contact with food • Part II. Technical guide on paper and board used in food contact materials and articles – a supplementary guide to Resolution CM/Res (2020) 9 that provides additional requirements for food contact paper and board • BfR XXXVI (Paper and board for food contact), • BfR XXXV/1 (ICooking Papers, Hot Filter Papers and Filter Layers) and • BfR XXXVI/2 (Paper and Paperboard for Baking Purposes)	efforts. - https://www.citpa-europe.org/sites/default/files/Food%20Contact%20Guidelines_2019_final.pdf ECMA GMP initiatives. The first GMP version from 2011 is descriptive and provides guidance for the different steps in the carton manufacturing process : https://www.ecma.org/industry-topics/guidelines-and-gmp/ecma-good-manufacturing-practice-for-food-safety/ecma-gmp-1.1.html As it is in between standard in the sector to have a GFSI certification in place, the decision was taken to focus in Version 2 on providing guidance on how to comply with BRCGS and FSSC 22000 : https://www.ecma.org/publications/ecma-gmp-2.1/ FEFCO GMP Standard, updated 2020 - FEFCO GMP standard is developed for the manufacturing of packaging made of corrugated board in order to support companies to fulfil the legal requirements according to EU Regulations 1935/2004/EG for food contact materials and EU Regulation 2023/2006 on good manufacturing practices https://www.fefco.org/technical-information/standards-guidelines

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		English: https://www.bfr.bund.de/en/bfr_recommendations_on_food_contact_materials-308503.html German: https://www.bfr.bund.de/de/bfr_empfehlungen_fuer_materialien_im_lebensmittelkontakt-308425.html Several other national regulations on paper and board (This list is not necessarily exhaustive): 1. France: Fiche MCDA n°4 (V02 – 01/01/2019) „Aptitude au contact alimentaire des matériaux organiques à base de fibres végétales destinés à entrer en contact avec des denrées alimentaires" 2. Italy: ital Decree DM 21_03_1973, Chapter IV "Papers and Cardboard products" 3. Netherlands: Warenwetregeling verpakkingen en gebruiksartikelen, Hoofdstuk II. – Papier en karton 4. Denmark: Ban on PFAS in Paper and board: BEK nr 681 af 25/05/2020 (Gældende) "Bekendtgørelse om	

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		ødevarekontaktmaterialer og om straffebestemmelser for overtrædelse af relaterede EUretsakter“ Chapter 3	
10. Plastics	harmonised	10/2011/EC (EU)2018/2013 on BPA BfR Recommendation III Polyethylene (catalyst(residues), polymer production aids) BfR Recommendation V ‘Polystyrene produced exclusively from styrene’ (polymer production aids) BfR Recommendation VI ‘Polystyrene Copolymers and Graft Polymers’ (polymer production aids) BfR Recommendation VII Polyethylene (catalyst-residues), polymer production aids) BfR Recommendation X Polyamide (catalyst residues and other polymer production aids) BfR Recommendation XVII Polyterephthalic acid diol esters (catalyst, catalyst residues, coatings) BfR Recommendation XXXIX Commodities based on	

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		Polyurethanes (polymer production aids) BfR Recommendation XLVI Cross linked polyethylene PE-X (polymer production aids)	
11. Printing inks	non-harmonised	Switzerland: SR817.023.21 Germany: 21st ordinance amending the consumer goods ordinance	https://www.eupia.org/key-topics/food-contact-materials/migration-testing/
12. Regenerated cellulose	harmonised	2007/42/EC	
13. Silicones	non-harmonised	Résolution ResAP(2004)5 on silicones for FCM (2004) CM/Del/Dec(2004)907/6.1e (adoptée par le Comité des Ministres le 1 décembre 2004, Annexe à la Résolution ResAP(2004)5 Spain RD847/2011 EFSA 2012:EN-139 (ESCO WG) Bundesinstitut für Risikobewertung (BfR standard). June2020. Recommendation XV on Silicone Articles, Bundesinstitut fur Risikobewertung. French Arrêté of 25 November 1992. Silicone elastomers intended to come into contact with foods and beverages. Bundesinstitut für Risikobewertung (BfR). 03/2022. Determination of volatile compounds in silicone consumer products; https://www.bfr.bund.de/cm/343/d	guidelines-on-compliance-testing-for-silicone-elastomers-1.pdf (silicones.eu)

FCM	Harmonised/ non-harmonised	Regulations and recommendations from authorities	Recommendations from industry associations
		etermination-of-volatile-compounds-in-silicone-consumer-products.pdf	
14. Textiles	non-harmonised	Belgium: Arrêté royal Dénominations textiles (2007-04-16)(French)	
15. Varnishes and coatings	non-harmonised	1895/2005/EC (BADGE, NOGE, BFDGE) Dutch Warenwet specifically Chapters I and X (EU)2018/2013 on BPA	https://cepe.org/wp-content/uploads//2020/05/TSC33-NIAS-GUIDELINES-May-2019-v1.7.5-1.pdf https://cepe.org/wp-content/uploads//2020/05/Migration-guidelines-v6.3-Oct-2017-1.pdf For externals see: https://www.eupia.org/key-topics/food-contact-materials/migration-testing/
16. Waxes		BfR Recommendation XXV on 'Hard paraffins, microcrystalline Waxes and mixtures of these with waxes, resins and plastics' Dutch Warenwet specifically Chapter X Coatings. Solvent-free material consisting of waxes and waxy products.	
17. Wood		Dutch Warenwet specifically Chapter IX Wood and Cork	
18. Recycled plastics	harmonised	(EU) 2022/1616	

In addition to the references in Table 2, the manufacturers and/or suppliers of chemicals to be used in FCMs, i.e., a sector Group of Cefic, have published and continue to publish their guidelines on Food Contact Additives (Framework Regulation (EC) 1935/2004, n.d.) which contains recommendations for NIAS. Additional guidelines can be found by BfR (English: https://www.bfr.bund.de/en/bfr_recommendations_on_food_contact_materials-308503.html; German:https://www.bfr.bund.de/de/bfr_empfehlungen_fuer_materialien_im_lebensmittelkontakt-308425.html).

Whilst the number of non-harmonised FCMs is significantly larger than the harmonised FCMs, plastics are a significant proportion of the FCM market. More complex is the situation usually encountered, where the FCM combines two or more different FCMs, e.g., a printed laminated yoghurt pot lid. These are sometimes referred to as multi-layer, multi-materials.

All materials can be a source of migrating substances (both IAS and NIAS). There are many sources for NIAS other than the obvious ones. For example, substances used during manufacture or processing can react to form the final FCM. Other potential NIAS sources originate from the use of aids to polymerisation (AP) and/or polymerisation production aids (PPA).

There are many obvious sources of potential NIAS, many of which can be predicted, but there are many unexpected and frequently unknown NIAS. Clear guidance from the European Commission on the treatment of NIAS for various FCMs would be beneficial for all stakeholders.

3. RECOMMENDATIONS AND INDUSTRY GUIDANCE FOR VARIOUS NON-HARMONISED FCMs

In the absence of harmonised legislation, national rules must be used. A baseline study by (Simoneau et al., 2015) analysed the existing regulatory frameworks at the national or sectorial level to demonstrate compliance with the general safety requirements for materials that are not harmonised at the EU level. The current situation is complicated because different countries use different rules and regulations with countries not covering every FCM on the market (baseline study). The Council of Europe and BfR recommendations attempt to fill gaps but they are not legally binding. General recommendations are given in Resolution CM/Res(2020). Additionally, several industry associations have published guidelines to fill the vacuum (see Table 2).

In addition to the information given in Table 2, some of the non-harmonised FCMs are described further in this section along with the origins of potential NIAS formation.

Biopolymers

The term "Biopolymer" is used for natural polymers produced by the cells of living organisms produced from natural sources, they are not always biodegradable or compostable. e.g., PET or MEG from sugar cane. A more general definition describes biopolymers as materials obtained from renewable sources.

A short overview of bioplastics, which are relevant for FCMs, is given by Niaounakis 2013- "Biopolymers: Reuse, Recycling and Disposal." Elsevier, Amsterdam. Table 3 contains a brief description of different classes of biopolymers.

Table 3: Different Classes of Biopolymers

Polymer type	Polymer characteristics
Starch-based polymers	• Biodegradable polysaccharide • Alternative for polystyrene (PS) • Used in food packaging, disposable tableware and cutlery, coffee machine capsules, bottles
Cellulose-based polymers	• Biodegradable polysaccharide • Low water vapour barrier, poor mechanical properties, bad processability, brittleness (pure cellulosic polymer) • Regulated under 2007/42/EC • Coated, compostable cellulose films • Used in the packaging of bread, fruits, meat, dried products, etc.
Polylactic Acid (PLA)	• Biodegradable, thermoplastic polyester • Possible alternative of low- and high-density polyethylene (LDPE and HDPE), polystyrene (PS), and poly terephthalate (PET) • Transparent, rigid containers, bags, jars, films
Polyhydroxyalkanoates (PHA)	• Biodegradable polyester • Family of many, chemically different polymers • Brittleness, stiffness, thermal instability
Biobased polypropylene (PP) and polyethylene (PE)	• Non-biodegradable vinyl polymer • Mainly based on sugar cane • Identical physicochemical properties
Partially biobased polyethylene terephthalate (PET)	• Alternative to conventional PET • Up to 30% biobased raw materials • Used in bottles
Biobased polyethylene furanoate (PEF)	• Non-biodegradable polyester based on a heteroaromatic 5-ring structure • Better barrier function than PET • Up to 100% biobased raw materials • May be used in the future in bottles, fibres, films
Aliphatic (co)polyesters	• Biodegradable polymers including e.g., polybutylene succinate (PBS), polyethylene succinate (PES), and polyethylene adipate (PEA) • Used in disposable cutlery

Polymer type	Polymer characteristics
Aliphatic-aromatic (co)polyesters	• Biodegradable polymers including e.g., polybutylene adipate terephthalate (PBAT), polybutylene succinate terephthalate (PBST). • Used as fast food disposable packaging, PBAT for plastic films
Polycaprolactone (PCL)	• Biodegradable polyester • Low melting temperature, easily biodegradable • Used in medical applications, as PCL blends in FCMs
Polyvinyl alcohol (PVOH)	• Biodegradable vinyl polymer • Used for coatings, adhesives, and as additive in paper and board production

Those most commonly used in packaging include polyhydroxyalkanoate (PHA), polylactic acid (PLA), polyglycolic acid (PGA), cellulose and starch. It should be noted that PHA and PLA are in the scope of the Plastics Regulation 10/2011. Due to poor mechanical properties (stiffness, heat resistance, low barrier property) and insufficient chemical resistance they are often modified and enforced with fillers.

Starch and PLA are commercially available. Starch is biodegradable but PLA is only compostable under controlled industrial conditions. They are not water and heat resistant and they do not have adequate barrier properties. Polyglycolic acid (PGA) that has excellent barrier characteristics, is used to improve the barrier properties of PLA and starch-based polymers.

The first cellulose-based plastics were developed about 150 years ago. The main modifications are to cellulose acetates, which are still extensively used, but their thermoplastic properties require large amounts of additives. Newer materials are made by modification with fatty acid monomers and they show thermoplastic behaviour without additional substances.

To select the appropriate test conditions required to demonstrate product safety it is important to understand the chemical and physical properties of the different biomaterials. It is not always possible to use the food simulants listed in 10/2011. Some materials react with the food simulant (e.g., hydrolysis, transesterification) or can be

dissolved by the simulant. It is important to demonstrate prior to exposure that there are no reactions (chemical or physical). It is also necessary to consider the influence of test temperatures ranges.

Since the raw materials are obtained from renewable sources the expected NIAS can vary a lot in nature and concentration, even for the same type of material.

There are no specific guidelines or regulations for biopolymers other than those that are within the scope of 10/2011. It might be useful to refer to FSA PROJECT A03070 "Biobased materials used in food contact applications: an assessment of the migration potential", which is publicly available.

Regenerated cellulose film is regulated under regulation Directive 2007/42/EC, which contains a positive list of substances that can be used for its manufacturing.

Cork

Cork stoppers commonly used for wine and champagne do not have specific European Legislation. Major standardisation work has been undertaken to thoroughly revise international standard ISO 633, titled *Cork — Vocabulary*, the latest version of which was published in 2019 in a bilingual French/English version. Cellules d'evaluation De L'aptitude Au Contact Alimentaire Des Produits Constitutifs Et Fournitures De Bouchage Pour L'emballage Primaire Des Champagnes. (CESPROP-CECA (France)) has established the requirements for cork stoppers.

Nowadays, cork stoppers are made from natural whole cork and from complex cork, in which natural cork either as thin layers or agglomerated or micro-agglomerated particles are mixed with adhesives. The combination of these agglomerations, with natural cork discs constitute many cork stoppers.

Most of the potential migrants are from the adhesives used to build these cork stoppers. Thus, primary aromatic amines, isocyanates, solvents and other substances as well as other NIAS need to be analysed. Specific migration analysis must be carried out in such a way that represents actual liquid contact.

As most of the complex cork stoppers built with adhesives need to be cured, it is extremely important to be sure that the curing process is fully complete and residual components from adhesives are not present. Thickness of adhesive used and

thickness of natural cork layers or micro agglomerates are also important parameters to take into account before carrying out the migration testing, when the cork stoppers for the test are constructed in the laboratory. It is recommended that migration tests are carried out on industrially produced cork stoppers.

The recommended simulants are 3% acetic acid and 20% ethanol

For global migration the experimental conditions should be 10 days at 40ºC and for specific migration 10 days at 60ºC according to the Plastics Regulation. .

Place the cork stopper in a 0.375L bottle containing the simulant. This bottle represents the worst-case scenario, due to its small size. The cork stopper should be placed as in the real situation.

Rubber and Elastomers

Many different definitions of rubbers and elastomers exist across the different European Member States. A definitive overview is given in the JRC baseline study (Simoneau et al., 2016).. Thermoplastic elastomers fall under the definition of plastics in Regulation 10/2011.

The flexibility of rubber makes it suitable for specific applications such as conveyor belts, gloves, teats, seals, hosing products, meat netting, gaskets, dairy equipment, tubing and synthetic corks. Rubbers may be of natural or synthetic origin. An overview of the manufacturing process for rubber is given in Figure 1.

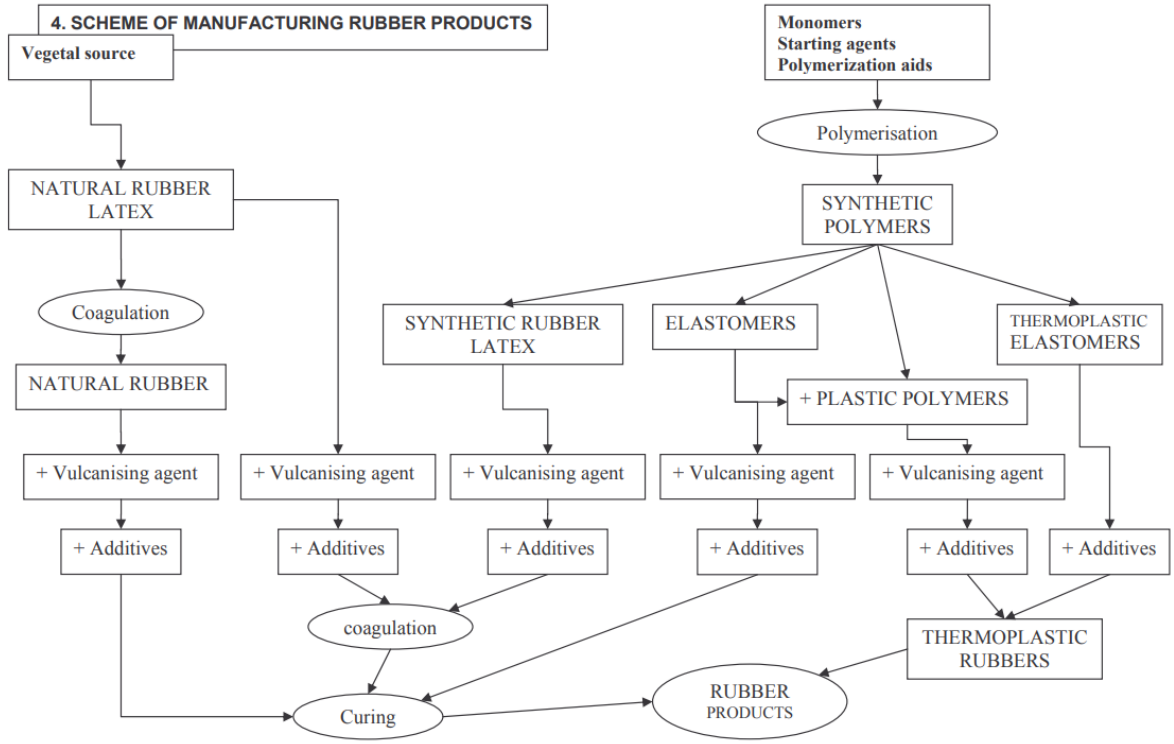

Figure 1: Overview of the manufacturing process for rubber products (ReSAP(2004)4)

Only limited studies have investigated the presence of NIAS from rubber FCM. Recently, Kühne et al., 2021 used extraction (with tetrahydrofuran (THF) for migration experiments, followed by GCxGC-FID-MS and ICP-MS, to identify the substances (Kühne et al., 2021). The presence of the following substances was reported in the THF extract: diethylhexyl phthalate (DEHP), 1,2-cyclohexane dicarboxylic acid diisononyl ester (DiNCH), benzothiazole, diethylhexyl adipate (DEHA), Diethylhexyl terephthalate (DEHT) and fatty acids. Afterwards, the migration solutions (10% EtOH and 50% EtOH) were also analysed, and it was seen that there were still a substantial number of substances present. Furthermore, it was found that lead and other heavy metals can be released from elastomers. Forrest et al., 2006 also studied the migration of low molecular weight compounds from elastomers by extracting the elastomers with acetone, followed by GCxGC ToF-MS analysis. Another study was conducted by (Bouma et al., 2003) who identified extractable amounts of alkanes, alkenes, antioxidants, plasticisers and sterols in rubber netting used to package meat. Finally, different studies have reported the presence of volatile compounds (Curran et al., 2016; Linssen et al., 1998).

No material-specific EU legislation exists for rubber in contact with food. However, there is a specific regulation concerning the release of N-nitrosamines and N-

nitrosatable substances from elastomers or rubber teats (EU Commission Directive 93/11/EEC). No other specific regulation is available for rubber at the EU level. Therefore, for rubbers national legislation or recommendations must apply. The Council of Europe has developed a Resolution on rubber products intended to come into contact with foodstuffs (ReSAP(2004)4). Here, the compliance testing is explained, and different categories can be distinguished based on the expected migration and destination of use. For the execution of the migration tests, the test conditions (time and temperature) presented in the guidelines on testing conditions for kitchenware from the EURL-FCM should be applied (Beldi et al., 2021). However, in these guidelines, the prescribed conditions are based on the test conditions for plastic materials, and it is also stated that, if for any reason, the indicated food simulants are not appropriate, testing with food should be considered. The results obtained in food always prevail over those obtained in food simulants. Finally, different standards are available for specific applications of rubber and/or specific substance limitations in solvents and temperatures and for Surface/Volume ratio considerations. Since rubber products are rarely used as food packaging but mainly for applications such as conveyor belts, tubing, gaskets, etc., the type of contact with food is dynamic and short-term and the surface-to-volume ratio is so low that expected migration should be very low or even negligible. Therefore, an alternative approach is often used where the rubber FCMs are categorised based on relative contact area, contact temperature, contact time and recurrent use, which is translated in the factor 'R_{Total}' (ReSAP(2004)4):

- Category 1: feeding teats and rubber products for contact with food.
- Category 2: Products with an R_{Total} higher than 0.001, meaning that they have conditions of contact with food which may cause significant migration.
- Category 3: Products with an R_{Total} less than 0.001, meaning products with minimal contact with food and hence low migration is expected.

The selection of the migration conditions is based on the conditions described in Regulation (EU) No. 10/2011 for plastics. However, these conditions are not always suitable. For example, some simulants might lead to excessive swelling, and consequently, the migration will be overestimated. Recently, Kühne et al., 2021 studied the swelling of several elastomers when in contact with the following simulants: rapeseed oil, 50% EtOH, 10% EtOH, 3% acetic acid and water. They concluded that

food simulants have the potential to alter the morphology or even disintegrate elastomers. In conclusion it is critical to select a suitable simulant.

Silicones

Silicones do not have a harmonised legislation at EU level. However, there are some guidelines published by the Joint Research Centre (JRC-EU reference lab) concerning the migration of silicone kitchenware articles and resolution ResAP (2004)5, v1. (2004) and EFSA 2012:EN-139 (ESCO WG) provide some recommendations. Spain has a National regulation RD847/2011 which lists the starting substances to produce silicones and their OM and SML limits. The German Federal Institute for Risk Assessment (BfR) recommendation XV lists starting substances, additives, crosslinking agents, catalysts, catalyst inhibitors for silicone oils, elastomers and resins. Furthermore, it lays down limits amongst others for volatile organic compounds (VOC),

Silicone elastomers are manufactured from siloxane pre-polymers with some functional groups such as vinyl-, hydrogen- or hydroxyl- which are crosslinked in the presence of low levels of catalysts. As a result, silicone elastomers are three-dimensional chemically cross-linked polydimethylsiloxanes. The finished chemically cross-linked product cannot be dissolved in organic solvents, but typically swells to a certain extent.

The most important criteria for the determination of compliance of silicone elastomers for food contact with current legislation is a limit of volatile substances of 0.5% and is mandatory according to Recommendation XV of the BfR and French Arreté of 25 Nov 1992 on silicone elastomers

The first analysis should be to confirm that the release of total volatile substances is below 0.5%. For this purpose, the specimens should be dried over anhydrous CaCl2 or silica gel with a moisture indicator in a desiccator for 48 h at room temperature. Once dried, the specimen is heated at 200°C for 4 hours (BfR standard, 2022). The weight difference between before and after heating will confirm if it passes the test.

Migration assays should be applied using different replicates from those heated as described above. The specimens should be dried over CaCl2 in a desiccator for 48 h at room temperature.

Tenax (polyphenylene oxide) is recommended to simulate high temperature applications. Kitchenware articles may be tested with simulants A (10% ethanol) and B (3% acetic acid).

Baking moulds to be used at temperature above 175ºC can be tested either 4 h at 100ºC under reflux or 1 hour at 200ºC using Tenax as simulant.

D2 simulant (vegetable oil) or ethanol 95% are not appropriate simulants in this case, as they interact with silicone, overestimating the migration values.

The same protocols of analysis of volatile and non-volatile NIAS applied to any plastic can be used for silicones. Special attention should be paid to the siloxane oligomers. A specific method using NMR was developed by Helling et al. for analysis in foods (Helling et al., 2010, 2012). Method for extraction of oligomers in silicones and foods with subsequent analysis by GC-MS can be found in Fromme et al., (2019) and Zhang et al., (2012).

Rigid Coated Metal Packaging

Rigid light metal packaging is used for food and beverages. In most cases, but not all, the metal in contact with the foodstuffs is coated. The coatings must comply with the Framework Directive ((EC) No. 1935/2004). In some cases, only part of a can (e.g., a can end) is coated. Metal closures for jars and bottles are within the scope of EU Regulation 10/2011. Can coatings are not covered by harmonised legislation, and National Legislation and/or the Council of Europe Resolution (AP(2004)1) are used. The most comprehensive national legislation is that from the Netherlands (Commodities Act Regulation on packaging and consumer articles coming into contact with foodstuffs (Commodities Act (Packagings and Consumer Articles) Regulation [Warenwetregeling verpakkingen en gebruiksartikelen]) often referred to as the Warenwet. Chapter X deals with coatings and contains lists of substances, which can be used. This is in addition to those substances listed in Regulation (EU) 10/2011 where there are no restrictions on use other than limits for migration or quantities present. For uncoated metal, the rules for metals and alloys (see Table 2) should be followed. Industry has published guidelines where issues have been found and solutions are proposed (TSC34 migration testing guidelines for rigid metal packaging coated with organic coatings intended for direct food contact version 6.3

10th October 2017). Whilst the industry guidelines primarily concern specific migration, they are equally applicable for determination of NIAS.

Can coatings contain thermoset resins and are cured around 200+ºC for minutes. The coatings form a thin layer on the metal substrate typically 3-20 µm. In contrast to plastics, organic coatings do not form a self-supporting film. Cans and closures for foodstuffs have a wide range of surface area to volume ratios ranging from about 4 (e.g., large beverage cans) to 20 (e.g., for small fish cans). It is common practice to quote levels of migration as µg/6dm² or µg/dm² which the end user can use to calculate the relative concentration.

In many cases, food simulants in 10/2011 are suitable for testing coated metal. 3% acetic acid is unsuitable for testing sheets of coated steel for overall migration as it causes rusting resulting in the gravimetric determination including rust and not organic matter. In reality, cans do not undergo excessive overall migration, because of the absence of air and in some cases the buffering effect of some foodstuffs. Aluminium cans can also be corroded by 3% acetic acid and this is unsuitable as a simulant for aluminium cans as well (CEN TC 194 and Oldring, 2016). Overall migration of organic constituents can be demonstrated by testing in 10% (or 20%) and 95% ethanol (and/or isooctane). The conditions for overall migration testing, except 3% acetic acid, are also suitable for testing for NIAS. 3% acetic acid can be used for specific migration as long as the substances being measured are unaffected by the presence of rust or corrosion.

The recommendation for some beverages, such as dairy and cloudy fruit (fruit juice pulps) when processed under sterilisation conditions, is to use simulant D2. However, some organic coatings, particularly polyesters, can undergo swelling and possibly delamination from the substrate. Determination of migrants in the beverages clearly shows an over-estimate of the actual concentrations in many cases. Industry guidelines propose the use of simulant A and simulant D2 to cover the characteristics of aqueous and fatty foodstuffs.

The temperature and time conditions chosen for migration testing need to take account of the limitations of the testing equipment used. Although industrial food cans may exceptionally be sterilised at temperatures up to 135°C, laboratory retorts are not generally able to operate reliably at 135°C. Therefore, instead of carrying out

sterilisation of 30 mins at 135°C, using the Arrhenius equation sterilisation could be carried out for example for 40 mins at 130°C or 70 mins at 121°C.

Due to the low film thickness and chemistry of the organic coatings, the bulk of the overall migration occurs during the sterilisation stage of 1 hour at 121°C or 30 minutes at 130°C. In some cases, if it can be demonstrated that there is no migration after the sterilisation stage, the 10 days storage period testing is not required. An alternative method is to extract the coating and use 100 % transfer assumption.

If the actual conditions of use of the metal packaging are known, these conditions can be used instead of those specified in legislation or guidelines. For an overview of metal packaging for food contact consult the ILSI monograph (Oldring & Nehring Packaging Materials 7: Metal Packaging for Foodstuffs). Marin-Kuan et al., 2023 published a review of an interesting approach of combining both chemical and biological testing to coated metal sheets. Results from different laboratories were compared. Not surprisingly some of the results differed. This is an interesting approach combining chemical and biological analysis.

Printing Inks

Printed food packaging is used to provide information to the final consumer and plays an important role in the presentation and advertising of foodstuffs. Some of this information such as weight, vendor details, information about composition, presence of allergens and nutritional details, etc is legally required. In addition, printing is carried out for decorative and protective purposes. There are exceptional instances where printing inks are applied to the inner side of the packaging or on inserts, e.g., for promotional purposes, and have intentional direct food contact. Direct food contact inks represent a special case and comprise less than 1% of food packaging applications. Such inks are subject to specific requirements and these will not be treated in this report. This report deals with printing inks applied on the non-food contact surface of food packaging (packaging inks) as outlined in the information leaflet of the European Printing Ink Association (EuPIA, 2009b) - B&W book, Printing inks, ILSI 2011).

In terms of Regulation, positive lists are found in only in a few member states, namely France, Netherlands and Solvenia. Additionally, an older Council of Europe Resolution is also used (Resolution ResAP(2005)2).

The most prominent printing ink Regulation in Europe, even worldwide, can be found in Switzerland (SR 821.023.21) - published first time in 2010. This list covers nearly 5500 substance entries divided into two lists: Currently, List A contains substances with a SML based on available risk assessments and represents ~25% of the entries. The majority of the entries (~75%, Part B) are generically listed with a SML of 0.01 mg/kg as there are no official risk assessments.

The most recent update for printing inks has been published by Germany and comes into force no later than 2026 and will take several years to transition. The list covers only assessed entries which is a minor modification of the Swiss list. For all non-listed substances, the German authorities expect many new applications for listing within the transition period. All substances that have not been assessed must not migrate above 0.01 mg/kg with exception of CMR substances which must not be used. In terms of NIAS it is currently not clear if the non-migration principle should be applied or if the ink industry is able to publish self-derived limits in line with what is currently done.

In all publications to date no clear migration test conditions are defined as the ink is not used in direct food contact. Generally, migration conditions focus on the printed substrate, i.e., plastic and/or paper & board – see also multi-materials.

Multi-materials

In many cases, it is not possible to meet all the packaging design requirements using a single monolayer material. The whole rationale for the use of multilayers is to create a single packing structure that will combine the properties of different base materials in order to meet design requirements. (B&W book, ILSI, Multilayer Packaging 2011).

For migration and especially for NIAS, no clear and unique testing requirements exist with the exception of the functional barrier concept laid down in Regulation 10/2011. Typically, the direct food contact layer is characterised. Provided there is a functional barrier, substances other than those listed in the Union list may be intentionally used behind this barrier, if they do not migrate above 0.01 mg/kg. CMR substances should not be present and substances in nano form may not be used without a positive EFSA or Member State opinion. This rule may also be applied to NIAS. Substances for which genotoxicity cannot be excluded, need a specific evaluation. The multi-materials concept is slightly in contrast to the assessment of individual layers represented by the

Plastic Regulation, but drives the discussion as to what should be finally assessed: layers or final articles. In terms of food safety, the final article surface being in contact with food is relevant. For the NIAS testing however, the final article is a more complex topic and needs very good communication within the value chain.

Currently no clear migration test conditions are defined. Consequently, migration conditions focus on the direct food contact layer, i.e., typically plastic.

Adhesives

According to IUPAC, adhesion is the "process of attachment of a substance to the surface of another substance". According to the Union Guidelines on Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food, adhesion "is the force of attraction between molecules in different layers".

There are different types of adhesion: adhesion by covalent bonding (in this case both layers are chemically modified) and adhesion by physical bonding (no chemical modification of either layer). A basic requirement for good mechanical adhesion is good wetting of the substrate by the adhesive.

Adhesive formulations are often very complex and contain numerous single components. Multiple parameters influence the migration of adhesive compounds through a packaging material into food. These are, apart from the concentration of the compound in the adhesive layer, type of adhesive, raw materials of the polymer, additives used in the formulation, substrates and their barrier properties, application of the adhesive, end uses of the adhesive in the packaging and the packaging itself, the type of food to be packed and its filling and storage conditions. Testing should be carried out on the cured adhesive.

The migration testing conditions for plastics are not always appropriate for use with adhesives. A specific FEICA guidance paper (see Table 2) on migration testing of adhesives intended for food contact materials explains points to consider when testing adhesives for migration. An alternative option to demonstrate compliance is the use of a worst-case calculation or migration modelling using scientifically sound, recognise methods.

Due to the lack of legislation, test conditions applicable only for plastics are often taken as guidance to test adhesives. In this case, the procedure is prone to error

because material specific properties and the way adhesives are used are different compared to plastics. Amongst others, these differences include:

1. Adhesives are mostly applied in small quantities and at defined locations within the packaging material
2. Adhesives intentionally contain low molecular weight fractions that would be dissolved when applying liquid food simulants directly to the adhesives
3. Adhesives intentionally contain fractions with low softening points that would soften when being treated at elevated migration test temperatures e.g., 60°C

For further advice on the migration testing of adhesives, reference is made to an available testing guideline from, the Association of the European Adhesive and Sealant Industry (FEICA).

Paper and board

In principle there are 4 general standards for 'migration' procedures for paper and board.
However, these standard procedures leave many open issues:

- Some extraction procedures are used, although they are not in every case suitable to determine the total residual content. This causes a lot of confusion, however, the procedures can be used for 'screening purposes'
- There is no food category specific assignment for a paper 'extraction'/migration procedure.
- Paper and board procedures overestimate migration even more than procedures for plastics
- Surface to volume ratio is not clearly defined
- In some cases, the LOQs are higher than the values required nowadays

Attempts to use Biotests for the evaluation of paper and board have encountered issues particularly surrounding migration and clean-up along with required sensitivity for potentially genotoxic substances. Biosafe (Bradley et al., 2008, 2010; Honkalampi-Hämäläinen et al., 2010) was an EU funded project specifically designed for bio-testing paper and board. Kourkopoulos et al., 2022 have reviewed sample preparation and bio-testing between laboratories. "The review showed a wide variability of protocols, approaches, and conditions used in scientific studies, which

are difficult to compare. Challenges on sample preparation procedures are presented involving the interlinked steps of sample preparation, conditions used and their impact in chemical analysis and in vitro bioassay testing". Tables 4 and 5 give reference standards for paper and board in contact with food.

Table 4: General Migration standards for Paper and Board in contact with food

Standard	Title	Extraction/Migration	Food
EN 645 (1994) EN 647 (1994)	Cold Water Extract Hot Water Extract	10 g of cut paper are suspended in 200 mL of water at 23 °C and incubated for 24 h under gentle shaking 10 g of cut paper are suspended in 200 mL of boiling water at 23 °C and incubated for 2 h in a water bath at 80 °C under gentle shaking	Aqueous food in direct contact at RT
EN 14338 (2004)	Migration using modified MPPO as simulant	MPPO, 60 – 80 mesh 1 dm2 paper in a petri dish (ID > 11,5 mm) in direct contact with 4 g MPPO, t/T should match the foreseeable usage conditions of the paper extraction of MPPO with 2x 20 mL solvent (e.g., acetone)	Dry, non-greasy food, hot contact (baking paper)
EN 15519 (2008)	Organic solvent extract	10 g of cut paper are suspended in 200 mL of solvent (**isooctane, 95% EtOH**) and incubated for 2 h at 20 °C or 24 h at 20 °C (long term storage); for hot contact choose 2h at 60 °C.	Direct contact to greasy food

Table 5: Standards for Specific Leachables and / or Extractables from Paper and Board

Standard	Title	Target	Screening	Residual Content	Migration	Extraction/ Migration	Analytical procedure	X
DIN 54603 (2008)	Determination of Glyoxal Content	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	Photometry Reaction with 2-hydrazono-2,3-dihydro-3-methyl-benzothiazol	
DIN 54604 (1988)	Determination of Starch Content	X		X		8M HCl / DMSO digestion	enzymatic analysis of glucose, photometric determination	
CEN/TS 17497 (2020)	Determination of Bisphenol A	X		X		Extraction 24h at 23°C in acetonitrile	HPLC-FID, LOQ 0,05 mg/kg paper	
CEN/TS 17630 (2021)	Determination of Anthrachinon	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract' DIN EN 14338 Simulant MPPO (dry food, not fatty) DIN EN 15519 ‚organic extract' 95% EtOH, 2h at 60°C	Aqueous ‚extracts' are extracted with toluene, MPPO is extracted with acetone GC-MS LOQ 0,05 mg/kg paper	
EN 920 (2000)	Dry matter content in an aqueous extract		X		X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	after filtration drying at 105 °C, gravimetric determination of residue LOQ: 1000 mg/kg paper / 1 mg/dm2 (paperweight: 100 g/m2)	For paper and board used for filtration or cooking
DIN 52924-2 (1999)	Determination of soluble extractable substances		X	X		Min. 3 g cut paper, 6h soxhlet extraction with petrol ether, bringing to dryness	saponification with ethanolic KOH, washing with water, gravimetric determination of unsaponificable	Determnation of parafflin/wax in paper & board

Standard	Title	Target	Screening	Residual Content	Migration	Extraction/ Migration	Analytical procedure	X
								unsaponificable matter)
EN 646 (2018)	Determination of color fastness		X		X	Glasfiber paper serves as ‚mostly inert' substrate to be soaked with simulants: 1. Water, 2. 3% acetic acid, 3. Alkali solution; 4. Vegetable oil longtime contact: 24 h at 23 °C midtime contact: 4 h at 23 °C short contact: 10 min at 23 °C hot contact: 30 min at 90 °C (aqueous), 30 min at 120 °C (fatty)	The color transfer to the glasfiber paper is evaluated using a grey scale	
EN 648 (2018)	Determination of fastness of fluorescent agents		X		X	See EN 646	The transfer of fluorescent agents to the simulnat soaked glasfiber papers is evaluated using a fluorescent calibration scale	
EN 1541 (2001)	Determintion of formaldehyde in an aqueous extract	X			(X)	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	Photometry Reaction with acetylacetone LOQ: 1 mg/kg paper / 0,001 mg/dm2 (paperweight: 100 g/m2)	

Standard	Title	Target	Screening	Residual Content	Migration	Extraction/ Migration	Analytical procedure	X
EN 14719 (2005)	Determination of Diisopropylnaphthalin	X		X		2 g cut paper is extracted with 25 mL acetone for 16 h at RT followed by 15 min ultrasonic treatment	GC-MS LOQ: 0,6 mg/kg paper / 0,0006 mg/dm2 (paperweight: 100 g/m2)	
EN 14453 (2005) (EN ISO 18856)	Determination of Phthalates (Diisobutylphthalate (DiBP, Dibutylphthalate (DBP), Di-(2-ethylhexyl)phthalate (DEHP)	X		X	X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract' DIN EN 14338 Simulant MPPO (dry food, not fatty) DIN EN 15519 ‚organic extract' iso-octan (or other organic solvents), 2h at 60°C	– Aqueous migrates: according EN ISO 18856: + enrichment on SPE RP-18 + elution with EtOAc – Organic extracts are evt. concentrated – MPPO is extracted with ethylacetate – Analysis: GC-MS	
EN 17163 (2019)	Determination of primary aromatic amines (PAA)	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	Analysis of the aqueous migrates using HPLC-MS LOQ: 0,001 – 0,02 mg/L	22 PAA according to 2002/61/EG
EN ISO 14453 (2014)	Determination of acetone soluble substances (in pulp)	(X)	X	X		Soxhlet or soxtec extraction of 10 g sample for at least 4 h (at least 4 draining/h) with acetone	– Evaporation of acetone – Drying at 105 °C – Gravimetric determination – LOQ: 0,05 %	Aceton soluble substances are a measure for 'wood extractives: fatty acids, resin acids, sterols, sterolester, fatty alcohols, di- and triacylglycerols, waxes, lignans

Standard	Title	Target	Screening	Residual Content	Migration	Extraction/ Migration	Analytical procedure	X
EN ISO 15318 (1999)	Determination of 7 specified PCB	X		X		2 g paper are extracted with 50 mL ethanolic KOH solution (2 % m/v) under reflux for 60 min, dilution with water	– clean-up with RP18-SPE, elution with n-hexane – GC-ECD	
EN ISO 15320 (2011)	Determination of pentachlorophenol in aqueous extracts	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	– Acidified aqueous extract is purified via Phenyl-SPE – Elution using n-hexane – Derivatisation using acetic anhydride – Determination via GC-MS or -EC – LOQ: 0,05 mg/kg	
EN 13676 (2001)	Polymer coated paper and board intended for food contact – Detection of pinholes						– Sample is cut into 12cm * 12 cm pieces and clambed into a migration cell – Ethanolic dye solution is poured onto the coated surface and incubated for 5 min – Dye solution is decanted and wiped off – Pinholes are identified	Detection of pinholes or breaks in polymer coated paper and board
EN 12497 (2005)	Determination of mercury in an aqueous extract	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	– 'extracts' are acidified with HNO_3 – addition of $K_2Cr_2O_7$ and hydroxylammonium chloride – Addition of Sn(II)Cl	

Standard	Title	Target	Screening	Residual Content	Migration	Extraction/ Migration	Analytical procedure	X
							– LOQ: 0,06 mg/kg	
EN 12498 (2018)	Determination of cadmium, chromium and lead in an aqueous extract	X			X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	– 'extracts' are acidified with HNO_3 – – LOQ: 0,1 mg Cd/kg 0,6 mg Pb/kg 0,25 mg Cr/kg	
EN 16418 (2014)	Determination of the cytotoxicity of aqueous extracts using a metabolically competent hepatoma cell line (HepG2)		X		X	DIN EN 645 Cold Water ‚Extract' DIN EN 647 Hot Water ‚Extract'	– HepG2-cells are incubated in water samples for 19 h – The uptake rate of a radioactive tracer (5,6-^{3}H-uridin the RNA of HepG2 cells.	

4. SAMPLING

Testing, and therefore sampling, is carried out by many stakeholders: enforcement authorities, import controls, business operators and third-party laboratories. When sampling and preparing the samples, precautions should be taken to ensure the safety of the persons taking the samples and to avoid any changes to the samples, which could affect:

- chemical composition of the material or article (residual content of a migrant, polymer structure)
- physical constitution, e.g., density
- the representativeness of the sample, e.g., contamination which is a major concern where NIAS are concerned. Importantly the source of NIAS should originate from the constituents of the FCM and not from extraneous sampling contaminants

Sampling can be performed at any point in the lifetime of the FCM or its component parts, as an FCM may contain several different materials in its structure, it is important to document the date, since content and nature of NIAS might be affected by the time of sampling. As an example of an FCM containing numerous constituent FCM consider kitchenware. It is very common to find kitchenware tools where metal, wood, ceramic, polymers, silicones, adhesives and printing inks are often part of the final objects. These objects also require migration tests and determination of NIAS. In these particular cases, the final form (shape) of utensils should be considered, as defined in Regulation 284/2011/EU.

EU and Member States have regulations on sampling which should be strictly followed. Sampling should be performed by an authorised and/or trained operator. Sampling for verification of compliance in the context of official controls should follow Regulation (EC) No 882/2004 (European Commission, 2004) on official controls on feed and food.

A detailed record should be kept of each sample taken. As a minimum, the following details should be recorded for each sample:

- Sample identification: detailed description of sample (e.g., material type(s))
- Date and time of sampling
- Place of sampling (i.e., full address of facility/retail outlet from which the sample was taken)
- Source of sample (e.g., detailed description of the stage in the production batch, location in the stack of a given material or article or location within a reel of film from which the sample was taken; a photographic record could be helpful)
- Type of sample (e.g., material, article, starting substance, product from an intermediate stage of the manufacturing process, food)
- Labelling information according to Regulation (EC) No 1935/2004
- Number of samples taken
- Amount and/or size of each sample
- Sample storage conditions from production up to and including the point of sampling (indicate whether or not lag-time or set-off could have occurred)
- Sample expiry date
- Reason for sampling
- Name and signature of the responsible person and sampler

Selection of representative samples

Substances in materials and articles can be heterogeneously distributed and care must be taken to ensure representative quantities and number of test samples. It is recommended to have a minimum of 3 replicates of each sample.

To the extent that FCMs are produced in accordance with the requirements on GMP laid down in Regulation (EC) 2023/2006 (European Commission, 2006) and have consistency in their properties and composition, any sample taken should be representative of any batch of that product, irrespective of the number of production runs. A change in product composition or its manufacturing parameters should give cause to re-examine migration behaviour. Testing needs to be justified and is dependent on material properties and production parameters. Re-testing may be carried out at a lower frequency following a GMP approach if consistency is

demonstrated and documented. Each batch to be examined should be sampled separately. Large batches can be divided into sub-batches, which can then be sampled separately.
If the sample is intended to represent a range of materials, the selected sample should represent the worst-case situation in migration testing, e.g., containing the highest concentration of additive or co-monomer or thickness of the sample (Marin-Kuan et al., 2023b).

The recommendations related to NIAS sampling for labelling and packaging are described in Table 6. these are equally applicable to the analysis of IAS.

Timing

To determine the optimum timing for sampling, the business operator should consider the presence of any material in his product that has not yet reached its definitive physical or chemical state following production. For example, inks may need to dry, two-component adhesives are subject to a chemical curing process, or plastics can crystallise after extrusion. These processes should be allowed to come to equilibrium before taking the sample. The critical time for a final FCM is not when the article leaves the FCM-producing company but when it is sold for use in contact with food. This sets the lower limit for timing when sampling an FCM.

The upper limit is set by the maximum age of the FCM at which it is still suitable for use. Consideration should be given to the following aspects (in particular for SML testing):

- Set-off can affect the amount of substance present on the food contact side of the FCM to be tested.
- Equilibration between the layers of a multilayer FCM can be addressed by waiting for the material to come to equilibrium,

Sampling Dos and Don'ts

Some of the dos and don'ts associated with sampling for analysis of NIAS are summarised in Table 6.

Table 6: Some Dos and Don'ts associated with Sampling for Analysis of NIAS

Action	Do	Don't
Ingredients and/or raw materials	• Take portions of the ingredients and raw materials used during manufacture at the same time as you sample the FCM. These can then be tested by the same techniques as the sample (for NIAS) and used to investigate the origin of the NIAS. • Consider sampling blank and control samples of the FCM at the same time as the to be tested FCM e.g. take a portion of uncoated metal whilst sampling for coated metals, take a sample of plain paper as well as the printed paper FCM	
Packaging of sample	• Wrap in an inert aluminium foil or in glass • Wrap samples individually whenever possible • If cannot wrap individually wrap with food contact surface next to food contact surface and NOT to the outside surface • Exception would be the study of potential set-off • If possible, keep the wrapped samples under vacuum or in thermos-sealed barrier bags	• Don't use lubricated or surface treated aluminium foil
Labelling	• Identify each specimen with name and/or unique article/lot number and date • Use printed labels if possible. • For single sided FCMs ensure that the test laboratory knows which surface to test	• Don't use marker pen or self-adhesive label on the specimen. • Don't mark food contact surface of the test specimen • take care with marking/labelling the non food contact surface of other FCMs such as paper where

Action	Do	Don't
	• Avoid adhesives to be fixed on the FCM	any adhesives or inks might migrate through the paper into any simulants/food/solvents • Do not place a label directly on the food contact surface as the adhesive may contribute migrants
Shipping samples	• Ensure all information is shipped with samples • Uniquely identify samples	• Don't use boxes made with recycled board • It is often useful to retain samples of the packaging/boxes in case there are 'strange' NIAS. If you have saved a portion of the packaging this can be tested to see if the NIAS originates from the packaging of the sample • Don't use marker pen or self-adhesive label on the specimen
Testing	• Ensure that the test laboratory knows which side to test for migrants • In flexible packaging take some meters (layers) inside the roll, not the last ones.	• Don't label the box nor the sample • Don't cut the samples in small pieces for testing, as it overestimates the migration (edge effect). It is sometimes necessary to cut the sample to increase the surface in contact with the simulant/extractant
Surface-to-volume	• Ensure that the S/V ratio is agreed upfront	
Size & form of test samples	• Ensure that the sample material can be exposed to simulants • Thickness should be the same as in the final article • You should be able to cut test specimen out of large articles • Bottles and caps can be filled with the simulants, but closures are	• Avoid cut edges

Action	Do	Don't
	required. Be sure that the right closures are supplied with the samples. • Blanks of closures should be tested • Cups and caps can be filled; flat sheets can be exposed from a single side; full immersion only if homogenous monomaterial is available	
Status of material	• Ensure, that material has not been used • If the article is filled, test the food at the end of shelf life	• Only unused material can be tested, filled or formerly filled material is not suitable for testing

5. GENERAL STEPS FOR NIAS ANALYSIS

Once the samples are in the laboratory, a number of steps are required for their analysis. The main points for consideration are:

1. Identification of the materials to be analysed.
2. Decision about the migration tests to be used.
3. Decision about what analytical techniques will be used – extraction or migration
4. Sample preparation
5. Instrumental analytical technique
6. Data processing and software tools required for identification.
7. Calibration
8. Quantification and semi-quantification
9. Validation and Uncertainty

The next section will describe the procedure in each case.

Identification of the materials to be analysed

This information should be supplied by the producer or supplier. In the absence of data, if the sample is not correctly identified, confirming the material or materials involved in the sample should be the first step. Differentiating between monolayers and multilayers is important, as it determines not only the extraction medium but also the simulants to be used in migration tests and the preferred type of migration, either single-sided or by total immersion in the simulant. For this purpose, Fourier-transformed infrared spectroscopy (FTIR) or Raman Spectroscopy (Raman) can be used (Commission et al., 2017; Heintz et al., application note AN52690). The resulting spectrum can be compared to the spectra library, usually available in the instrument's database. For flexible materials, both sides should be analysed to check if they are identical. Identification of the food contact side is crucial, as using the correct side in migration tests is critical. Generally, the presence of inks on a non-food contact side is obvious, whilst the presence of coatings is more difficult to determine. However, it is essential to know if a coating is present. The supplier of the material should be encouraged to state that a coating(s) is present and give a generic description of its

chemistry. When no other information is available, spectroscopy may indicate the presence of a coating.

Selection of the migration tests to be used

The type of contact, single side or total immersion, and simulants should be selected for the migration tests. Single side is usually the preferred mode as it better simulates real contact and avoids cut edges and is required for multilayers with non-symmetrical structures. When more than one layer is present, determination of migration from the separate layers may be possible if the individual layers before lamination are available. Analysis data from such layers will assist in building an overall picture of potential migration and possible sources of any NIAS detected. As above, the selection of simulants and migration conditions for plastics should be conducted according to Regulation (EU) 10/2011 unless these are considered unsuitable, e.g., causing swelling or other physical or chemical changes [see Table 2]. For many non-harmonised FCMs, the conditions specified for plastics are unsuitable and can give erroneous results. For kitchenware and tableware FCM, which usually involve several different materials, the JRC Guidelines can help (Beldi et al., 2021) . In the case of suspected NIAS, specific tests may be required, e.g., primary aromatic amines, mineral oils, bisphenol A, etc. As established in Regulation (EU) 10/2011, the worst-case scenario should be applied when selecting the migration conditions, which means the highest temperature and longest time of intended use to cover all intended applications. Additional guidance on the experimental design of migration tests and the alternative of exhaustive extractions are given by Nerin et al. (2022), and include the characteristics of materials and migrants. The advantages and disadvantages of migration and extraction testing are summarised in Table 7.

Table 7: Advantages and disadvantages of extraction and migration testing

	Advantage	Disadvantage
Migration	• Direct quantitative results for simulated applications are obtained • Only the components of interest (migrants) are present • Often needs additional concentration steps	• testing is complex, costly and time-consuming • due to low concentration, identification of unknowns can be more time consuming • You may not detect substances due to the detection limit of the generic screening method • Some potential migrating substances (e.g. PAA, BPA, MOSH, MOAH etc) need specific analysis as they don't have sufficient sensitivity In general screening procedures. • Reaction products can form between simulants and migrants which may not be formed in actual foods
Extraction	• Rapid test • Identification of components does not need additional steps as the concentration of potential migrants is higher • Results can be used for a wide range of applications applying migration modelling to identified compounds or 100 % migration concept using worst-case (total transfer) calculations	• Determine the limit of interest to decide which peaks need to be identified. • Too many peaks to identify which will increase resources required. • Usually, overestimation of migration calculated by 100% migration or modelling • Demonstration of completeness • A great analytical effort to identify many compounds that may not migrate

Decisions about the analytical techniques to be used

The selection of analytical techniques for NIAS is critical for samples containing a number of unidentified (unknown) compounds, which require identification. Such identification means that the response of the analytical techniques chosen be as specific as possible so that elucidation of the chemical structures of the compounds and identification of the substance is unequivocal. This is the most difficult task, as few analytical techniques provide unequivocal identification of many compounds. Among them, undoubtedly, high-resolution mass spectrometry (HRMS) is the best. It is true that spectroscopic techniques provide absorption or emission bands or peaks corresponding to the functional groups. However, the response is not specific for every molecule and the identification of unknowns based on these data is really difficult, even more so in the absence of standards.

Another important consideration is the sensitivity of the analytical technique. The level of 10 ppb migration, is a generally recognised limit for non-listed substances in many FCMs, and is rather difficult to achieve in some cases. Even with the most sophisticated and advanced analytical technology, a general screening does not identify every single NIAS that may be present. Consequently, different and complementary techniques need to be applied. The detection limit is the key to selecting specific analytical techniques.

Sample preparation

There is a clear difference between sample preparation for direct analysis of FCMs and simulants after exposure. Direct analysis is normally carried out on solid samples, whilst the analysis of simulants, except MPPO, is on liquids.

The selection of the analytical technique(s) also determines sample treatment. SPME in immersion mode cannot be used in organic solvents. Compatibility between solvents and selected techniques is an important issue that will need careful consideration. With non-polar solvents and solvents insoluble in water, liquid chromatography with reversed phase cannot be used, unless a change of solvent is applied. In this case, HILIC phases could be used. Solutions high in aqueous content cannot be injected into GC-MS, as the MS source will be damaged. Solvents with high sensitivity in UV-VIS cannot be used to analyse migrants by UV-VIS, as the signal from

the solvent will overlap that of the migrants. FTIR cannot be used for aqueous simulants.

Extraction of FCMs is usually carried out with organic solvents. To evaluate potential NIAS, exhaustive extraction by applying a solvent that can penetrate the polymer or even partially or fully dissolve is recommended. The extracting solvent or solvents should be selected to provide the maximum solubility of the substances. Sequential extractions can be used. All extracts coming from 1,2,3…extractions are mixed together and the results obtained compared to those obtained from 1 extraction, 1+2 extractions, 1+2+3 extractions, etc., because the separate analysis of each extraction is not sensitive enough to establish the optimum number of extractions. The use of ultrasonics can help accelerate the extraction process. Soxhlet extraction is a good approach and can be recommended for semi-volatile and non-volatile substances. Importantly, volatile compounds will be lost by evaporation during the process. High temperature accelerates extraction and increases efficiency, but special care should be taken when using organic solvents to avoid the formation of new NIAS or when analysing volatile substances. Accelerated solvent extraction (ASE) can be used to facilitate the process. This system consists of enclosing the solid sample and the solvent in a stainless steel cell and applying pressure and temperature. Under pressure, the solvent will remain in a liquid state, and extraction will occur at high temperatures, with enhanced efficiency and without losses. In cases where a more extended period for swelling improves extraction, static extraction or Soxhlet may be better alternatives.

Sample preparation of solid samples often involves grinding or milling the sample to increase the surface area as much as possible to facilitate extraction. If milling is applied, it is recommended to carry it out under cryogenic conditions, preferably under liquid nitrogen, as this avoids altering NIAS or even producing further NIAS. In case of volatiles, special care is needed to avoid losses during milling.

Volatile NIAS can be extracted by thermal desorption (TD) or static headspace (HS) from solid samples or Purge &Trap (P&T)(García Ibarra et al., 2018; Nerín C et al. 1995; Nerin C et al., 1998) from simulants and solutions, in both cases coupled to GC-MS. Static headspace coupled to GC-MS can also be used to analyse volatile NIAS in polymers (Ouchi et al., 2019).

HS works under equilibrium conditions, and needs optimisation of times and temperatures to ensure that any NIAS are forced into the headspace for analysis. The vapour phase in equilibrium with the sample, under optimised temperature and time, is injected into the GC column. It can be applied in manual mode with a tight syringe, especial for gases, or automatically coupled to a GC. The manual option requires skill to ensure reproducibility, but is a good option when an automatic instrument is not available. In automatic HS-GC it is recommended to use on-column injection to avoid problems with sequential injections when there is automatic control of pressure in the GC injector. To facilitate vapour sampling from the vial, the system injects into the vial a fraction of carrier gas, so that, vacuum effects occurring during the sampling are avoided. This action slightly dilutes the sample to be injected and consequently, affects the sensitivity of the procedure.

In contrast, P&T does not work under equilibrium conditions as a carrier gas removes the volatiles constantly (dynamic headspace). While purging, all volatile substances are trapped into an adsorbent, either active charcoal, MPPO (tenax) or other substance. Once the purge is finished, a valve closes the purge and the trap is rapidly heated at high temperature, thermally desorbing all substances into the GC-MS. In an ideal case, the total amount of volatile substances originally present in the sample are introduced into GC-MS and arrive at the detector. This is an absolute analytical procedure and is probably the most sensitive one for volatile substances. Consequently, very small amounts of samples should be used to avoid saturation of the detector. P&T does not respond to concentration but to the total mass of the compounds (Nerín et al., 1998). It can be applied to both liquid and viscous samples. In cases where the purge gas cannot be bubbled through the (liquid) sample but purges the gas phase only, volatiles may not be completely removed, and calibration in the matrix is necessary.

Both HS and P&T can be used for either solid or liquid samples, i.e., simulants after exposure. In both cases, the use of non-volatile solvents is recommended as to prevent their vapours masking migrants or cause unacceptable high pressure in the headspace vials.

For enrichment from aqueous simulants, solid-phase extraction devices could be used. There are several approaches to consider. Stir bar solid extraction (SBSE) is one of them, where a magnetic bar coated with an appropriate adsorbent is immersed

into the simulant, and magnetic stirring is applied. After an optimised time and temperature, the stir bar is desorbed in the injection port of the GC-MS.

Solid phase extraction (SPE) is very common, for both volatile and non-volatile substances. SPE is usually applied to isolate the analytes from other sources of interference and to concentrate the analytes from the liquid simulants. This consists of passing the liquid simulant after exposure through a bed or a cartridge containing the stationary phase, where either the analytes (migrants) or the interfering substances are retained. After this step, the SPE is eluted with an appropriate solvent. The mode of action of the stationary phase can be adsorption, partition or ion exchange (Aznar et al., 2009). There are many types of cartridges commercially available, and the analyst should select the appropriate cartridge for each specific analysis. All of the cartridges are single use.

Over recent decades, several approaches have been developed and proposed for analysing trace amounts, minimising volumes of solvents used and developing extraction devices. These microextraction techniques burst onto the market, some with very high success rates. Among them, solid phase microextraction (SPME) and liquid phase microextraction (LPME) (Osorio et al., 2018; Pezo et al., 2007) were probably the best known. SPME can work either in HS mode or by total immersion in the solution. In total immersion, the technique can be used for semi-volatile and non-volatile substances (Song et al., 2019; Su et al., 2020). Different stationary phases (fibres) with different polarities and even mixed phases to cope with various substances have become available. Careful selection of the fibre, temperature and extraction time should be used to reach equilibrium. Without equilibrium, the reproducibility of the SPME analysis can fail, and errors increase. SPME can be manual or automatic, and in both cases, the thermal desorption of volatiles happens in the injection port of the GC-MS. For non-volatile substances, the desorption is usually carried out via a solvent or the mobile phase used in LC (Nerın et al., 2002). Theoretically, the SPME fibres can be reused up to 100 times, but the analyst should continually check the performance of the fibre. Volatile, semi-volatile and non-volatile substances can be analysed by SPME, although the appropriate fibre and experimental conditions should be optimized in each case.

LPME works with semipermeable PP capilars, with the extraction occuring through the pores of the capilar. There are different modes, using either two phases, where the extractant is inside the capilar and the simulant/solution to be extracted is outside the capilar (Salafranca et al., 2009) or three phases, where the aqueous solution outside the capilar is the donor, and that inside the capilar is the acceptor, with the extractant filling the pores of the capilar walls (Rodríguez et al., 2008). As usual, the extractant should not be miscible with aqueous simulants, and the basic rules for extraction are applied. Although the process can be manual the use of an automatic system developed by (Pezo et al., 2007) is recommended. The capilar is single use and the size of capilar determines the final volume of extract and thus the enrichment factor, e.g., from 10 mL simulant to 150 µL extract.

In general, if the extracts or simulants are stored in the refrigerator before being analysed, shaking in an ultrasonic bath and warming to their original temperature (in case cooling has caused precipitation) is recommended before the final analysis, this will ensure that all migrants are solubilised.

Instrumental analytical technique

A wide variety of analytical techniques with commercially available instruments can be used to analyse NIAS, as described by Nerin et al (Nerín et al., 2022). However, if the main purpose is to identify unknown molecules, the range of instruments available is reduced, but they can provide specific signals unequivocally linked to each substance. A critical point in selecting the technique is the sensitivity required, which is the minimum concentration needed for detecting one substance (limit of detection, LOD) and measuring its concentration (limit of quantification, LOQ). An important consideration is the presence of several substances in the sample to be measured. In fact, some of the available techniques are good options for isolated substances, but they fail when a mixture of substances is present. In these cases, previous separation steps are necessary. Chromatography in its different versions would be selected for volatile, semi-volatile (gas chromatography,GC) or non-volatile substances (liquid chromatography, LC). In both cases, different detectors can be selected, depending on the chemical characteristics of the analytes. An overview of the techniques is given in Table 8 and discussed in Nerín et al., 2022.

Table 8: Overview of instrumental techniques for identifying and quantifying NIAS

Chemical type	Technique	Column separation (Examples)	Detector	Comments
Volatiles and semi-volatiles	GC-MS	• 5% phenyl PDMS or similar (DB-5 or similar) • Polyethylene glycol (Carbowax or similar)	MS (EI) (electronic impact)	Qualitative Spectral library available. Quantitative analysis.
Volatiles and semi-volatiles	GC-MS	• 5% phenyl PDMS or similar (DB-5 or similar) • Polyethylene glycol (Carbowax or similar)	MS (chemical ionisation) or MS-MS (ion trap) or MS-TQ or APGC-MS-QTOF (HR) Orbitrap	Qualitative and Quantitative Using High Resolution (HR) chemical structure can be searched in Chemical databases (ChemSpider or SciFinder)
Volatiles and semi-volatiles	GC-FID	• 5% phenyl PDMS or similar (DB-5 or similar) • Polyethylene glycol (Carbowax or similar)	FID	Quantitative analysis.
Volatiles and semi-volatiles	GCxGC-MS	• 5% phenyl PDMS or similar (DB-5 or similar) • Polyethylene glycol (Carbowax or similar)	MS (EI) (electronic impact)	Spectral library available. Quantitative analysis.
Non-volatiles	LC (UHPLC)	Reverse phase (C18)	MS-QTOF (HR) Orbitrap MS-IMS-QTOF (HR)	Qualitative analysis Own library or database in each lab. chemical structure can be searched in Chemical

				databases (ChemSpider or SciFinder) Chemical databases High experience is required
Non-volatiles	LC (HPLC or UHPLC)	Reverse phase (C18) HILIC phase (for small polar NIAS)	MS-MS (triple quadrupole)	Quantitative analysis using certified standards
Non- volatiles	LC (HPLC or UHPLC)	Reverse phase (C18) HILIC phase (for small polar NIAS)	UV-VIS or fluorescence	Quantitative analysis using certified standards

Chromatography is the interaction between chemical substances carried by a mobile phase and a substrate, called a stationary phase. As a consequence of the strength of interactions between the compounds and the two phases, the compounds injected into the system arrive at the detector at different times, called. "retention times (RT)". Polar substances strongly interact with polar stationary phases and their RT are very large. The opposite occurs with non-polar substances in a polar stationary phase. When screening a sample, it is unknown which type of substances will appear. For this reason, it is recommended to use stationary phases of medium polarity and if possible, a further phase with very different polarity.

In LC, only C18 is mentioned, as it is quite universal. There are also many stationary phases available, but the most universal one is recommended for screening.

For identification and quantification purposes, several analytical techniques are available. More information and details about them are provided in the publication by Nerin et al., 2022.

Data processing and software tools required for identification

Instrument and software tools are extremely important in LC-MS, as they help the user to interpret the data by searching the molecular formula and fragments and provide a list of potential theoretical candidates that agree with all characteristics. Chemical databases play a fundamental role in the elucidation of chemical structures. As well as the libraries linked to vendor software, other publicly available MS/MS libraries like MS-DIAL, MassBank, RIKEN and GNPS libraries can be very useful. Other public software

packages are MS-CleanR and the in-silico fragmentator (MS-FINDER) (Tsugawa et al., 2015, 2016). ChemSpider and SciFinder are currently the best available and are both publicly available. Databases of packaging CPPdb provided by Groh et al., 2019 and FCCdb (Groh et al., 2019; Groh et al., 2021)and other specific libraries are also a great help (Song, Canellas, et al., 2022; Song, Dreolin, et al., 2022) and the NIST Library is also available. Some NIAS, such as oligomers arising from polymers, are not included in any database, and their elucidation has to be made based on MS spectra and experience of the laboratory in collaboration with polymer scientists. Recently, an extensive database specific for FCM containing more than 10,000 compounds with analytical data such as retention time (experimental in some cases and predicted in others), values of ion mobility (CCS) (experimental in some cases and predicted in others), and mass fragments has been developed (Song et al., 2022) and will be soon freely available in the public domain (Song et al., 2022) via the website of WATERS.

In addition to the tools provided by the software and specific tools from each instrument, other tools can facilitate identification. Comparison of chromatograms between sample and blank facilitates the identification of those compounds present in the sample and absent in the blank. Very sensitive analytical instruments always give many signals, but not all correspond to NIAS. Thus, it is important to apply criteria to select the best markers corresponding to the potential NIAS. Some software linked to the HRMS instrument brands can generate marker matrices based upon user-defined criteria which can be automatically transferred to other statistical software, e.g., EZInfo software for a multivariate analysis (MVA). One good option is to use the S-plot, which shows the Accurate Mass/Retention Time (AMRT) dissimilarities between two groups. The AMRT pairs are plotted by covariance – the magnitude of change (x-axis), and correlation – the consistency of the change (y-axis) values. In this way, the markers, show the compounds mainly belonging to component A and those mainly belonging to component B.

Calibration and validation

Calibration is very important in any analysis to get the correct response for the specific concentration of the analyte and the instrument itself. MS detectors need calibration for the MS response in the range of analysis. The calibration is usually made with specific compounds that cover the whole range of MS. Especially in HRMS,

uncalibrated instruments will provide erroneous measurements of the substances. This calibration is different from that linked to the specific analytes, where the calibrants are commonly the certified standards of the same analytes. Using certified standards provides confirmation of identities of NIAS found by RT and mass spectral matching, and calibration plots are built and used for quantification.

Quantification is the measurement of the exact concentration of any migrant in food simulants or food. To quantify, standards (certified standards or standards with known purity) corresponding to each previously identified compound are required. The main problem is that the identified NIAS standards are often not commercially available. In these cases, estimated concentrations can be applied, by using standards with similar chemical structures to those potentially identified. If HR-MS was initially used, fragmentation profiles could be an excellent tool to confirm the behaviour of potential candidates identified. It is extremely important to confirm the identification. Occasionally, a candidate with full data (elemental formula, fragments, retention time, molecular size) confirming the molecule, has resulted in a wrong identification. The Schymanski approach is a useful tool to show this(Schymanski et al., 2014).

Unfortunately, the response of compounds in detectors, either in MS, FID or UV-VIS, are not the same. Some compounds are very sensitive, meaning their signal is very high with low concentrations, while others have poor sensitivity and low response for high concentrations. This fact makes it very difficult to establish a common system for semi-quantification. Therefore, the most appropriate approach is selecting compounds with similar chemical profiles as the identified NIAS.

Once the compounds are identified by GC-MS, quantification can be achieved using either an MS detector or FID, always using certified standards for calibration plots. In the absence of standards corresponding to each individual compound, other standards with a similar chemical structure could be used for this purpose, even though the number of carbons is different from the specific analyte. After identifying non-volatile compounds, quantification is achieved by using LC-MS-MS with triple quadrupole, which is much more sensitive than MS-QTOF, or by UV-VIS or fluorescence, if the corresponding certified standards are available. UV-VIS is not always as sensitive as MS-MS, and often the NIAS already identified in LC-HR-MS do not give any signal in UV-VIS. In contrast, fluorescence is a very sensitive detector, although it is only applicable to a few compounds, and most NIAS are not fluorescent.

Validation and uncertainty

Validation usually means that the analytical method is accurate and gives the true value of the original sample under analysis. It requires the determination of the limits of detection (LOD) and quantification (LOQ), recovery, if applicable, uncertainty, repeatability, robustness, linearity, linear range, selectivity, specificity. One option for validation is to use standard addition, which means doing the calibration plot over the sample. This technique is very useful to validate quantitative performance in the presence of matrix.

6. ALTERNATIVES TO MIGRATION/EXTRACTION TRIALS

Worst case calculations

If the identification and concentration of a substance in an FCM are known, it is possible to assume that everything will migrate into the foodstuff. If the level is below an SML (for a listed substance) or a level considered safe (for a NIAS), then it is permitted in plastics (Regulation (EU) 10/2011) to use worst case to demonstrate compliance and safety of the FCM.

Modelling

Once identified and the concentration (C_p0) in the FCM is determined (e.g., by exhaustive extraction), the concentration of the migrant in food or food simulant can be estimated by mathematical modelling of diffusion. For unknown migrants, migration modelling must be used with caution and, at best, is only an approximation. When migrants have not been fully identified, but are (semi)quantified in the material and characterised in terms of molecular mass and polarity, diffusion coefficients and partition coefficients can be estimated and modelling can also be applied.
Several migration modelling tools exist that solve the Fickian second law by numerical algorithms and apply them to monolayers and multilayers. Prerequisites for the applicability of modelling are described in the modelling guideline (Hoekstra et al., 2015). In plastic layers, diffusion usually follows Fickian 2nd law if the substances are homogeneously distributed in the layer, i.e., substances may not bloom out or are located on the surface only. The model needs geometrical information for the packaging and filling (layer thicknesses, surface-to-volume ratio), the identification and concentration of the migrant in the material (C_p0) and knowledge or estimates on the diffusion coefficients in the layers and partition coefficients between the layers. Adhesives or printing inks are calculated as layers. Food is considered as a layer, too.

Modelling parameters (diffusion coefficients, partition coefficients) should be chosen such that the modelling slightly overestimates experimentally determined migration. Additionally, to the approach to estimate diffusion coefficients in the modelling guideline (Hoekstra et al., 2015), less overestimating approaches have been developed in the meantime (Nerin et al., 2022). By mathematical modelling, the

conformity of a material with a migration limit or another benchmark can be checked, but non-conformity should be verified by an experimental migration test.

7. RECOMMENDED APPROACHES AND BEST PRACTICES

Analysis and Reporting

Detailed factors that need to be considered and the information that should be included in the report are mainly covered in Nerin et al., 2022.

Sharing Information

There are many different players in the Supply Chain, and they can be summarised as follows (courtesy N. Kernoghan):

- Substance manufacturer: Any operator who manufactures or produces a chemical substance for use in food contact plastics (e.g., monomers and additives)
- Manufacturer of plastic intermediate materials; (i.e., the producer of the resin).
- Manufacturer of non-plastic intermediate materials; (e.g., adhesives, inks and coatings)
- Manufacturer of final materials and articles (i.e., the packaging manufacturers)
- Users of food contact materials and articles (i.e., the packer/fillers)
- Distributors
- Importers
- Retailers
- Final Consumers

This document only concerns those involved with the users of the FCM. Retailers and consumers are outside the scope of this paper.

The legal requirement for sharing information in the supply chain may vary depending upon the FCM. Plastics require a legally defined Declaration of Compliance (DoC). Non-harmonised FCMs may require a DOC in some member states. Irrespective of the legality, it is essential that at each step in the supply chain, communication is established with their respective suppliers and customers. Suppliers need to know that their substance or product is being used for food contact, and the nearer to the food industry (packers and fillers) the suppliers are, the higher the knowledge of the types

of food being packaged. The most straightforward classification is: e.g., all foodstuffs, alcoholic, non-alcoholic, fatty or acidic. This enables appropriate simulants to be used for testing. In addition, process times and temperatures given as an envelope (to protect IP) are needed to ensure realistic testing. If there are further constraints, such as a high surface-to-volume ratio, they must be communicated.

Every actor in the supply chain needs to understand if the substances and/or products they are purchasing are suitable for direct food contact. They need a qualitative composition (e.g., under a non-disclosure agreement) and possible presence of other substances, such as known NIAS, which may affect their internal risk assessment(s). Customers should be made aware of substances that they may have to analyse in their product(s) to ensure compliance and safety of their product.

In the absence of clear EU legislation for transferring information in the supply chain, the industry continues to develop guidelines. Over-arching principles have been agreed between over 30 professional associations representing most of the FCM [REF CSG with active members being listed in Annex 1]. Each sector has (or is developing) guidelines for how this will be translated to their particular FCM needs.

A generalised schematic is given in Figure 2. The proposal is for there to be two documents (A&B). Document A will be based on the legal requirements of a DoC for plastics, even if applied to non-plastic FCMs. Document B will be business to business (B2B) and is for those disclosing and those requiring confidential information to agree on the substance content.

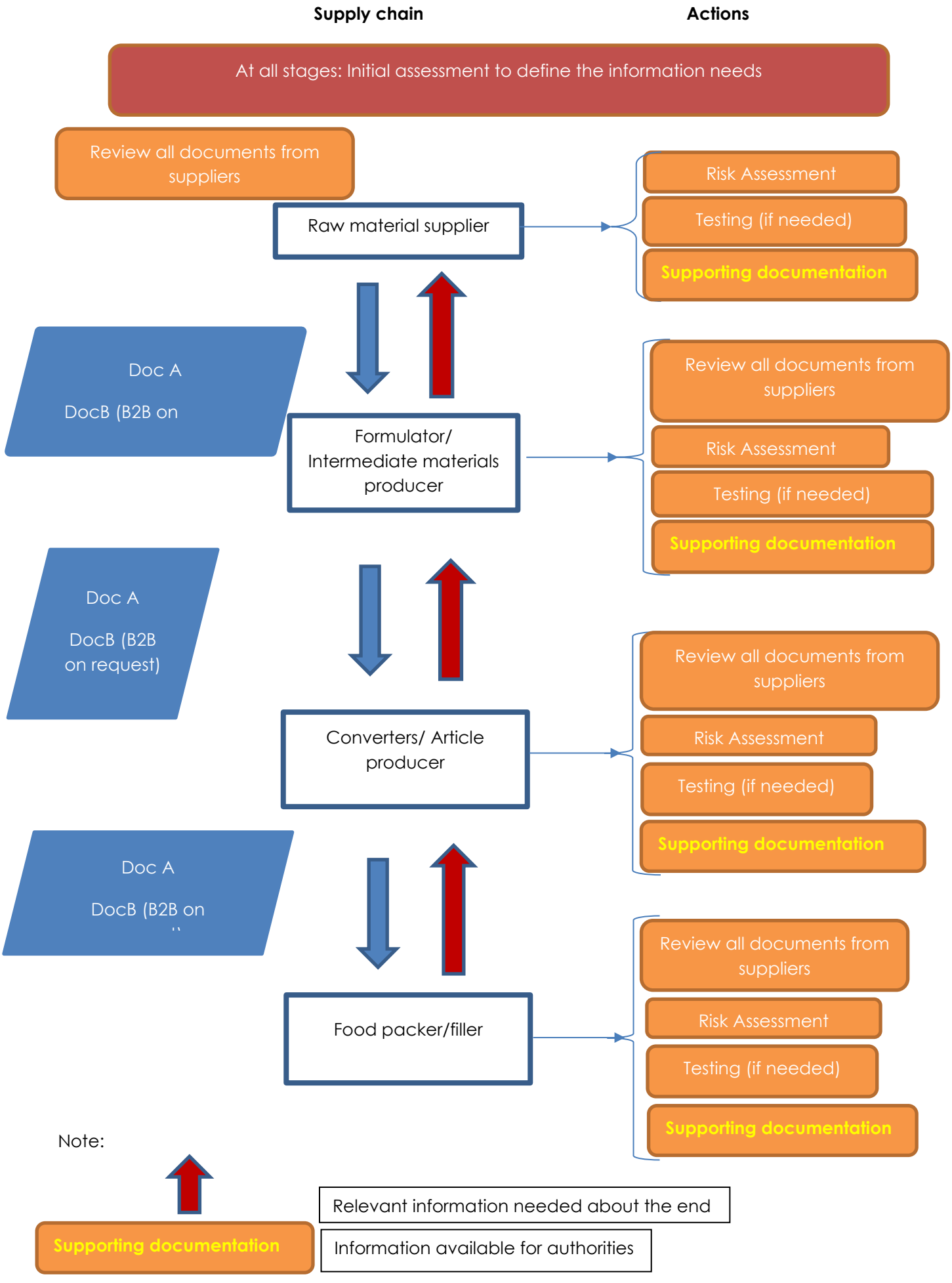

Figure 2: Communication along the Supply Chain

Requirements for the different actors in the supply chain

An analytical strategy is highly dependent on the available information of composition of the FCM. At each step in the supply chain, the amount of this information and analytical requirements differ. 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 the composition. There are several different actors in the supply chain, and each has a different viewpoint.

Raw materials suppliers

Suppliers of raw materials are at the starting point of the supply chain. Therefore, NIAS in the raw materials may be found at each step in the supply chain. Downstream users should be informed about these by their raw material suppliers. This will enable the downstream user to select suitable raw materials and to perform targeted analysis for the indicated NIAS. The raw material supplier will guarantee the purity of the raw material with the downstream user. A significant change in the impurity profile must be communicated.

Intermediate suppliers

Some NIAS can be predicted based on knowledge of the production process and input from the raw material supplier. Targeted analysis for these predicted NIAS should be performed. In addition, general screening for unknowns should be carried out.

Intermediate suppliers manage the quality of their raw materials according to ISO-certified quality systems. The quality system is established to control the quality of the intermediates. Intermediate suppliers cannot take responsibility for the final article.

The intermediate producer cannot systematically foresee how an intermediate is processed to manufacture the final article and the final application. Therefore, unless informed explicitly by the material manufacturer, a risk assessment for NIAS is usually performed for the recommended applications assuming standard food contact conditions. Typically, an intermediate supplier will carry out an extraction test to screen for potential migrating substances, considering the information obtained from

the raw material supplier and in-house knowledge of the production process and intermediate properties.

Material suppliers

The suppliers of final food contact materials or articles are responsible for compliance with end use regulations. Using information from intermediate suppliers or raw material suppliers, a targeted analysis of some NIAS is possible. However, new NIAS can be generated during the processing of intermediates, and some NIAS may be lost, e.g., residual solvents from printing inks may be present or removed during processing. It is clear that information should be supplied both up and downstream so that appropriate checks can be carried out within the supply chain, data shared and finally a full and complete analysis of the final article carried out.

Convertors and/or food manufacturers

A converter changes a material into an FCM. Food manufacturers can act either as "users of FCMs" or as "manufacturers of FCMs" if they operate physical processes such as extrusion, laminating, blow-moulding, injection moulding, printing, coating, calendaring, thermoforming, stretch blow moulding, etc. to the material they received.

As "users of FCMs", food manufacturers should investigate NIAS in surveillance mode as the supplier will have already performed a full safety assessment. As the food manufacturer may not repeat a full safety assessment of the FCM, an agreed methodology between food industries and enforcement bodies would be beneficial, and this could be used to check the plausibility of the supply chain statements.

Governmental institutions and enforcement viewpoint

Until now, the control of FCMs has been limited to the analysis of IAS. In the opinion of scientific experts of official control bodies, relevant NIAS should also be included in supporting documents and/or a Declaration of Compliance. Finally, the recommendations described in this document are very important for high quality analysis of NIAS and are needed to guarantee the quality and comparability of the results obtained by different stakeholder laboratories.

8. FUTURE PERSPECTIVES

The focus of this document is the NIAS testing of Food Contact Materials, either harmonised or non-harmonised, with the emphasis on non-harmonised. This document tries to summarise the existing situation using available information. In the absence of regulations, the norms and recommendations provided by industry and other bodies are the best (only) tools for determining NIAS. Regulators, authorities and industry need harmonised guidelines for determining NIAS and assessing their risks. This last aspect will be the topic of a future B&W book and publication. It would be highly appreciated if the European Commission would publish more guidance on testing and risk assessment of Food Contact Materials.

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10. ANNEX 1. COMPOSITION OF ACTIVE MEMBERS OF CROSS SECTOR GROUP

- APPLIA Europe – Domestic Equipment Manufacturers
- Cefic-FCA – food contact additives
- CES – Silicones Europe
- CEPE – Coatings
- CEPI –European Paper Industries (pulp and paper) CERAME-UNIE – European Ceramic Industries Association
- CONCAWE – Division of Oil Refiners Association
- ED/ESGA/Institut du Verre - Glass Alliance Europe
- EEA: European Enamel Association
- EuPC – European Plastics Converters
- EUPIA – Printing Inks
- EUROFER
- European Wax Federation
- FEICA – Adhesives
- FoodDrinkEurope
- FEC – The European Federation of Cutlery, Flatware, Hollowware & Cookware Industries and Brands
- FEFCO - Corrugated Packaging
- Flexible Packaging Europe
- Intergraf - European Federation for Print & Digital Communication
- Metal Packaging Europe
- Nickel Institute
- PET Europe – PET manufacturing industry
- PlasticsEurope
- WBT - World Association Bottle & Teats

11. GLOSSARY

AMRT = Accurate Mass/Retention Time
AP = Aids to Polymerisation
APGC-MS-QTOF (HR) = atmospheric pressure gas chromatography-mass spectrometry-quadrupole-time of flight (high resolution)
ASE = Accelerated solvent extraction
B&W = Black and White
CCS = collision cross section
CMR = carcinogenic- mutagenic-reprotoxic
DBP = Dibutylphthalate
DEG = diethylene glycol (2,2'-Oxydi(ethan-1-ol)
DEHA = diethylhexyl adipate
DEHP = Di-(2-ethylhexyl)phthalate
DEHP = diethylhexyl phthalate
DEHT = Diethylhexyl terephthalate
DiBP = Diisobutylphthalate
DiNCH = 1,2-cyclohexane dicarboxylic acid diisononyl ester
EFSA = European Food Safety Authority
EFSA CEF Panel = Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
EtOAc = ethyl acetate
FCMs = Food Contact Materials
FCN = food contact notification
FDA =Food and Drug Administration
FTIR = Fourier-transform infrarred spectroscopy
GC-ECD = gas chromatography. Electron capture detector
GC-MS = gas chromatography-mass spectrometry
GCxGC ToF-MS = gas chromatography-gas chromatography- time of flight-mass spectrometry
GCxGC-FID-MS = gas chromatography-gas chromatography- flame ionization detector-mass spectrometry
GMP = Good Manufacturing Practices
HPLC-FID = high performance liquid chromatography- flame ionization detector
HRMS = high-resolution mass spectrometry
HS = static headspace
IAS = Intentionally Added Substances
ICP-MS = inductively coupled plasma-mass spectrometry
JRC = Joint Research Center
LC = liquid chromatography
LOD = limit of detection
LOQ = limit of quantification
LPME = liquid phase microextraction
MEG = monoethylene glycol (ethane-1,2-diol)
MOHs = mineral oil hydrocarbons
MPPO = modified polyphenylene oxide (Tenax)
MS-IMS-QTOF (HR) = mass spectrometry-ion mobility spectrometry- quadrupole-time of flight (high resolution)

MS/MS = mass spectrometry/mass spectrometry
MVA = multivariate análisis
NIAS = Non Intentionally Added Substances
OML = Overall Migration Limit
P&T = Purge &Trap r Dynamic headspace
PAAs = Primary aromatic amines
PBAT = polybutylene adipate terephthalate
PBS = polybutylene succinate
PBST = polybutylene succinate terephthalate
PCL = Polycaprolactone
PDMS = polydimehyl siloxane
PE = polyethylene
PEA = polyethylene adipate
PEF = polyethylene furanoate
PES = polyethylene succinate
PET = polyethylene terephthalate
PFAS = polyfluoroalkyl substances
PGA = polyglycolic acid
PHA = polyhydroxyalkanoate
PLA = polylactic acid
PP = polyproplylene
PPA = Polymerisation Production Aids
PS = polystyrene
PVC = Polyvinyl Chloride
PVOH = Polyvinyl alcohol
RA/RM = risk assessment/risk management
RT = retention time
SBSE = Stir bar solid extraction
SML = specific migration limit
SPE = solid phase extraction
SPME = solid phase microextraction
TD = thermal desorption
UHPLC = ultra high performance liquid chromatography
UV-VIS = ultraviolet-visible spectroscopy
VOCs = volatile organic compounds

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