EuPIA Guidance on Migration Test Methods for the evaluation of substances in printing inks and varnishes for food contact materials

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1. Scope

This EuPIA Guidance document is an industry guideline for the evaluation of the migration of components of packaging inks applied to the surface of food packaging materials and articles intended to come into contact with food (for both direct and non-direct contact). It recommends testing in worst-case conditions (by a screening approach) and **is not intended to replace compliance testing of the final printed Food Contact Materials**.

The recommended testing methods for the evaluation of the migration of components have been defined in conjunction with food packaging regulations.

This document should be read in conjunction with other EuPIA documents on printing inks for food packaging, for instances the EuPIA GMP [1] and the EuPIA Guidance on the Risk Assessment of NIAS and Non-Listed Substances [2].

The ink itself shall not be tested as such since its composition may change during the printing process. In addition, the substrate greatly influences the migration properties of the components of the ink.

2. Background

Regulation (EC) No. 1935/2004 requires that the finished article for food contact materials must be tested and / or evaluated under real conditions of use. Screening tests can be based on experimental-analytical testing methods or on theoretical migration estimations via calculation or migration modelling. Testing the inks, coatings and varnishes with model systems and conditions can only be considered as a screening tool and should be used only if worst-case calculation or migration modelling cannot be conducted due to missing information, or if the results of these calculations exceed the specific migration limits (SML) associated with components of the inks, coatings, and varnishes.

The specific methods of migration testing and analysis are described either in EU Regulations [3] on materials and articles in contact with foodstuffs or in international Standards [4] [5] [6], with the exception of the preparation of printed samples. For this purpose, substrates and simulants are recommended to check the migration behaviour of components of packaging inks, coatings and varnishes under worst-case conditions.

The draft JRC guideline [7] states: “As a matter of principle, screening approaches need always to be at least as conservative as the verification method. Therefore, test conditions which are at least as severe, should be applied. For an estimation of migration conservative theoretical considerations which overestimate migration are needed. As a logical consequence, screening tests can only be conclusive in that they demonstrate compliance, but they cannot demonstrate non-compliance**.** In the event of exceeding a migration limit by screening, compliance may be checked then by using a more appropriate verification test using food simulants or even foodstuffs. Since, from experience, screening results will be in most cases conclusive concerning positive compliance declaration, screening tests offer advantages over verification methods with regard to time and costs.”

The JRC guideline is only applicable to plastic materials and articles in the scope of the plastics regulation [3]. In the absence of harmonised regulations on other Food Contact Materials (FCMs) the conditions used in the Plastics Regulation are often also applied to non-plastic FCMs. However, plastic simulants and/or conditions may cause physical damage or changes to the non-plastic FCM leading to erroneous results. This is also true for printing inks (see below). Hence, testing conditions better suited to the specificity of each FCM needs to be proposed [8]. This document is aimed at providing specific guidance for printing inks for FCMs.

3. Definitions

Printing Ink
The term “printing ink”, or in short just “ink”, in this paper includes:

(a) mixtures of colourants with other substances which are applied on materials to form a graphic or decorative design together with
(b) other coloured or uncoloured overprint varnishes/coatings or primers which are normally applied in combination with (a) in order to enable the printed design to achieve specific functions such as ink adhesion, rub resistance, gloss, slip/friction properties

Printing inks do not include coatings which are applied with the prime objective of enabling the material or article to achieve a technical function such as heat sealing, barrier, corrosion resistance, as opposed to a graphic effect, even though they may be coloured.[1]

Non-Direct Food Contact (Non-DFC)
Non-Direct Food Contact inks are a subset of FCM inks where the ink is used on the non-food-contact surfaces of food packaging and articles intended to come into contact with food. There is a potential for migration of components from the ink/coating/varnish.

Direct Food Contact ink (DFC)
Direct Food Contact inks are a subset of FCM inks. A DFC ink is defined as an ink that is intended to be, or can reasonably foreseeably be, in direct physical contact with food. For DFC applications the diffusion path between ink/coating and food is short, and so there is a greater potential for migration.
DFC applications can be categorized according to the exposure probability (intentional/foreseeable) and the potential duration of the application (short term/long term). Typical examples are given in annex D.

Transient food contact is a specific type of DFC in which inks can foreseeably be in contact with food for relatively short periods of time. The diffusion path between ink and food is short, but there is also a very limited time in which migration can occur. In this situation the potential for migration exists but is not as high as for long term DFC FCM’s

Migration
In the printing industry, when we refer to migration, this concept in its simplest form is the transfer of components from the FCM into the foodstuff itself.

Transfer of printing ink components from a printed packaging material or article into food or food simulant may occur either

- by direct migration from the ink printed on the food contact surface in situations, where the food is directly in contact with the print
- by migration through the substrate
- via contact to the reverse side in a reel or stack (known as “set-off migration”) or
- by gas phase transfer.

[1] However, the migration test methods detailed out in the guidance can also be applied to coatings and varnishes which are applied with the prime objective of enabling the material or article to achieve a technical function such as heat sealing, barrier, or corrosion resistance.

As there are several different mechanisms of migration taking place, the assumption that the degree to which a printing ink component will migrate directly relates to the component's molecular weight cannot be relied upon. Smaller molecules **will likely** migrate more readily than larger molecules, and molecules with a mass greater than 1000 Daltons (or 1500 Daltons for fluoropolymers) **are generally** considered to be of no concern as they are too large to be absorbed from the gastro-intestinal tract. However, there may be exceptions where a substance with a molecular weight of greater than 1000 Daltons will readily migrate and accordingly will have a Specific Migration Limit (SML) which will limit the acceptable level of migration.

Intentionally used Substances in printing inks for FCMs [2]
This covers all chemical substances which are intentionally used in the production and use of the printing ink and which have an intended and specific function within the final ink and without which the performance of the ink would change. These substances may be added as single components or as mixtures of various substances. The term "use" of raw materials or substances in inks in this paper means always that these raw materials or substances are added intentionally (IAS).

Non-Intentionally Added Substances in printing inks for FCMs (NIAS) [2]
Substances and raw materials used in the manufacture of printing inks may contain impurities originating from their manufacturing or extraction process. These impurities are non-intentionally added (NIAS) but present in the substance which is intentionally used in the manufacture of the printing ink. Further, during the manufacture and use of printing inks reaction and degradation products of used substances can be formed. These reaction and degradation products are non-intentionally present in the printing ink (NIAS).

Non-Listed Substances (NLS) [2]
NLS are substances which are not required to be listed according the current FCM legislation and in many cases not yet officially evaluated. According to the current legislation printing inks for FCM may contain substances which are not listed or fully evaluated. The safety of such substances needs to be demonstrated in accordance with internationally recognized scientific principles on Risk Assessment.

4. Recommended methods

4.1. "Worst case" – calculation and migration modelling

Migration testing can be replaced by the calculation of the maximum possible migration. A formula and an example for "Worst case" calculations are given in Annex A. For digital printing applications see Annex B. For coatings that undergo a significant change in composition during processing this worst case (total mass transfer) assumption is incorrect (e.g. UV and conventional offset).

The FCA ("Food Contact Additives" Sector Group of Cefic) guidance on the risk assessment of NIAS and NLS states "For predicting the migration of substances, mathematical modelling can be applied, which has been significantly developed in recent years. These tools have been validated for some of the commonly used plastics and provide an overestimation of the possible actual migration. For guidance on migration modelling JRC (Joint Research Centre) issued a guidance document" [9].
"Modelling on plastics has been accepted by EFSA as an option to calculate migration [10]. Modelling is only applicable under "non-swelling" conditions. For other materials, like paper and paperboard, the development of a modelling tool is in progress" [8].
There are a few companies who offer software systems for migration modelling (non-exhaustive list of tools) such as: INRA Safe Food Packaging Portal version 335, FABES MIGRATEST Software or AKTS-SML Software, FACET, among others.

4.2. Accelerated migration testing

4.2.1 Preparation of test samples

Printing and drying

For testing, printed samples should be used preferentially, which have been produced and dried under typical conditions of industrial practice. This is especially true if converting and/or drying has a considerable influence on the composition of the printing inks or varnishes, as for instance in reactive (UV, EB, 2-component systems) or solvent-based systems.
Printed three-dimensional objects can also be tested (cups, in-mould-labelled plastic containers).
Alternatively, the ink can be applied to the substrate under laboratory conditions, so that the printing and drying process resemble the reality as much as possible.
To demonstrate that a packaging ink is likely to meet industry requirements, the ink should be applied to the relevant substrate in such a way as to reproduce, as far as possible, the printing and drying processes which are used in practice. In addition, where the final packaging application is known, the composition of the resulting print (i.e. the identity/type of individual ink layers applied and their associated relative film weights) should reflect that application as closely as possible.

For a generic test, where the worst-case print scenario is not known, a representative film weight has to be used (see Table 1). Care should be taken when selecting the substrate used for the test sample, which should by preference be the material chosen for the actual application. In case this is not available, a worst-case substrate such as OPP (30 - 40 µm thickness) for plastic applications or fresh-fibre cardboard (200-300 g/m²) for typical cardboard, paper and corrugated fibreboard applications would be suitable, as neither are a sufficient barrier for most migratable substances.

Table 1: Model systems of printing inks (for 100% coverage). When the coverage is different, a factor should be applied accordingly.

Printing ink or varnish system		**Substrate**	**representative film weight, dry [g/m²]**
Oil-/resin-based	conventional offset (absorption) printed with water-based overprint varnish (OPV)	cardboard	1 – 2
UV/EB-curing	UV/EB-offset	cardboard PP-cup	1 – 2 1 – 2
	UV/EB-flexo	BOPP	1 – 2
	UV/EB-coating	cardboard	4 – 7
	UV/EB-screen printing	PP	10 – 20
	UV/EB-ink-jet	cardboard BOPP	see below*
Solvent- or water-based	gravure	BOPP cardboard	1 – 2
	flexo	BOPP paper or cardboard	1 – 1.5
	2-component-systems, solvent-based	BOPP	1 – 2
	overprint varnish offset, water-based	cardboard	2 – 3
	screen printing, solvent-based	PP	10 – 15
	ink-jet	cardboard BOPP	See below*

*For inkjet, there are many different technologies with different print limitations. It is recommended that the end user prints a sample which reproduces as typically as practicable the ink coverage required for the application. When considering a generic test, in which no particular end use is defined, it is recommended 'test' samples be printed as an area fill corresponding 100% coverage.

Applications, which are not covered by the models in Table 1 must be tested with appropriate formulations and testing conditions. It must be ensured that all elements of the production process are considered to allow for an accurate risk assessment (e.g. drying, curing conditions, stacking, wrapping, shaping, pasteurizing, sterilization, etc.). Applications such as metal printing, cup printing, or printing inks for packaging and food contact materials which are intended for higher temperatures or differing storage conditions fall into this category.

Print samples which have been produced and dried according to their typical industrial application may also be produced using other substrates and be tested with other simulants, as long as the model

system is equivalent and represents the major part of the practical application of the respective ink system.

Storage and conditioning

Conditioning of printed samples to be subjected to migration analysis is dependent on how the material is delivered; typically, the printed samples are either on a roll, as a stack of sheets or as three-dimensional objects. Printed samples originating from a roll or coming from a stack of sheets should be, upon arrival to the laboratory, cut to a suitable size (typically A4), stacked (print to non-print side, containing preferably 20 or more test specimens), and the stack should then be wrapped in aluminium foil. The aluminium foil should not contain any coating that can interfere with the subsequent analysis. Ideally, a “blank” stack of material should be wrapped separately in aluminium foil and should be subjected to the same conditioning and analysis as the printed samples under scrutiny. Samples originating from a roll of material do not need further conditioning if the roll of material has already been subjected to conditions typical of production. If possible, three-dimensional objects should be stacked and wrapped in aluminium foil in a manner like two-dimensional objects. If this is not possible, the printed samples should be wrapped in aluminium and subjected to temperatures and humidities either typical of production (if not already subjected to such) or as defined in Annex C.

When sampling for further analysis of a stack, the top and the bottom 5 layers should be discarded (for stacks containing more than 20 layers). Sampling is then done from the middle of the remaining substrates.

4.2.2. Selecting migration parameters

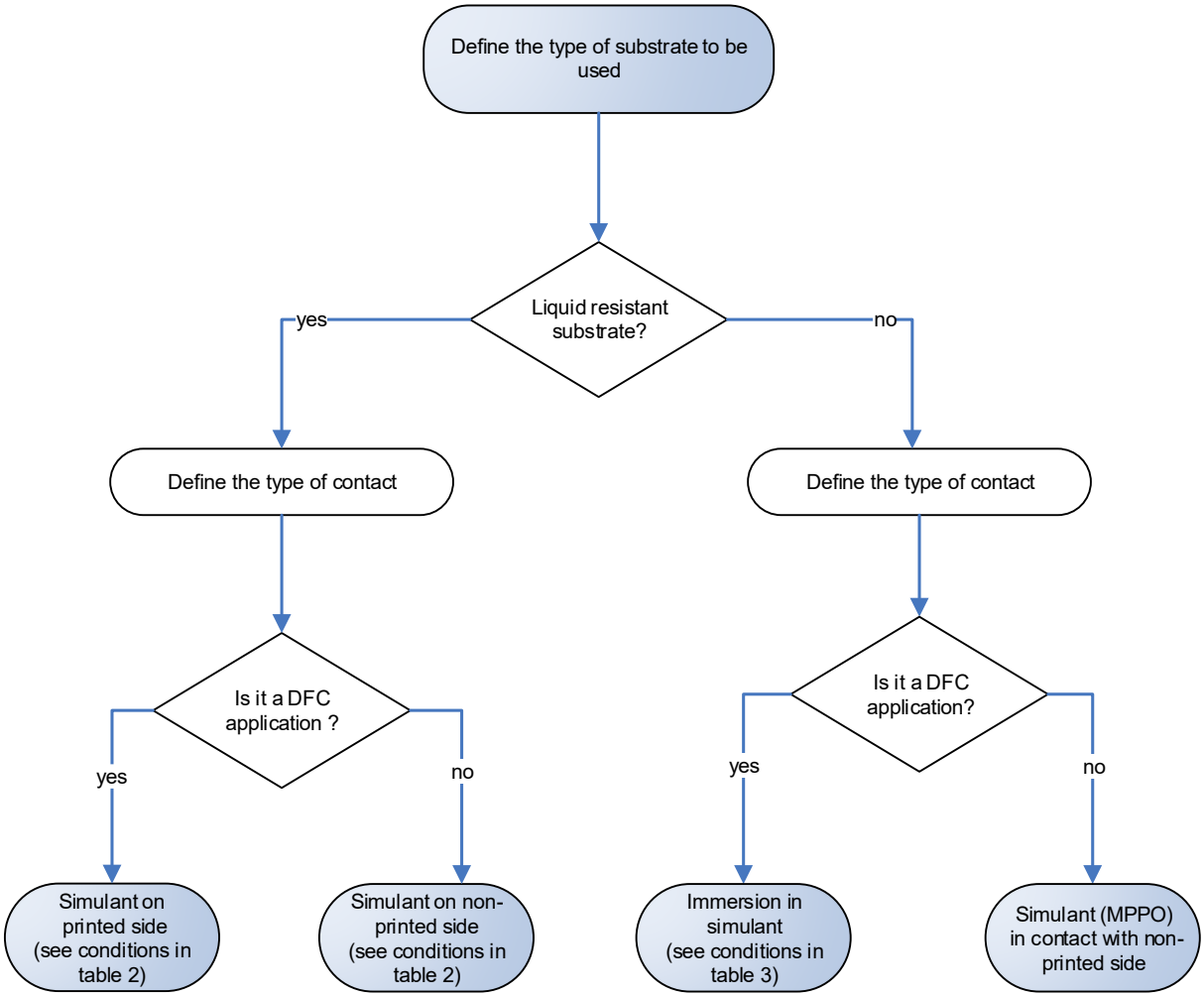
Selection of migration cells

Assorted designs of migration cells are shown in EN 13130-1:2004. The surface area to volume ratio is a crucial factor where there may be reduced migrant solubility. Therefore, a minimum ratio of 1 mL : 1 cm^2 is recommended. For 95% ethanol, a reduced area to volume ratio can be used, as it is a stronger solvent for typical migrants.
Ethanolic solutions used over 10 d at 60°C can result in leakage from the migration cell; this leakage is mainly evaporative in nature. Minimum recovery of the simulant should be 80%.

It is important that the correct side of the sample is exposed to the simulant. For example, *direct* food contact applications require that the printed side is in contact with the simulant. Conversely, for *non-direct* food contact applications, the reverse side should be exposed to the simulant.

Selection of testing conditions

To define the appropriate conditions, it is required to determine the nature of the substrate and the type of contact (non-direct/direct) and the food properties:



Definition of immersion/migration conditions

The worst-case simulants and testing conditions mentioned in tables 2 and 3 should be used, if the real case is not known explicitly. or if a worst-case testing is needed. Otherwise it is recommended to choose simulants and testing conditions that resemble the real case as close as possible.

If there is evidence that the simulants given in tables 2 and 3 do not represent worst-case conditions for specific migrants, a more appropriate simulant should be used (see section 4.4).

Alternatively, the Arrhenius equation can be used as a screening approach to calculate different time-temperature conditions as also mentioned in section 2.1.4 of Annex V of the Regulation (EU) No. 10/2011. The Arrhenius equation can only be used for plastics where the migration is controlled by diffusion and the polymer properties are not greatly affected by increasing temperatures for accelerated test conditions.

Selection of immersion/migration conditions

In this section worst-case simulants and testing conditions for migration tests (table 2) and immersion tests (table 3) are defined, which should be used, if the real case is not known explicitly, or if a worst-case testing is needed. Otherwise, it is recommended to choose simulants and testing conditions that resemble the real case as close as possible. Short contact time is only relevant for DFC application.

A Migration conditions

Table 2: Worst Case migration (printed or non-printed side) testing conditions

Food Type	**Liquid - Moist**				**Dry**			
Simulant	EtOH 95%*				MPPO***			
Food contact time [d]	< 1		> 1		< 1		> 1	
Food contact temperature [°C]	< 40	> 40	< 40	> 40	< 40	> 40	< 40	> 40
Testing temperature [°C] **	max 40	max 60	max 40	max 60	40	60	40	60
Testing time [d]**	1	1	10	10	1	1	10	10

* Other simulants can be used for some specific applications (see also justified deviations, section 4.4).
** The temperature and time of the testing conditions may be adapted to the real contact conditions
*** MPPO is also recommended as simulant for high-temperature applications [7]. However, MPPO is known to overestimate migration of some migrants compared to real food, and a reduction factor or measurement in real food might be needed for compliance measurements [11] [12].

Regulation (EU) No. 10/2011 specifies three different testing regimes (10 d at 40°C, 10 d at 50°C, and 10 d at 60°C) dependent on product storage conditions. The regulation also states that substrates should not be altered by the applied conditions [13]. If this is case, please refer to section 4.4.

B Immersion conditions

Table 3: Worst Case immersion testing conditions (based on EN 645, EN 647, EN 15519)

Food Type	**Liquid hydrophilic**				**Fatty (liquid or dry)**			
Simulant	Water				EtOH 95%**			
Food contact time [d]	< 1		>1		< 1		>1	
Food contact temperature [°C]	< 40	> 40	< 40	> 40	< 40	> 40	< 40	> 40
Testing temperature* [°C]	23	max 80	23	max 80	23	max 60	23	max 60
Testing time* [h]	24	2	24	24	2	2	24	24

* The temperature and time of the testing conditions may be adapted to the real contact conditions
** Other simulants can be used for some specific applications (see also justified deviations, section 4.4).

For immersion in organic solvents including special cases, testing conditions may need to be modified. Testing temperatures should not exceed the boiling point of the solvent. Additionally, duration of immersion test longer than 24 hours is not necessary.

For paper and cardboard applications, the sample preparation depends on the grammage of the paper and board substrate. The details are given in the table 4 below:

Table 4: Sample preparation dependent on grammage

paper grammage [g/m²]	sample weight [g] for 200 ml of liquid simulant
< 50	5
> 50	10

Specific test methods for DFC application

For some applications listed in Annex D it might be necessary to do additional testing, examples can be found in Annex E.

4.3. Specific migration: analytical identification and quantification

4.3.1. Targeted analysis (IAS/NLS/NIAS)

Targeted analytical methods are employed for the quantification of IAS, NLS and known NIAS in migration samples. The selection of analytical techniques for the determination of specific migration depends on (i) the physical and chemical properties of the potential migrants (e.g. volatility, polarity, functional groups and concentration), and (ii) the nature of the food or food simulant (e.g. aqueous or fatty).

The website of the European Union Reference Laboratory for Food Contact Materials (EURL-FCM) provides a collection of more than 400 analytical methods concerning specific migration. [6] Additional methods are described in the CEN Standards [5].

For targeted analysis of known organic compounds, gas chromatography or liquid chromatography coupled to mass spectrometry (GC/MS and LC/MS) are recommended for most migrants. Additional techniques such as the ones shown in Table 5 may also be applicable depending on the chemical nature of the migrants and the matrix.

Accurate quantitation is achieved by calibration against analytical standards of the migrants. When a standard of the migrant is not available, the migrant can only be quantified against either (i) a solution of the migrant with an assumed purity, or (ii) one or more structural analogues for which analytical standards are available. It should be noted that, even when the analogue is structurally similar to the analyte, these alternatives may result in inaccurate quantitation.

Table 5: Sampling and Detection methods for analytical identification and quantification

	Sample Introduction	Detection Method	Example Analytes of Interest*
GC	Headspace (HS) Solid Phase Microextraction (SPME) Purge and Trap	Mass Spectrometry (MS or MS/MS)** Flame Ionization Detection (FID)	Monomers, Residual Solvent Analysis, Glycols
	Liquid injection: Hot split and splitless injection Programmable Temperature Vaporization (PTV) Backflush Injection	Mass Spectrometry (MS or MS/MS)** Flame Ionization Detection (FID)	Monomers, Oligomers, Plasticizers, Photoinitiators, Glycols, Additives
LC	Liquid Injection: HPLC UHPLC***	Mass Spectrometry (MS or MS/MS)** Diode Array Detection (DAD)	Oligomers, Photoinitiaors, Primary Aromatic Amines, Antioxidants, Polymeric Plasticizers, Additives
Trace Metal Analysis	Liquid Injection	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	Al, Ba, etc.

*Analytes are not limited to the examples listed in the table. Crossover between sampling methods and detection methods may occur for analytes of interest.

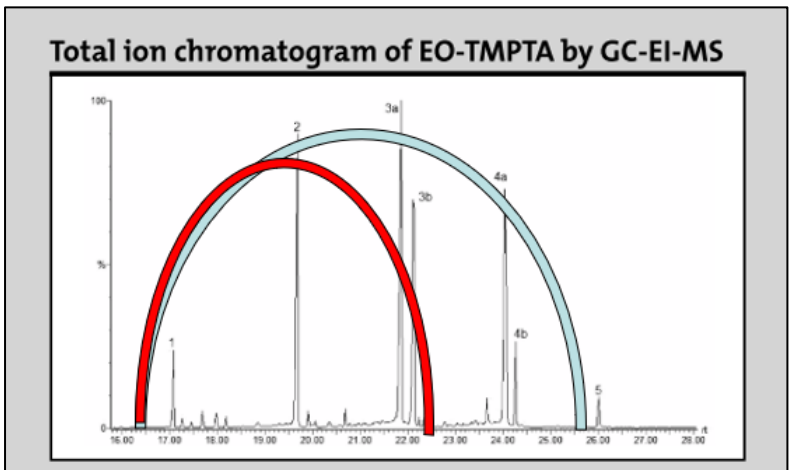
**The analyte of interest should be considered when choosing the appropriate ionization technique for MS detection.

*** Electrospray ionization (ESI) provides the widest range of applicability including large molecules and thermally labile compounds. Atmospheric pressure chemical ionization (APCI) is well suited for compounds with aromatic structures and some lipids. Atmospheric pressure photoionization (APPI) is well suited to nonpolar compounds.

Quantitation of substances that have a molar mass distribution

Printing inks may contain substances that follow a so-called molar mass distribution. Built into the chemical structure of these substances are repeating units (often alkoxylations). The mass distribution arises because the number of incorporated units is not uniform within the raw material. For example, an alkoxylated substance may be composed of 5% species that have a single alkoxylation unit, 20% species that have two alkoxylation units, 60% species that have three, and 15% species that have more than three.

The presence of the mass distribution poses additional challenges to the quantitation of the substance, especially when analysing in migration simulants. After all, the migration potential may differ greatly between the species. The result is that the mass distribution observed in the raw material or analytical standard used for the calibration for the analytical method may not be observed anymore in the migration simulant. This is illustrated in the figure below.



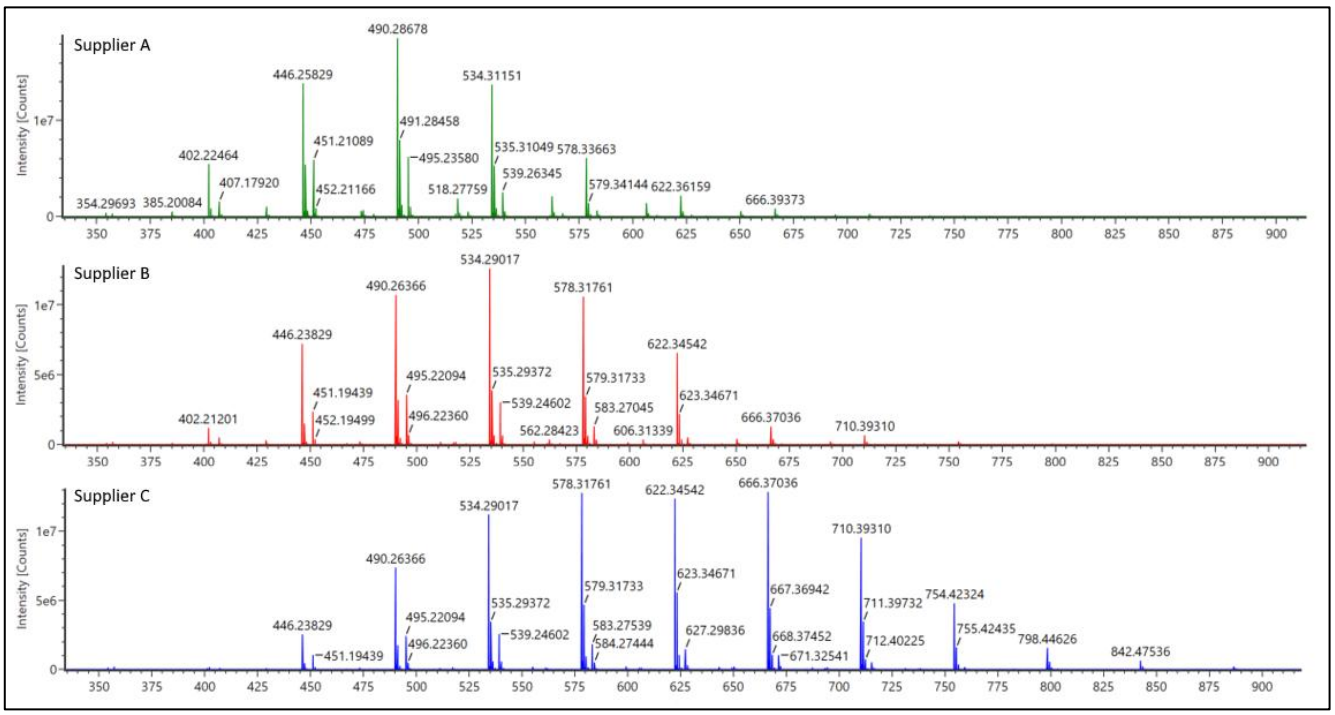
Mass spectra of ethoxylated acrylate monomers used on food packaging prints.

Common Name	RI	Total EO units	Characteristic fragment ions, m/z (%)	MW
EO-TMPTA	1828	0	Peak 1: 55(100), 68(11), 152(10)	296
	2085	1	Peak 2: 55(100), 99(64)	340
	2323	2	Peak 3a: 99(100), 55(58)	384
	2352	2	Peak 3b: 55(100), 99(56)	384
	2592	3	Peak 4a: 99(100), 55(49)	428
	2611	3	Peak 4b: 55(100), 99(77)	428
	2852	4	Peak 5: 99(100), 55(61)	472

GC-MS total ion chromatogram of EO-TMPTA, a substance with a molar mass distribution, as published in [14] *.The red and blue arches were added by EuPIA to illustrate that, for a specific food packaging application, the masses which migrate (red arch) may not overlap with the masses that can be detected in the EO-TMPTA raw material (blue arch).*

Failing to adequately address this can result in massive over-estimations of the migration concentrations; massive under-estimations of the migration concentrations; or may even lead to non-detection of migrated substances.

Further complicating this matter is the fact that two raw materials "A" and "B" may have the same CAS number whilst having very different mass distributions. This may occur for example when A and B are sourced from two different suppliers which synthesise their raw materials under differing conditions of production (see illustration below). On top of that, a single raw material supplier will often offer several versions of a certain substance, in which the different versions have a different molar mass distribution.



Mass spectra of three raw materials. All three raw materials have the same CAS number, but were sourced from different suppliers. Large differences in the mass distributions were observed, especially in the lower mass ranges.

Ideally, each of the species within the distribution are quantified against an analytical standard of said species, and subsequently the migration concentrations are summed across all species in order to assess if migration remains below the SML. Where available such standards should be used, however generally analytical standards for separate species are not commercially available.

To address the pitfalls in quantifying substances with a mass distribution in migration simulants, the following recommendations are made:

1. In absence of analytical standards for each of the species, one should first determine the molar mass distribution in the raw material, preferably using a universal detector. Once the contribution of each species is known, the distribution should be ratioed to the reference material when creating the calibration curves for each of the species. This will allow accurate quantitation of each separate species in the migration simulant. Finally, the migration concentrations of all species are summed to achieve the final migration concentration.

2. The method under (1) should include all migrating species.

3. Calibration of the analytical method should be performed with an exact sample of the raw material that is used in the printing ink formulation. Printing ink suppliers are encouraged to provide such samples when needed by third-party partners.

4. When migration of substances with a mass distribution are reported, the migration report should state which reference material was used for the quantitation, which species of the substance were considered in the quantitation method.

4.3.2 Non-targeted analysis (NLS/NIAS)

Non-targeted analytical methods are employed to screen for unpredicted NIAS. A thorough characterisation of the raw materials prior to migration testing is essential for determining the type of NIAS that should be considered. Screening of unpredicted NIAS is preferably conducted by GC/MS and LC/ESI (positive and negative)-MS analysis. These techniques are selective and sensitive. Spectral libraries and structural elucidation tools are available that help identify the compounds detected. The combination of the two techniques allows migrants with a wide range of molecular masses, polarities and volatilities to be detected.

The recommended scanning ranges for GC/MS and LC/ESI-MS scouting methods are m/z 40-500 and m/z 80-1000, respectively.

Identifying unpredicted NIAS

Unpredicted NIAS are frequently present at very low concentrations in the migration samples. The following sample preparation strategies are recommended to increase the likelihood of detection of unpredicted NIAS at trace levels in food and simulants.

A. Extraction of printed samples

Printed samples are extracted with migration simulants using the minimum amount required to cover the printed surface followed by sonication to facilitate the extraction of compounds. In the resulting solution, the potential migrants are present at higher concentrations than in actual migration samples, thus increasing the probability to detect low-level substances.

B. Pre-concentration of migration samples

Direct extraction of printed samples may result in the dissolution of the printed ink. The analysis of a sample that contains vast amounts of raw materials may present strong and broad chromatographic peaks that interfere with the detection of co-eluting NIAS present at lower levels. Under those circumstances, it is preferable to concentrate actual migration samples for the screening of unpredicted NIAS instead of extracting the print with solvent. Techniques such as vacuum concentration can be used for reducing the amount of solvent in the migration samples, hence concentrating unpredicted NIAS. It should be noted that sample concentration may result in loss of volatile NIAS.

The resulting solutions from A and/or B are analysed by GC/MS and LC/MS applying screening methods, and the m/z ratios of the peaks observed are recorded. A search for these ions is later performed during the analysis of the actual migration samples. Extracted ion chromatograms are useful for revealing unpredicted NIAS present at low levels.

GC/MS data identification is predominantly made by comparison of the acquired component mass spectrum to commercially available libraries. The NIST database is the world's most widely used mass spectral reference library.[2]

Identification using LC/MS can also be performed using mass spectral libraries. However, current commercial LC/MS spectral databases include limited information regarding inks. As a result, the identification of unpredicted NIAS relies primarily in structural elucidation.

[2] A general guidance for library matching using the NIST MS Search Program is as follows: matching Score: > 900 – excellent match, matching Score: 800-900 – good match, matching Score: 700-800 – fair match.

Library match and/or structural elucidation are insufficient to confirm identity. Ideally, the identity is confirmed by comparison to standards. Accurate identification requires sufficient information on the synthesis process of the ink raw materials [2], especially when no standards are commercially available.

Quantitation

After identification the migrant should be quantified by target analysis (see section 4.3.1).
If the chemical structure on the NIAS remains unknown despite structure elucidation efforts, quantitative estimation of the NIAS is conducted by reference to the response of a known amount of another compound deliberately introduced to the test solution, i.e. an internal standard. There can be a significant error as a result of this type of calculation, as compounds can respond quite differently to one another in mass spectrometry.

4.4. Justified deviations from the recommended methods

Changes which do not occur under worst foreseeable conditions of use

The aim of the methods in this document is to provide a guideline reference for the execution of worst-case tests to assess whether a product is fit for purpose. However, whenever a method effectuates a physical or other change to the test sample, the test must be carried out under the worst foreseeable conditions of use in which these changes do not occur [13].

Situations in which the recommended methods are not suitable can be divided into (i) physical changes to the printed test substrate, and (ii) chemical changes to the migrating compounds. Known examples are given below.

Examples of physical changes to the printed test substrate

- Regulation (EU) No. 10/2011 specifies three different testing regimes (10 d at 40°C, 10 d at 50°C, and 10 d at 60°C) dependent on product storage conditions. The regulation also states that substrates should not be altered by the applied conditions [13]. Therefore, it is recommended to use 10d at 40°C and extrapolate to 10 d at 60°C where required using migration modelling. Higher temperatures can be used for migration testing if the substrate is not altered. For example ethanolic solutions used with polypropylene substrates (≤ 35 µm thickness) at 60°C can result in penetration of the film by the solvent, producing extraction rather than migration testing. Similar changes are known to occur when other plastics are subjected to ethanolic solutions at 60°C.

- Acetic acid solutions cannot be used with aluminium foils due to the formation of aluminium acetate and resulting damage to the substrate.

- Olive / vegetable oils contain components which can penetrate silicone elastomer matrices, which results in an overestimation of migration compared to real food when using these substrates; the same applies to the simulants isooctane and 95% aq. ethanol. A proposed solution is to use MPPO which does not penetrate silicone elastomer matrices.

- For polyamide substrates, isooctane is the preferred worst-case simulant: 95% aq. ethanol solutions have the same polarity range as polyamide, leading to substrate damage.

- Swelling effects can occur e.g. when iso-octane is in contact with polyolefins or when food simulants with high ethanol contents (50% or 95%) are in contact with polyesters, in particular at elevated temperatures (60°C).

- For some DFC applications 95% aq. ethanol is not suitable as a simulant due its possible degradation of the ink layer.

Examples of chemical changes to the migrating compounds

- Cases of the degradation or further reaction of photoinitiators during exposure to simulant solutions have been reported. For example, Irgacure 819 (CAS No. 162881-26-7) yields TPO-L (CAS No. 84434-11-7) in ethanolic solutions. Such conversions may cause false positive and/or false negative results if the chosen solution poorly simulates the properties of the real food.

- Deuterated benzophenone internal standards are known to undergo exchange reactions with non-deuterated species in some solutions.

- Acrylates may be transesterified in alcoholic solutions.

- Thermal decomposition of ink/coating components during analysis has been reported, producing detectable artefacts: notable examples include some pigments/pigment additives, polyurethanes, photoinitiators and ATBC/tributyl aconitate.

5. References

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6. List of abbreviations

AAS	atomic absorption spectroscopy
APCI	atmospheric-pressure chemical ionization
APPI	atmospheric-pressure photoionization
aq.	aqueous
BOPP	biaxially oriented polypropylene
Bp	boiling point
CAD	charged-aerosol detector
d	day(s)
DAD	diode array detection
ESI	electrospray ionization
FID	flame ionization detector
GC	gas chromatography
q-TOF	quadrupole-time-of-flight detection with collision induced fragmentation
HPLC	high performance liquid chromatography
HS	headspace
IAS	Intentionally added substance
ICP	inductively coupled plasma
LC	liquid chromatography
MPPO	modified poly (phenylene oxide)
mol. wt.	molecular weight
MS	mass spectrometer (detector)
NIAS	Non intentionally added substance
NLS	Non listed substance
OES	optical emission spectrometry
OPP	oriented polypropylene
PAA	primary aromatic amine(s)
PI	photoinitiator
PTV	programmable temperature vaporizer
SPME	solid-phase micro extraction
TOF	time of flight
UHPLC	ultra-high-performance LC

Annex A: Calculation of maximum possible migration; formula and example

The formula below is intended for calculations

- near the specific migration limit of compounds which are present at ppm levels in a coating
- in worst-case scenarios
- that are not limited to the Euro cube convention
- independent of the area used in the migration experiment

The formula can be rearranged to calculate the maximum tolerable content in an ink or coating from a given SML.

$$c_{max} = m_{ink} \cdot c_{ink} \cdot a_{spec} \cdot 0.01$$

c_{max}	maximum content of a migrant in foodstuff in the worst case, in [µg/kg] i.e. [ppb]
m_{ink}	mass of liquid ink or coating applied to packaging in [g/m^2]
c_{ink}	content of migrant in ink or coating in [ppm] i.e. [µg/g]
a_{spec}	specific surface area of foodstuff in [dm^2/kg], is 6 dm^2/kg for the EU cube*

The factor 0.01 comes from conversion of dm^2 to m^2, with 1 dm^2 = 0.01 m^2 or 100 dm^2 = 1 m^2.

Example. Does the content of compound A in ink or coating comply with the SML (worst case)?

compound A (not evaluated toxicologically) working quantification limit = 10 µg/kg (ppb)

4 g of ink or coating applied per m^2 m_{ink} = 4 g/m^2

compound A content in ink or coating is 40 ppm c_{ink} = 40 µg/g

packaging complies with Euro cube a_{spec} = 6 dm^2/kg

c_{max} [µg/kg] = m_{ink} [g/m^2]* c_{ink} [µg/g] * a_{spec} [dm^2/kg] * 0.01

= 4 * 40 * 6 * 0.01 [µg/kg]

= 9.6 [µg/kg] (ppb)

In the worst case, the maximum content of compound A in foodstuff would be slightly lower than the SML.

*For inkjet, there are some applications (product identifications/codes) where the print area is fixed while the overall packaging area might not be known. It is recommended to estimate the total amount of ink printed (m_{ink}) for this application. The worst-case concentration in the food (based on the mass of a small candy bar, 25 g) can then be determined:

$$C_{max} = m_{ink} \text{ [g]} * c_{ink} \text{ [µg/g]} / 0.025 \text{ kg}$$

Annex B: Calculation of maximum possible migration: Digital printing applications

For digital printing applications producing articles with full ink coverage (many graphical and industrial end uses) the treatment outlined in Annex A is appropriate, with ink weight calculated as a function of film thickness (known for a given printing device) and ink density.

$$m_{ink} = f_{ink} \cdot \rho_{ink}$$

m_{ink}	mass of liquid ink or coating applied to packaging in (g/m^2)
f_{ink}	film thickness of coating (µm).
ρ_{ink}	density of liquid ink or coating applied (g/cm^3)

However, for some applications (e.g. continuous inkjet printing where the coverage of the ink on the substrate is limited), the mass of ink deposited per m^2 (m_{ink}) is calculated from the number of drops deposited in the printed image and the mass of each drop, both of which are known for a given printing device.

$$m_{ink} = (\frac{4}{3}\pi r^3 \cdot n \cdot \rho_{ink})/A$$

m_{ink}	mass of liquid ink or coating applied to packaging in (g/m^2)
r	droplet radius (cm)
n	number of drops printed
ρ_{ink}	density of liquid ink or coating applied (g/cm^3)
A	area of packaging (m^2)

The calculated mass can then be applied via the treatment in Annex A.

Annex C: Storage/Conditioning of print samples

Time / Temperature / Air humidity:
As described, conditioning of the aluminium-wrapped stacks of printed substrates should preferably be conducted at the customer's premises under realistic conditions. Alternatively, storage carried out in the laboratory should be conducted either according to the customer's requirements, at ambient humidity for 6-10 d at 23±2 °C or according to conditions relating to real applications.

Pressure:
Preferably, a uniform pressure should be applied to the stack of two-dimensional substrates wrapped in aluminium foil. If no other data is available a minimum pressure of 1 kg/dm² should be applied to the stack, such that the substrates are in intimate contact – thus the whole area of the printed substrates to be analyzed should be subjected to pressure [15]. It has been shown that pressure does not have a major influence on the set-off. Higher pressure can be applied if deemed appropriate.

For stacks of three-dimensional objects, a pressure should be applied typical of real-life conditions without deforming the three-dimensional structure. A realistic contact between each substrate/object should be ensured.

Annex D: Typical examples of DFC application

The table below contains a non-exhaustive list of typical indicative examples. In real applications, the specific case needs to be considered.

Table 7 Examples of DFC applications

Contact category	Contact time	Applications
intentional	long term	**Internal technology coatings like:** antifog, anti-mist coating, slip agent, protection lacquer aluminium foil heat seal lacquer blister/dairy foil (inside ink + OPV)
		direct print inside retail pack (e.g. lucky winner codes)
		cold seal adhesives
		ice cones stored with biscuit (outside ink + OPV)
	short term	paper cups
		paper straws
		clamshell (fast food) boxes (inside) Fries sleeve
		party plates
reasonably foreseeable	long term	confectionary inlays / chocolate box inserts
		tea bags with cardboard tags
		muffin cups (see also the paragraph “specific methods”)
		self-adhesive labels/ fruit labels
	short term	pizza boxes exterior fast food boxes / sandwich board(outside)
		burger/sandwich wrapper bakery bags
		tray liners place mats printed table clothes
		paper kitchen towels napkins

Annex E: Specific test methods for DFC application

Similar to the testing conditions in 4.2.2., the worst-case simulants and testing conditions specified below should be used, if the real case is not known explicitly, or if a worst-case testing is needed. Otherwise it is recommended to choose simulants and testing conditions that resemble the real case as close as possible.

- *thermo-extraction for muffin cups*

  Food contact side MPPO migration test conducted at elevated temperature with subsequent ambient temperature incubation for 3 d. Migration cells are incubated in the oven at elevated temperatures to simulate baking (180°C up to 60 minutes)

- *paper straws*

  Cut one straw into pieces of length ≤ 1 cm. Weigh ±1 gram of straw pieces into a 50 mL conical glass flask with a wide neck ground glass stopper and note down the amount weighed. Add 20 mL of simulant and incubate at the temperature indicated in Table 8. Make sure that the straws are fully immersed for the duration of the test. If necessary, filter the extract and adjust volume to 25 mL. After quantification, calculate back to the amount of the substance per paper straw.

Table 8. Test conditions for paper straws

Simulant	Water Extract for PAA analysis	Water	3% Acetic Acid	50% Ethanol
Temperature (°C)	23	23 or 60	23	23 or 60
Time (hours)	24	2	2	2

- *PAA analysis by migration or immersion testing*

  The Plastic regulation (EU) N° 10/2011 requires that “Plastic materials and articles shall not release primary aromatic amines, excluding those appearing in Table 1 of Annex I, in a detectable quantity into food or food simulant. The maximum detection limit is 0.010 mg of substance per kg of food or food simulant. The detection limit applies to the sum of primary aromatic amines released.
  For PAAs classified as CMR 1A or 1B according to Regulation (EC) No 1272/2008, a migration limit of 0.002 mg/kg applies.

  For further details, refer to BfR recommendations XXXVI on paper and board for food contact and BfR Opinion No 021/2014 as of 24 July 2013 - The French information note 2006-156 of DGCCRF section on paper and cardboard - The Dutch Commodities Act (Packaging and Consumer articles) Regulation, chapter II.

  When the pigments used in the tested inks may contain residual PAA, it is recommended to measure their content, obtained by migration or extraction, in the simulants. PAAs can be determined in a cold-water extract that is prepared according to the current version of the DIN EN 645:1994-01.

Recommended conditions for migration testing:

- 2 dm² for 100 mL or a minimum ratio of 1 ml :1 cm² according to CEN standard EN 13130-1
- use appropriate food simulant
- 10 d at 60°C (can be adapted according to final application)

Recommended conditions for immersion testing:

- 10 g of samples in final volume of 250 mL of simulant or equivalent ratio (see EN 645 for details)
- distilled water
- 24 h at 23°C

Recommended analytical methods:

Analytical methods using HPLC-MS/MS involving positive electrospray ionization (ESI+) are commonly used, as described through scientific articles.[3] Additionally, a European standard was published in May 2017.[4] This document describes two representative methods to determine the extractable amount of 22 specific PAA in a water extract of paper, board and pulp samples using a HPLC-MS/MS method.
Initially applicable for determination of the 22 PAA mentioned in the annex of Directive 2002/61/EC, this method could be extended to analysis of further amines, as soon as appropriate validation is provided.

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