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BfR Guideline for risk assessment of non-intentionally added substances (NIAS) in the area of food contact materials

This guideline was developed by the BfR with advice from experts from the BfR Commission for Consumer Products. A targeted consultation was held with stakeholders in the area of food contact materials and the draft guidance was discussed with members of the EFSA FCM Network. A summary of the comments submitted, along with a brief explanation from the BfR regarding their consideration or non-consideration in the final version of this guideline, is presented in the annex.

Preliminary remark

This document is to be considered in connection with the BfR Guideline for the safety assessment of substances for the manufacture of food contact materials[1]. It is intended in particular to assist in the preparation and assessment of dossiers for the inclusion of new substances in the BfR Recommendations for food contact materials or in Annex 14 of the German Consumer Goods Ordinance. This document is not intended for compliance testing. However, the concept presented here or parts of it can also serve as guidance for other risk assessment projects in the area of food contact materials.

1 General information

According to Article 3 of the Regulation (EC) No 1935/2004 (“Framework Regulation”), food contact materials (FCMs) must be manufactured in such a way that they do not transfer components to food in quantities that may endanger human health. Risk assessments

[1] Guideline for the safety assessment of substances for the manufacture of food contact materials and articles:
EN: https://www.bfr.bund.de/cm/349/guideline-for-the-safety-assessment-of-substances-for-the-manufacture-of-food-contact-materials-and-articles.pdf
DE: https://www.bfr.bund.de/cm/343/leitlinie-fuer-die-sicherheitsbewertung-von-stoffen-zur-herstellung-von-lebensmittelbedarfsgegenstaenden.pdf

conducted by the BfR in the area of FCMs are carried out in accordance with the EFSA Note for Guidance[2] (NfG) in a stepwise, migration-dependent approach.

In addition to the intentionally added substances (IAS) used in the production of the FCM, the assessment also includes non-intentionally added substances (NIAS). In case of dossiers for new substances, NIAS refer to impurities and by-products in the substance(s) applied for as well as reaction and degradation products formed during production of food contact materials and resulting from the use of the substance(s) applied for.[1] Only NIAS with a molecular weight of less than 1000 Da are relevant for evaluation.[2] However, if substances (e.g. oligomers) are expected to be degraded in the gastrointestinal tract, they should be considered in the assessment, even if their molecular mass is larger than 1000 Da.

Table 1 : Data requirements depending on the migration according to EFSA NfG

Data request	**Migration (µg/kg food (simulant))**		
	< 50	**50 - 5.000**	**> 5.000 - 60.000**
At least 2 studies on genotoxicity[3] (mutagenicity, aneugenicity, clastogenicity) e.g. OECD TG 471 and TG 487	+	+	+
Subchronic toxicity (OECD TG 408)	-	+	+
Proof of absence of accumulation in humans	-	+	+
Chronic toxicity/ carcinogenicity	-	-	+
Reproductive/ developmental toxicity	-	-	+
Toxicokinetics (ADME)	-	-	+

IAS and NIAS must fulfil the requirements of the Framework Regulation (see above) in equal measure. However, it can sometimes be very difficult to prove the safety of NIAS. A first hurdle is the chemical-analytical identification and quantification of an often large number of unknown chemical structures. In addition, the provision of sufficient test material for toxicological tests can be problematic. The assessment approach presented here aims to generate – with reasonable technical effort – sufficient data for NIAS migrating into food to enable a risk assessment. However, it is important to emphasize that the document is not a rigidly prescribed procedure but a guideline that outlines the BfR's general expectations and scientific approach for the assessment of NIAS. Deviations from the procedure are possible, provided they are scientifically justified. The document, therefore, often deliberately omits strict boundaries, such as analytical thresholds in NIAS screening or the number of unidentified substances detected. Certain minimal requirements are described, and expert judgement is included. This approach has been chosen to allow both evaluators and dossier submitters sufficient room for a well-founded scientific discussion.

Traditionally, the prerequisites for the toxicological assessment of a substance are its identification and exposure quantification. However, strategies have been developed that may allow for the conclusion, that possible health risks are not to be expected even in the

[2] EFSA Note for Guidance For the Preparation of an Application for the Safety Assessment of a Substance to be used in Plastic Food Contact Materials: https://www.efsa.europa.eu/en/efsajournal/pub/rn-21

[3] EFSA Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2379

situation where not all migrating substances were identified. The minimum of chemical analytical methods that should be used in terms of substance characterisation are described in section 2 “Chemical/analytical identification and quantification of NIAS”. The procedure for the assessment of migrating NIAS is described in section 3 “Toxicological data requirements and assessment”.

TTC Concept

In 2019, EFSA emphasised that the TTC (Threshold of Toxicological Concern) approach is a screening and prioritisation tool.[4] It should not be used for substances for which EU food/feed legislation requires the submission of toxicity data. Based on the EFSA NfG, toxicological data must be submitted. Accordingly, BfR does not use the TTC concept for risk assessments in the area of FCM. However, the exposure threshold of 0.0025 µg/kg body weight/day for genotoxic carcinogens is accepted according to data analysis of the carcinogenicity potency database by Kroes and co-workers.[5] For organophosphates/carbamates, exposure has to be below 0.3 µg/kg body weight/day.[4]

2 Chemical/analytical identification and quantification of NIAS

The following section describes the requirements for the chemical/analytical determination of NIAS as part of the preparation of dossiers for the inclusion of new substances in the BfR Recommendations on food contact materials or in Annex 14 of the German Consumer Goods Ordinance. However, the analytical approach described is not applicable for compliance testing of final food contact materials, but it can also be understood as an orientation to which analytical methods the BfR believes can be used to identify and quantify NIAS that migrate from food contact materials into food.

2.1 General procedure[6]

The substance or mixture of substances to be used in the process of manufacturing a food contact material is referred to below as the “commercial product”[7]. NIAS can already be identified and quantified in the commercial product (e.g. impurities or by-products from the manufacturing process). The generally higher content of NIAS in the commercial product compared to the finished FCM can facilitate identification and quantification. The extract[8] of the finished FCM shall also be analysed. Based on the determined content, the theoretical worst-case transfer of NIAS from the finished FCM into the food can be calculated.

In general, if this theoretical worst-case calculation of the migration leads to the need to submit toxicological data (see Table 1), but such data are not available, a targeted

[4] EFSA Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5708

[5] Kroes et al., 2004: Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. https://doi.org/10.1016/j.fct.2003.08.006

[6] Note: Irrespective of the procedure for assessing NIAS, intentionally added substances (IAS) must always be adequately identified. IAS migrating into food with a molecular weight < 1000 Da must be quantified using targeted analysis (LOD, LOQ, recovery, calibration function, appropriate standard, stability).

[7] “Commercial product” refers to the substance or mixture in its formulation and as further used in the process. It is only relevant for dossiers for inclusion of substances or mixtures into the BfR Recommendations or Annex 14 of the German Consumer Goods Ordinance. It does not refer to and should not be confused with the finished food contact article to be put on the market.

[8] The term “extract” refers to an extraction as exhaustive as possible in a suitable solvent. Extraction efficiency should be demonstrated.

determination in the migrate[9] of the finished FCM or, if applicable, a migration modelling must be carried out.

Predictable NIAS (e.g. decomposition products of antioxidants, initiators, UV stabilisers or catalysts) should be determined in a targeted analysis. Quantification in the commercial product or extract/migrate of the finished FCM should be carried out using a suitable standard (identical or structurally related compounds). The specified LOD or LOQ must be analytically justified.

NIAS resulting from impurities/by-products in the starting substances for the manufacture of the commercial product should at least be taken into account by worst-case calculations and stated in the substance overview for dossiers to be submitted. Usually, relevant information can be taken from the specifications of the starting substances.

NIAS that are structurally closely related to each other (e.g. different oligomers) can be grouped appropriately and then quantified and evaluated.

Non-predictable NIAS:
Non-predictable NIAS are usually degradation and reaction products of the substance to be assessed that do not result directly from the intended function of a substance. They can arise during the manufacture of the commercial product or the finished FCM or during a post-treatment typical for this FCM.

At least a qualitative NIAS screening should be carried out from the commercial product. Signals that occur are then taken into account when analysing the finished FCM.

A NIAS screening shall also be carried out in the extract of the finished FCM (ideally in comparison to the untreated FCM). The requirements for this screening are described in section 2.2. To facilitate structural elucidation, the extract[8] should be significantly more concentrated than a migrate[9]. An at least semi-quantitative determination of the transferred substances should be carried out either in the extract or in the migrate. The worst-case transfer of NIAS found should be estimated using standard assumptions on surface/volume ratios according to the BfR Guideline[1].

An attempt at structure elucidation (see 2.3) must always be made if migration above 0.15 µg/kg food (corresponding to an exposure of 0.0025 µg/kg bw/day) is to be expected. The proportion of unidentified substances or signals in the migrate in relation to the total amount of migrating substances must be estimated.

In order to estimate the exposure more precisely, a substance found in the commercial product or the finished FCM can be specifically quantified in the migrate or its transfer into the food can be estimated by means of migration modelling.

Typical assumptions and procedures to estimate exposure from the different stages in the NIAS screening (commercial product, extract/migrate of the final food contact article) can be found in the aforementioned BfR Guideline[1].

[9] "Migration" in this document refers to the experimental or modelled transfer of substances into food or food simulants.

Table 2: Overview of screening procedures: Steps 1 and 2a are required for a NIAS screening, the subsequent steps can be adapted to the specific project or partially omitted. Step 2b is suitable, for example, for the differentiation of NIAS that are present in the final FCM due to the use of the commercial product to be evaluated from other unknown substances from the FCM matrix. The higher concentration of NIAS in extract 2a compared to migrate 3a can lead to a lower limit of quantification for the NIAS. Thereafter, the transfer of NIAS into food can be estimated without further migration studies (3a) using worst-case assumptions or migration modeling (3b).

Level	Screening object	Goal	Remark
1	Commercial product for evaluation	Identification and, if necessary, quantification of NIAS in the commercial product	
2a	Extract(s)[8] of the treated[10]/equipped FCM as exhaustive as possible	Identification and quantification of the content of reaction products	Material-dependent; depending on the number of expected reaction products; The concentration in the extract is expected to be greater than that in a migrate (3a) → more sensitive NIAS detection. Quantification is optional if quantification is subsequently carried out in step 3a.
2b (optional)	Comparison with untreated/non-equipped FCM	(Quantitative) comparison of migrating substances from treated/equipped and untreated/non-equipped FCM	Only NIAS that migrate due to the treatment with the commercial product are relevant for evaluation.
3a	Migrate(s) of the treated/equipped FCM	Exposure assessment	This step is optional if quantification was carried out in step 2a.
3b (optional)	Migration modelling based on the contents in the treated/equipped FCM	Exposure assessment	This step can replace 3a if quantification was carried out in 2a.

2.2 Requirements for the NIAS in screening

- Sample preparation must take into account material properties and possible substance losses (volatile substances, losses in the filtration step). The recovery must be evaluated.
- At least a GC-MS method and an LC-MS method or equivalent measurement methods must be used. If scientifically justified, it is possible to deviate from this requirement.
- The methodologies used should be optimised in order to achieve low LOD/LOQ, e.g. by using a suitable standard mix (e.g. leachable mix), by using identified ion fragments for subsequent MS/MS, or by optimising parameters of the chromatography.

[10] "Treated" means, the FCM is equipped with the commercial product.

- The quantification should be carried out at least via a one-point calibration (GC) or at least a three-point calibration (LC) of known substances in the respective matrix (extract/migrate).

2.3 The suitability of the NIAS screening method must be demonstrated exemplarily. Requirements for structure elucidation

- As a minimum, GC- and LC methods combined with MS or high-resolution MS should be used in combination with (spectra) databases or structure elucidation algorithms.
- Additional detectors such as UV/VIS or fluorescence can support the structure elucidation process.
- Spectroscopic methods (NMR spectroscopy) can also be useful.
- The identified structure should undergo a plausibility check; e.g. chemistry/impurities of the starting material must be considered in structure elucidation.

2.4 Review of the NIAS screening method

- It must be shown that the screening method is suitable for detecting a broad spectrum of NIAS and determining them at least semi-quantitatively. Suitable standards (e.g. commercially available leachable and extractable mixes) of known concentration (close to LOQ) must be used for this purpose.
- To test the recovery, the standards used should be spiked to the sample to be analysed (commercial product or finished FCM) at a known concentration close to the LOQ.
- In order to test the efficiency of the signal detection method (peak finder algorithm) and to include matrix effects, the corresponding extract/migrate should be spiked close to the LOQ or the samples generated for recovery should be used.

2.5 Requirements for the analysis of organo-chemical substances

E.g. Organo-polymers or low-molecular weight organic compounds:

- Oligomers or known impurities/additives should be quantified in the extract/migrate of the finished FCM. Quantification of migration can e.g. involve target analysis, grouping methods (homologues or structurally very similar substances) or modelling.
- If oligomers are expected to be instable in the gastrointestinal tract, they should be considered in the assessment, even if their molecular mass is larger than 1000 Da.
- For screening for unknown NIAS the above mentioned requirements apply (2.2).

2.6 Requirements for the analysis of inorganic substances

E.g. fillers, inorganic pigments

- Elements are to be analysed using ICP-MS or equivalent measurement methods.
- Organic contaminants such as organometallic compounds should be determined according to the above specifications.

2.7 Requirements for the analysis of mixtures

E.g. distillation mixtures, mixtures of natural origin

The analysis for NIAS in mixtures should be carried out essentially as specified above,

depending on the main constituents. In addition, the following points must be considered:

- Tests should be carried out for typical contaminants (e.g. pesticides, heavy metals, residues of natural ingredients such as alkaloids or allergens).
- The substances present in the mixture should be characterised and quantified as accurately as possible (e.g. GCxGC-MS/FID).
- Particular attention should be paid to batch-to-batch variability; accordingly, several batches should be analysed over a longer period of time (seasons, production cycles, etc.).

2.8 Requirements for the analysis of nanomaterials

If after particle size distribution a fraction below 100 nm is found, particulate NIAS should be chemically/structurally characterised in the same way as corresponding IAS (imaging methods for particle sizes, size distribution, shape, etc.). For this purpose, the requirements of the EFSA opinions "Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health"[11] and "Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles"[12] must be taken into account.

Alternatively, scientific data to proof that there is no migration of nanomaterial can be shown.

On a general note, regarding the chemical/analytical identification and quantification of NIAS it should be pointed out, that deviation from the procedure as laid out above (item 2 of this document) may be acceptable, if scientifically justified.

3 Toxicological data requirements and assessment

The following section describes the basic procedure and toxicological data requirements for the risk assessment of NIAS as part of the preparation of dossiers for the inclusion of new substances in the BfR Recommendations for food contact materials and in Annex 14 of the Consumer Goods Ordinance. However, in the opinion of the BfR the procedure can also be applied to other NIAS risk assessments in the area of food contact materials.

3.1 Basic approach

The toxicological assessment is carried out according to the procedure shown in Figure 1 and is explained in detail below.

When evaluating the chemical-analytical data for the structural elucidation of NIAS, three results are conceivable:

- The structure or the essential structural features of the respective NIAS can be elucidated, or
- the structure of the respective NIAS cannot be elucidated despite reasonable efforts, or

[11] EFSA Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2021.6768

[12] EFSA Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles: https://www.efsa.europa.eu/en/efsajournal/pub/6769

- the structure cannot be elucidated, but not all (appropriate) analytical options have been exhausted (see section 2).

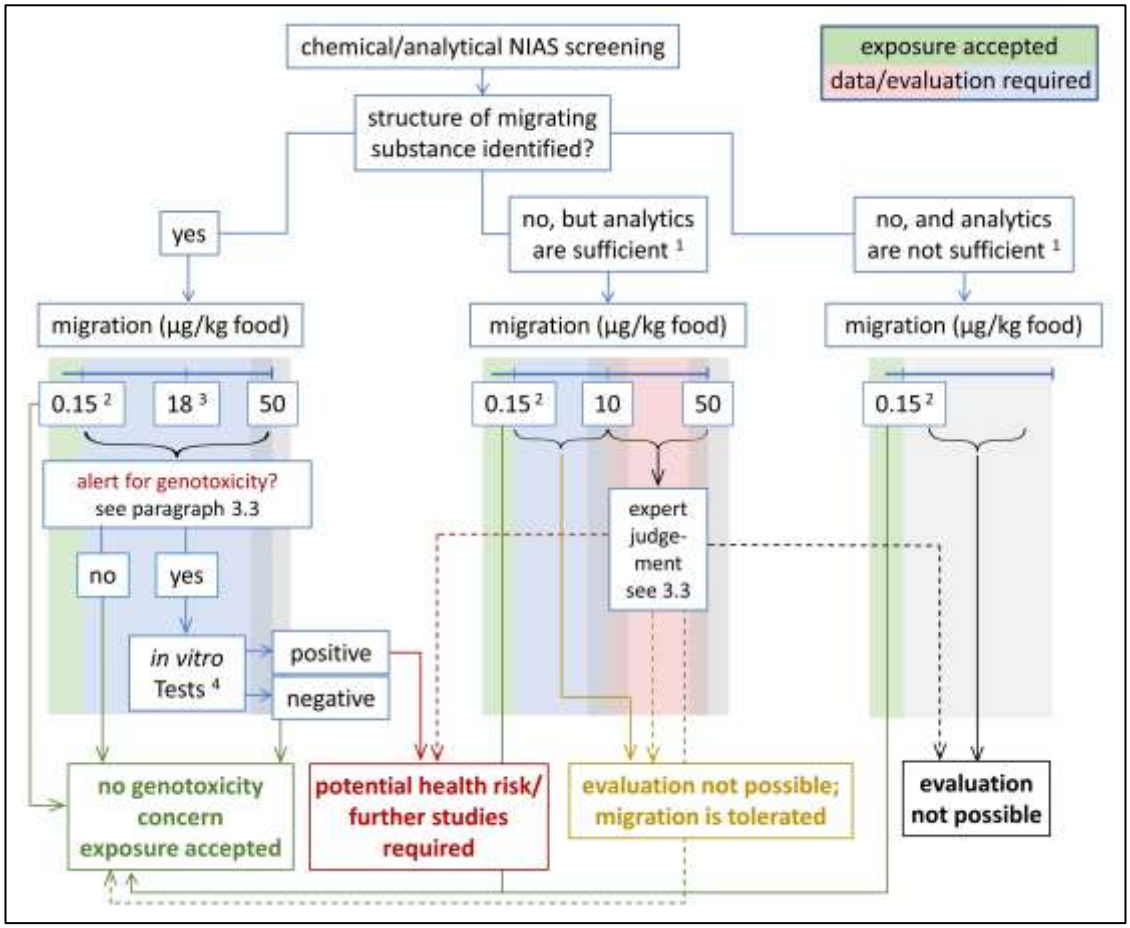

Figure 1: Flowchart for the toxicological evaluation of NIAS up to 50 µg/kg food.

[1] in the meaning of reasonable, technical effort for generating analytical data;

[2] based on carcinogenicity potency database[5]

[3] threshold for carbamates/organophosphates[4,5]

[4] OECD TG 471/487, or suitable tests for nanomaterials see EFSA Note for Guidance.

The data requirements for the toxicological assessment of NIAS (and IAS) are based on the migration of the substance into the food (simulant), in accordance with the requirements of the NfG (see Table 1). From this, the daily oral exposure of consumers can be estimated by applying the standard assumption that 1 kg of food in contact with the FCM is consumed per day. It should be noted that this is a conservative estimate because, on the one hand, migration into simulants overestimates the transfer into real food and, on the other hand, the assumption of 1 kg of food in contact with the FCM and being consumed per day usually overestimates the actual amount. Also, the quantification of NIAS migrating into food (simulant) can be subject to significant uncertainties resulting from limitations of the methodology (e.g. lack of individual standards and method validations or worst-case calculations or modelling of the actual migration). The limits shown in Figure 1 and discussed below to distinguish between different assessment situations are therefore not to be regarded as rigid values but as orientation values.

3.2 Assessment of substances with a migration of less than 0.15 µg/kg food

Applying standard assumptions, a migration up to 0.15 µg/kg food corresponds to a daily exposure of 0.15 µg per person. Even in the worst-case assumption that the respective substance is a potent mutagenic carcinogen (which is not the case for the vast majority of substances), the risk for an additional tumour disease is estimated to be one in one million persons.[5] This additional incidence is considered tolerable by risk management. Irrespective of whether or not the structure of NIAS has been elucidated, no toxicological data have to be submitted for this concentration range.

3.3 Assessment of substances with a migration between 0.15 and 50 µg/kg food

Substances whose migration exceeds 0.15 µg/kg of food must be evaluated according to the NfG with regard to their genotoxic potential. For the evaluation of IAS, experimental data from suitable genotoxicity tests must be submitted in order to obtain information on possible mutagenic, clastogenic and aneugenic properties. Ideally, this should be an OECD TG 471 and TG 487 study for soluble substances or other suitable tests for insoluble substances (nanomaterials, see NfG and EFSA Guidance on nanomaterials[12,13]). Further study requirements may arise.

In the assessment of NIAS, the data required by the NfG are in most cases not available or only available to a limited extent, as the substances are often not available in sufficient quantity and quality. In order to be able to carry out a risk assessment nevertheless, non-experimental data for the assessment of genotoxicity are also accepted for NIAS under the following conditions:

- **NIAS is identified, the structure is known:**
  As a first step a detailed data creation from well-established databases within the regulatory context is required e.g., EFSA OpenFoodTox, REACH database, eChemPortal. In the absence of experimental data, a well justified read-across is recommended. [1,13] If the analogue approach for read-across cannot be followed based on expert judgement, *in silico* predictions are also accepted for mutagenicity (i.e. the Ames test) and clastogenicity.[1] However, due to limitations of currently available *in silico* algorithms, for clastogenic and aneugenic effects as investigated with the *in vitro* micronucleus test, the experimental approach is preferred, if the substance is commercially available.
  If there are no indications of genotoxic potential, no further data need to be generated. If there are indications of genotoxic potential, experimental data are necessary for the assessment. The tests required by the NfG should always be carried out.
  If a NIAS is an organophosphate or carbamate, information on neurotoxicity (e.g. acetylcholinesterase inhibition test) should be provided. Alternatively, a maximum migration of 18 µg/kg food is also considered safe. This value corresponds to the threshold for carbamates and organophosphates in the TTC concept.[4,5]
  As long as oligomerisation does not introduce new functionalities, oligomers may be grouped and evaluated based on the toxicological assessment of the corresponding monomers (expert judgement). Consequently, the amount of migration of the oligomers should be added to the amount of migration of the monomers – especially

[13] EFSA Guidance on the use of read-across for chemical safety assessment in food and feed: https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9586

if the oligomers are expected to be unstable in the gastrointestinal tract and to decompose to the monomers.

- **NIAS cannot be identified despite reasonable chemical-analytical methodology:**
  A risk assessment is not possible. In a pragmatic effort/risk weighting and in view of the information provided in section 3.1, a migration up to 10 µg/kg food is tolerated. Migration between 10 and 50 µg/kg food are considered on a case-specific basis. For this, please refer to "Expert judgement" below.

- **Expert judgement**
  After sufficient effort, if substances migrating between 10 and 50 µg/kg food cannot be identified and the structure is unknown, read-across or *in silico* approaches cannot be utilized. Thus, case-by-case decisions will be made by expert judgement. Non-specific test methods, e.g. genotoxicity tests with a highly concentrated total migrate or extract, could be used to reduce the uncertainties in the assessment. Preferably, Ames- (OECD 471) and *in vitro* Micronucleus test (OECD 487) according to EFSA NfG should be applied, and the EFSA Recommendation "Genotoxicity assessment of chemical mixtures"[14] must be taken into account. In addition to these, data generated for the unidentified substances with new approach methodologies are supported for gathering more information on the unidentified substances and their possible mode of action. The decision on data requirements and as to whether the migration is tolerable or not is made by the evaluating toxicological and analytical experts.

- **NIAS cannot be identified and the chemical analytical methodology does not fulfil the minimum requirements:**
  A risk assessment is not possible.

3.4 Evaluation of substances with a migration of more than 50 µg/kg food

According to NfG NIAS migrating between 50 and 5000 µg/kg food must also be evaluated with regard to subchronic toxicity and accumulation potential in humans. This requires physicochemical data and a study according to OECD TG 408. For migration above 5000 µg/kg food, the chronic toxicity and carcinogenicity (e.g. OECD TG 453), the reproductive toxicity (e.g. OECD TG 443) as well as the absorption, distribution, metabolisation and excretion of the substance must also be evaluated.

If oligomers are expected to be unstable in the gastrointestinal tract and to decompose to the monomers, the amount of migration of the oligomers should be added to the amount of migration of the monomers – even if the molecular mass of the oligomers is above 1000 Da. Hence, data requirements for the monomers may increase.

A read-across is generally possible if the standard studies required are not available.[13] Whether an evaluation is possible on the basis of the available data is assessed by the evaluating toxicological and analytical experts.

[14] EFSA Guidance on Genotoxicity assessment of chemical mixtures: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5519

4 Annex 1: Summary of comments received during targeted consultation and answers of the BfR

With respect to the huge amount of comments received and the high number of comments more or less pointing to the same issues, the BfR decided not to provide individual responses to every comment, but set out a summary of the comments received.

The comments on the draft guideline can be divided into three main topics: general comments, comments on analytical requirements, and comments on toxicological requirements. Below, a summary of the received comments in these main topics is given, and important changes made to the document are outlined. Also, reasoning for not considering some of the comments is given.

Table 3: Summary of the comments on the draft NIAS guideline as provided to the BfR in a targeted consultation as well as respective answers of the BfR and changes included in the final guideline.

No.	Issue raised during targeted consultation	Answer of the BfR and actions taken (if any)
General comments:		
1	Concern was expressed, that the stated requirements may be misinterpreted as applying to routine compliance testing in the manufacture of food contact materials and articles. In this context, concern has also been raised that NIAS screening, as required here, is analytically unfeasible for most finished products, not least because there are no harmonised test methods and the time and cost involved would increase significantly.	The BfR clarifies that the guidance document is primarily intended for the submission of applications for BfR recommendations and dossiers under Annex 14 of the Consumer Goods Ordinance. Nevertheless, also apart from these cases, projects exist, where parts of the document may provide valuable guidance on how to perform risk assessment for NIAS found to be migrating from food contact materials (toxicological part) or how to set up an analytical research project for NIAS detection, identification and quantification. For example, in the updated risk assessment of NIAS from printing inks in bakery bags (opinion of the BfR No 008/2026), the BfR applied the toxicological part of this guideline. To clarify the matter, a sentence has been included stating that the document and the approach described therein do not refer or apply to compliance testing.
2	Figure 1 was criticised as being too complex.	Figure 1 was revised (also with respect to other comments) and simplified as far as possible.
3	Concerns were raised that the draft guidance document also refers to contaminants from recycling or other external sources, for which different methods to trace contaminants may be warranted.	The BfR clarifies that the analytical identification and tracing of contaminants throughout a recycling process and in the recycled material differs from the identification and quantification of NIAS during FCM production. Nevertheless, the flowchart may be applicable for the toxicological assessment of NIAS migrating from recycled FCM into food.

No.	Issue raised during targeted consultation	Answer of the BfR and actions taken (if any)
4	It was criticised that the guideline does not clearly state which materials it applies to.	The BfR clarifies that generally the guideline applies to substances relating to all FCM, for which the BfR carries out risk assessments.
5	It was requested to provide specific and more detailed definitions, for example for NIAS or worst-case scenarios in the document.	The BfR would like to point out that the guideline on the risk assessment of FCMs also applies. Reference is also made to this within the document. An explanation has been added to the text regarding NIAS in connection with the substances under application. The term 'commercial product' has repeatedly led to confusion and enquiries. A footnote containing an explanation has therefore been added.
6	It was suggested that the term 'no genotoxic risk' should be replaced with 'no genotoxic concern'.	The BfR agrees with this proposal and has made the corresponding amendment.
7	It was noted, that NIAS are generally not commercially available and that it is not possible to generate analytical and/or toxicological studies.	The BfR is aware of the fact that most NIAS are not commercially available for testing. This is the reason, why other methods are suggested in the guidance to derive information on release or physico-chemical and toxicological properties, such as in silico tools, semi-quantification, a well-justified read-across or at least a test on the concentrated whole migrate/extract. Possible approaches and methods are described in respective guidance documents of e.g. EFSA. However, if the suggested methodologies are not able to provide enough information or to dispel a concern, either more effort should be taken to investigate the substance in question, or more technological effort should be taken to make sure, that the substance is not released in significant amounts into food.
8	It was proposed that migration below 0.15 ppb in accordance with the TTC concept should only be accepted if it had been verified whether exclusion criteria apply.	The BfR did not implement this proposal into the final document, because the guideline is intended to be implementable with reasonable effort.
9	It was noted that the non-adult population seems to not be covered by the guideline. This comment is based on the assumption that 1 kg of packaged food is consumed everyday per default for an adult weighing 60 kg. This assumption does not apply to infants nor children.	The BfR clarifies that in this context, it is not intended to include a separate section for the assessment of NIAS in relation to non-adults. As in the Note for Guidance, the exposure thresholds triggering toxicological data are based on whole life consumption/exposure and do not discriminate between different population groups. Concerns arising for specific population groups such as infants or children, will always be addressed.
10	It was noted that the analytical part of the guideline does not address NIAS arising from storage.	The BfR is aware that these and other limitations are inherent to the concept. During assessment of dossiers, requests regarding NIAS from storage are made if expert judgement deems it necessary. In addition, the toxicological part may

No.	Issue raised during targeted consultation	Answer of the BfR and actions taken (if any)
		be used for risk assessment of NIAS found to arise from storage.
11	It was noted (and criticised), that the possibility of accepting unknown substances with migration levels of up to 10 ppb may represent a paradigm shift to current FCM assessment, which may reduce consumer safety.	The BfR is aware that this approach might cause irritation. However, this concept is not new to FCM (compare e.g. Regulation (EU) No 10/2011). The approach presented in the guidance is intended to include both, a sufficient level of safety for consumers and a manageable amount of analytical and toxicological effort for applicants or dossier submitters to characterise possible NIAS. We believe that the approach will stipulate efforts to more profoundly address NIAS (below and above 10 ppb), which will increase consumer safety. It has to be noted, that for every assessment, no matter how much effort is invested, uncertainties and data gaps will remain. This does not automatically mean, that there is a health risk for consumers. However, we emphasize that expert judgement is applied at every stage, and a rigorous approach to potentially critical structures is maintained (please also refer to answer to question No 14). In order to gain the best possible knowledge about the migrating NIAS it is important that throughout the entire process, the context of the substance(s) being assessed and its/their manufacturing process must be kept in mind. To this end, a new paragraph has been included stating that the identified structure(s) of the NIAS should undergo a plausibility check; for example, the chemistry and impurities of the starting material must be considered in structure elucidation. If the composition of the starting material (including impurities) and the manufacturing process are considered, it is quite unlikely that migration of additional substances with completely unexpected chemical entities (and, thus, toxicological profiles) occurs.
12	It was stipulated that the application of the guideline should not inadvertently require the most sensitive and broad analytical methods. Its scope should clarify the roles of supply chain actors and distinguish between NIAS assessments for BfR recommendations/Annex 14 (German Consumer Goods Ordinance) and migration evaluations under Regulation (EC) No 1935/2004. Concerns include the burden on small and medium enterprises and the potential need for a shared database of analytical results.	The BfR clarifies, that the guideline is aimed at applicants or dossier submitters, regardless of which part of the supply chain they come from; the BfR does not specify this. The guideline is aiming at a pragmatic approach, including both, a sufficient level of safety for consumers and a manageable amount of analytical and toxicological effort for applicants or dossier submitters to characterise possible NIAS.
Comments on analytical requirements:		
13	It was noted, that semi-quantitative determination using surrogate standards entails high levels of uncertainty. Furthermore, it was commented, that determining a structure cannot	The BfR is aware of these limitations. The document is intended to outline an approach that incorporates NIAS into the risk assessment

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	be carried out with certainty using the analytical methods mentioned.	of FCMs without losing sight of feasibility. Please also refer to our answer to comment No. 11.
14	It was noted that screening is currently usually carried out with a cut-off of 10 ppb, although even this limit is sometimes difficult to achieve. Doubts were raised as to whether screening with a limit of 0.15 ppb is feasible. This limit was deemed unachievable for several reasons: testing methods are not harmonised, and there would be a significant increase in processing time and cost for NIAS screening.	The BfR clarifies that the NIAS guideline was drafted with these challenges in mind. In view of toxicological requirements and the development of analytical methods, a 10 ppb cut-off is not justifiable in itself. There are substances and substance classes, which may pose health risks even at very low exposure. Therefore, reasonable efforts (as described in the guidance) should be undertaken to identify and (semi)quantify NIAS also below 10 ppb. However, migration of a substance up to 10 ppb does not automatically pose a health risk. Please also refer to answer to question No 11.
15	It was requested, that the analytical methods should be specified in more detail, whilst the absence of official procedures was criticised (e.g. for sample preparation, the consideration of potential losses, and the interpretation of analytical results from a screening).	The BfR clarifies that the guideline is intended to provide guidance on which aspects should be taken into account and what steps should be undertaken to secure reliability and accuracy of the data provided. In the quickly developing area of NIAS analytics and with respect to the high diversity of materials and substances, detailed guidance covering all aspects is not possible. Applicants and dossier submitters should therefore rely on the experience of experts and competent laboratories and provide scientific justification for their respective approach. However, the BfR is planning to publish assessment examples that demonstrate the successful application of the concept.
16	It was criticised that the NIAS screening requires both an LC-MS and a GC-MS method, but that this is not always possible due to the nature of the analytes.	The BfR would like to point out that, in principle, a deviation from the standard procedure is possible provided there is a sound scientific justification. For this, the properties of the substance(s) and the respective use should be taken into consideration. A corresponding sentence has been inserted at the relevant point in the document.
17	It was pointed out that a one-point calibration is not sufficient, particularly for LC-MS.	The BfR agrees, especially for LC-MS. The document was amended accordingly. At least a three-point calibration for LC-MS analysis is now required.
18	It was pointed out that the required targeted analysis of oligomers is usually not feasible due to a lack of standards.	The BfR agrees. However, in many cases the monomer may be a good surrogate for the oligomers or at least one oligomer is available as standard and can be used as representative for all oligomers. The document has been amended accordingly, and it has been noted that group analyses are also possible.
19	It was pointed out, that, even if oligomers have a molecular weight of more than 1000 Da, their stability in the gastrointestinal tract should be taken into account, because they might be	The BfR agrees, a corresponding note has been included in the document.

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	degraded and produce small molecules, which might be able to cross the intestinal border.	
20	It was pointed out that, for mixtures of natural origin, a certain degree of batch-to-batch variation occurs naturally and should be acknowledged and permitted.	The BfR is aware of these variations and emphasise that they will always be dealt with on a case-by-case basis. The variation in composition and NIAS profile should be addressed in the substance characterisiation and NIAS assessment. The paragraph in the guideline is intended to encourage applicants to take this variability into account from the outset.
21	The general requirement to demonstrate the thermal stability of mixtures (e.g. distillation mixtures, mixtures of natural origin) was criticised as unnecessary.	The BfR clarifies that this requirement was included with respect to the possible high number of substance, which might react with each other – especially at elevated temperatures, which might be present during FCM production or use – and form new substances. The BfR agrees, however, that this may not always be the case and not only for distillation mixtures or mixtures of natural origin, but also for any other situation, where numerous substances are present. Hence, this requirement specifically for the named mixtures has been removed. However, we would still like to stress, that this issue must be addressed in situations where formation of new substances is likely.
22	It was pointed out that nanomaterials can be of an organic or inorganic nature and that they are often firmly bound and do not migrate.	A separate section has been created for the analysis of nanomaterials, which also states that further investigation is not necessary if scientific data is available showing that no migration takes place. However, the BfR disagrees with any general assumption, that nanomaterials do not or cannot migrate.
23	With respect to the general procedure as outlined in point 2.1, it was asked for definition and a clarification on the difference between the terms “extract” and “migrate”.	Two footnotes explaining the terms were added.
24	With respect to Figure 1, it was requested to define more clearly what ‘analytical data is sufficient’ means.	The following footnote was added: ‘in the meaning of reasonable, technical effort for generating analytical data’. This is very much a matter of expert judgement, checking whether the points discussed in the guideline have been taken into account.
Comments on toxicological requirements:		
25	Many comments were related to the applicability of the TTC concept and criticized the rejection of the TTC concept in the NIAS Guideline. Frequently, the Cramer Classes were mentioned and it was suggested to use the these as boundaries triggering data requirements.	The BfR is aware that the TTC concept is still applied in many toxicological assessments by several international and European bodies. The availability of simple software tools implementing the TTC decision tree bolster the use. However, the TTC concept is not a risk assessment tool, but a pragmatic screening and prioritisation tool (see EFSA guidance on TTC). It does not replace solid toxicity data, where these

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		are required according to EU food/feed legislation. Assessments of the BfR shall be in line with European legislation for food contact materials and thus follow the respective guidance documents of EFSA. These state, that NIAS have to be treated the same way as IAS, since the possible toxicological impact on consumers does not depend on whether or not a substance was added intentionally. For IAS, the toxicological data requirements and the respective migration boundaries triggering them are given in Table 1 of the BfR NIAS Guidance as taken from the EFSA Note for Guidance. Assignment to a specific Cramer Class does not replace these data. However, two thresholds, that are listed in the TTC concept but do not originate from the data base of the TTC concept, have been included in the BfR NIAS Guideline: (i) the migration limit for DNA-reactive mutagens/ carcinogens, being 0.15 µg/person per day. No data is required when migration is below this threshold. (ii) the limit for neurotoxic organophosphates and carbamates, being 18 µg/person per day. Substances from these chemical groups must not migrate above this threshold unless toxicological data are available. In order to clarify this topic, a separate section on the TTC concept has been added to the BfR NIAS guideline.
26	It was criticised that bioassays were not considered.	The BfR clarifies that, as in the EFSA Note for Guidance, established bioassays – as the OECD 471 (AMES-test) and the OECD 487 (*in vitro* micronucleus assay) for genotoxicity testing – are included in the BfR NIAS guideline. In addition, for the genotoxicity assessment of unidentified (although sufficient analytical methodology was applied) substances migrating between 10 and 50 µg/kg, the possibility of expert judgement based on e.g. in vitro tests on concentrated migrates or extracts is included in the BfR NIAS guideline. Paragraph 3.3 was modified to further elaborate on this, the EFSA Recommendation of testing of mixtures (EFSA Guidance on Genotoxicity assessment of chemical mixtures) is now cited, and New Approach Methodologies (NAMs) are now also mentioned.
27	It was commented that the toxicological requirements are too high, like an assay according to OECD TG 408.	The BfR clarifies that According to the Note for Guidance a study according to OECD TG 408 is required, if the migration is above 50 µg/kg food (compare Table 1 of the BfR NIAS guidance). To provide a risk assessment according to European Legislation, data requirements have to be fulfilled (please also compare our answer to question No 24). Still, approaches like grouping or justified read-across are possible. For further

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		information, please consider our answer to question 7.
28	It was commented, that the 'read-across' method was mentioned in the text but not visible in figure 1 in the middle column.	The figure was modified and a link to chapter 3.3. was added in the figure.
29	The validity of the carcinogenicity potency database (CPDB) was questioned, due to its age.	The CPDB is a data collection of chronic, long-term carcinogenesis bioassays. It documents information of more than 45 years and includes 6153 experiments. The last update was performed in July, 2025. The BfR is of the opinion that, though a significant part of the data is older than 20 years, it still represents a valuable database for carcinogens and their respective effect or no-effect levels.
30	It was pointed out that oligomers might show a similar toxicity as the monomers, if no new chemical functionality is introduced.	The BfR agrees. The text of the document was adopted and it is now stated that 'As long as oligomerisation does not introduce new functionalities, oligomers may be grouped and evaluated based on the toxicological assessment of the corresponding monomers (expert judgement).'

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the German Federal Ministry of Agriculture, Food and Regional Identity (BMLEH). It protects people's health preventively in the fields of public health and veterinary public health. The BfR provides advice to the Federal Government as well as the Federal States ('Laender') on questions related to food, feed, chemical and product safety. The BfR conducts its own research on topics closely related to its assessment tasks.

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