German Federal Institute for Risk Assessment

In case of contradictions between the English and the German version of this document, the German version shall prevail.

Guideline for the safety assessment of substances for the manufacture of food contact materials and articles

Status as of 01.03.2022

The following information does not represent a conclusively defined scope of examination. Each submitted application is examined individually according to the current state of knowledge, which may result in additional claims.

1. Introduction

This guideline serves as an orientation aid for the preparation of documents required for a risk assessment; be it for the inclusion of substances in the BfR recommendations on food contact materials or the modification of substance entries.

When applying for the inclusion of substances, a dossier describing the identity and quantity of the possible transfer of substances relevant to the application into food must be submitted. Depending on the determined level of a potential transfer under the foreseeable worst-case conditions of use (see also 5.5), it is necessary to include appropriate guideline-compliant toxicological studies. The determination of these data is based on the Note for Guidance of the European Food Safety Authority, which has been developed for substances to be used in the manufacture of food contact materials.

Depending on the material group for which an application is made, different or additional information may be required in some points. Annexes to this document serve to point out special features of certain material groups.

- Annex I contains supplementary guidance for substances used in the manufacture of paper, board and cardboard (Rec. XXXVI, XXXVI/1-3).
- Annex II contains supplementary information on substances for the recommendations for plastics, silicones (Rec. XV) and elastomers (Rec. XXI).

2. Legal basis and applicable documents

- Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC.
- Commission Regulation (EC) No 2023/2006 of 22 December 2006 on good manufacturing practice for materials and articles intended to come into contact with foodstuffs
- Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food
- German Food and Feed Act (Lebensmittel- und Futtermittelgesetzbuch - LFGB)
- Consumer Goods Ordinance (Bedarfsgegenständeverordnung - BedGgstV) in the version of the announcement of 23 December 1997 (BGBl. 1998 I p. 5)
- European Food Safety Authority Guidance 2017. 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. Updated: 27 March 2021. EFSA Journal 6(2008)7, 21r. DOI: 10.2903/j.efsa.2008.21r
- Administrative Guidance for the preparation of applications for the safety assessment

of substances to be used in plastic Food Contact Materials. EFSA Supporting Publications 14(2017)5, 1224E. DOI:10.2903/sp.efsa.2017.EN-1224

- Guidance of the European Food Safety Authority 2008. EFSA Note for guidance for petitioners presenting an application for the safety assessment of a substance to be used in food contact materials prior to its authorization. Updated on 30/07/2008. https://efsa.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.2903%2Fj.efsa.2008.21r&file=efs221r-sup-0001-SupInfo.pdf

3. Definitions

3.1 General

- Substance relevant to the application:
  Substance for which an application is submitted and all substances whose transfer to food is caused by the use of the substance applied for.

- Migration (based on Regulation (EU) No 10/2011):
  Release of a specific substance or group of substances from a material or object into food or food simulants. This is a legal definition that goes beyond physicochemical migration (kinetic or thermodynamic) in the form of diffusion (see also the following detailed explanation under: "Transfer").

- Transfer:
  Used synonymously with migration. In connection with polymeric materials (e.g. plastics), where transfer is often dominated by physical processes such as diffusion and partition between different polymers or polymer and food (simulant), the term "migration" is usually used. In the context of the BedGgstV as well as of Regulation (EU) No 10/2011, transfer is referred to as "migration" regardless of the underlying process. A detailed description of the possible processes is described under 5.1.

- Non-intentionally added substance (NIAS):
  Impurity in the substances used or reaction intermediate formed in the manufacturing process, or a degradation or reaction product. NIAS can be distinguished as follows:
  - foreseeable NIAS
    These can be derived from the chemistry of the manufacturing or application process and the process and usage conditions. Knowledge of the relevant literature and own experience are helpful. For this reason, the synthesis conditions should also be listed in detail in the application.
  - unforeseen NIAS
    Due to the complexity of the application or unforeseen external influences, further NIAS may occur. Therefore, an additional comprehensive analysis ('screening procedure') should be carried out to find or exclude further NIAS.

  Even if substances are not intentionally introduced and are therefore NIAS by definition, their occurrence or formation is often intentional (e.g. reaction products of photoinitiators or stabilisers) or at least foreseeable. For their risk assessment, the same criteria apply as for the substances applied for[1] (see also point 4).

[1] EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2016. Scientific opinion on recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials. EFSA Journal 2016, 14(1):4357, 28 pp.doi:10.2903/j.efsa.2016.4357, see https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4357
"Regarding the identification and evaluation of all substances that migrate, experience gained over the years has shown that more focus is needed on the finished materials and articles, including the manufacturing process used. Substances used in the manufacture of plastic materials or articles may contain impurities originating from their manufacturing. Moreover, during manufacturing and use, reaction and degradation products can be formed, of which oligomers can be the dominant class. These substances

3.2 Material-specific: BfR recommendations

Details can be found in the respective BfR recommendations.

4. Application documents

For the evaluation of the substances for the purposes mentioned in point 1, a dossier shall be submitted in accordance with the EFSA Note for Guidance containing the following information:

- Identity of the substance
- Substance properties
- Intended application
- Type and quantity of transfer of substances relevant to the application from the food contact article into the food coming into direct or indirect contact with it under the most unfavorable foreseeable conditions of use
- toxicological data, depending on the level of substance transfers and, if applicable, on indications of, for example, carcinogenic, reproductive toxic, endocrine or neurotoxic effects of a migrating substance from existing studies or on the basis of structural properties.

This information is also required for impurities and reaction and degradation products ('NIAS', e.g. oligomers, reaction products of initiators or oxidation products of stabilisers/antioxidants).

When compiling these data, a technical dossier must be submitted in accordance with the requirements of the EFSA Note for Guidance. Where clarifications or deviations from the EFSA Note for Guidance are described within this Guidance, the guidance provided in this guideline applies. In all other respects, the EFSA Note for Guidance should be followed.

The following documents must be submitted:

- a complete version of the application in paper form
- the overview of substances as provided by the BfR (see Annex 1)
- an electronic version of the complete application (in searchable format, e.g. as a Word document or unprotected PDF; tables and calculations are to be submitted in Excel or Word).
- If the request contains data to be treated confidentially, an additional electronic version without the confidential data is required. In the case of requests under the Freedom of Information Act (Informationsfreiheitsgesetz, IFG), the data can be forwarded in this form.
- A confirmation that the submitter of the documents is the rights holder of the documents or has been mandated by the rights holder.

The application documents must be submitted in German or English.

5. Determining the transfer

The scope of the toxicological data to be submitted shall be based on the possible level of

have become known as non-intentionally added substances (NIAS) and are referred to as such in Commission regulations. Whether their presence is intentional or not, it is necessary to evaluate the safety of all migrating substances and not just of the starting substances - for example the monomers or additives alone - and the guidelines should be updated to account more fully for this more comprehensive approach."

transfer into the food. The higher the possible exposure of consumers through the transfer of the substances, the more extensive are the requirements for the toxicological information to be provided (see section 6).

5.1 Possible processes for transfer into food

Before measuring or estimating the transfer of substances from a material or article into food or food simulants, the nature of the transfer must be clarified. The transfer may occur via the following routes:

- diffusion from inside the food contact material or permeation through the material to the food contact surface;
- gas phase transfer (evaporation and recondensation), e.g. from the food contact material into dry food or from outer packaging via inner packaging (e. g. cardboard box with inner bag);
- set-off: via contact of the food contact side to the outside (e.g. coated side) in a roll or stack during storage of the material;
- by hydrolysis and/or oxidation, e.g. when polymers or metals come into contact with acidic or alkaline food(simulants);
- by abrasion (especially for nanomaterials);
- transfer from the surface in 'dry' foods (e.g. by contact with fine dry foods, especially with a greasy surface).

The absorption into the food depends on its nature and the storage conditions.

- The transfer into liquid or pasty foods with wetting contact is determined by the partition equilibrium (solubility ratio) at the interface between the food contact material and the food.
- For coarse-grained dry foods, migration occurs predominantly via the gas phase and is therefore particularly pronounced for volatile substances (boiling points up to the range of 350-400 °C when stored at room temperature). Coarse-grained dry non-greasy foods with a low free surface have a low adsorption capacity and thus a limited absorption of substances, whereas coarse-grained dry foods with fat on the surface have a high adsorption capacity and thus a high absorption of substances.
- Fine powders (e.g. flours) also absorb considerable amounts of substances via contact, i.e. without limitation in volatility. This is intensified if the particles have moist/oily surfaces.
- When storing the food with the contact material, temperature and duration are the most important factors.

5.2 General procedure for determining the transfer

Since the transfer of substances to food is often difficult to determine, models (conventions) have been developed. These are usually conservative and can greatly overestimate the real exposure. **The applicant is free to derive a more realistic exposure, whereby the assumptions made must be comprehensibly justified. In any case, the most severe of the foreseeable conditions in practice must be applied (*worst case*).** Because in certain situations the models can also underestimate the transfer that occur in reality, they must be applied with caution.

To determine the possible transfer to food, the approaches described below can be followed. They build on each other hierarchically, starting from deliberate overestimations. If the available toxicological data meet the requirements for this, the subsequent (more detailed) investigations can be omitted.

5.3 Calculation under the assumption of complete transfer, starting from the quantity used in the process

In the simplest case, the assumption is that the substances used or maximally produced

remain on/in the material during production and are completely transferred to the food. If under this (usually highly exaggerated) assumption the safety of the migration can be proven, no further steps are necessary. If reactions of the substance (e.g. photoinitiators, stabilisers) are to be expected, this approach alone is not sufficient (see 7.4). For polymeric compounds, the content in the formulation (commercial product) should be used.
These calculations and their entry in the table "Overview of substances" (Annex 1) are mandatory regardless of subsequent refined determinations.

5.4 Calculation assuming complete transfer, starting from the measured content on/in the food contact material or in the commercial product.

This procedure is usually applied to the finished food contact article. If this is not possible due to technological reasons, the amount of substance applied to the test substrate or introduced into the material can also be determined analytically in *worst case* test articles or materials with the maximum input amount, whereby the completeness of the extraction must be proven. Then, assuming a complete transfer from the food contact material or commercial product, the possible content in the food is calculated.

5.5 Determination of the transfer

For both, the migration measurement and the migration modelling, the most severe of the foreseeable conditions in practice (*worst case*) must be used with regard to food or food simulants, temperature and time. For this purpose, the properties of the substances that may be transferred (e.g. general solubility, solubility in the simulants used, polarity, volatility) as well as knowledge about the possible use of the finished food contact material are important. If the application (or specification of the material) restricts the possible uses in relation to the worst foreseeable conditions in practice (e.g. by excluding food categories), this should be taken into account when selecting the migration conditions. These restrictions may be listed as additional restrictions in the listing of the substance.
In the case of amphiphilic substances, it must also be taken into account when selecting extraction solvents or simulants that emulsifying substances occurring in food have an influence on the level of the transfer.
The extraction agents/simulants/test substances listed in the annexes are only to be understood as examples. The applicant has to check whether they actually represent the *worst case* or whether an alternative has to be chosen. In doing so, the suitability of the methods used shall be comprehensibly demonstrated.

In the application, under 2.1.4 Solubility, the solubility of the substance in the simulants used shall also be stated.

5.5.1 Migration measurement

For the analytical procedure, limit of detection and quantification, measurement uncertainty and recovery must be verified and substantiated.

5.5.1.1 Migration measurement in simulants

The starting point is the determination of the substances in simulants obtained with the finished food contact material or article under test. Exemplary conditions are listed in the annexes. If conditions are prescribed in the BfR recommendations, these are to be applied. In addition, the conditions of Regulation (EU) No. 10/2011 (Annex V, Chapter 2) may be used.

The simulants used can be restricted according to the current state of science or adapted to the physico-chemical properties of the substances to be determined.

5.5.1.2 Migration measurements in food

Measurements in food are necessary when there is uncertainty whether the migration in

simulants correctly reflects the migration in food. The choice of test foodstuffs and contact conditions must be made according to the state of scientific knowledge and must be justified. The correctness of the measurements in food must be proven (e.g. via recovery tests).

5.5.2 Migration modelling

Migration modelling must be carried out and documented in a comprehensible way according to the current state of knowledge and technology. It must not underestimate the actual migration.

Substance-specific migration can be calculated on the basis of the input quantity or the residual content of the substance in the material (in the case of multi-layer materials in the individual layers) using generally recognised diffusion models based on scientific findings. A conservative model developed for commercially available packaging plastics on the basis of so-called Ap values as plastic-specific parameters for their basic diffusion properties[2] has gained scientific and regulatory recognition at European level[3]. If no polymer-specific constants (Ap values) are available in literature for individual polymer-based layers (plastics, adhesives, coatings etc.) in multilayer composites, these can be conservatively estimated on the basis of scientific findings. For paper layers, a paper-specific constant of A_{PB}=15 (no barrier) and for aluminium a material-specific constant of A_{Al}=-25 (absolute barrier) can be used. In addition, further estimation possibilities are known from the literature, for example by interpolation via the glass-transition temperature[4] estimation based on analytical measured values of other migrants taking into account the molecular mass of the migrant, the temperature of the intended application and the matrix[5,6] estimation of substance-specific diffusion coefficients in the polymer based on the molecular volume and the correlating activation energy for diffusion[7,8].
In the case of direct contact, the suitability must be shown specifically for this case (absence of effects not considered in the model, such as material degradation, swelling, abrasion, etc.).

5.6 Indication of the results

The results from 5.3 to 5.5 are to be presented in tabular form and discussed for plausibility. A template for the overview can be found in Annex 1.

6. Toxicological part

The toxicological data to be submitted are regulated in a tiered approach according to the EFSA Note for Guidance (see table below). The requirements must be met for all migrating substances, both intentionally used and impurities as well as by-products and degradation products. In individual cases, *in silico* approaches such as read-across or QSAR (see below) can also be included in the considerations. If there are indications of toxic effects (e.g.

2 Begley et al., 2005. Evaluation of migration models that might be used in support of regulations for food-contact plastics. Food Additives and Contaminants, January 2005: 22(1): 73-90.

3 JRC, 2015. Practical guidelines on the application of migration modelling for the estimation of specific migration; EUR 27529 EN.

4 Rainer Brandsch, 2017. Probabilistic migration modelling focused on functional barrier efficiency and low migration concepts in support of risk assessment. Food Additives & Contaminants: Part A, 34:10, 1743-1766, DOI: 10.1080/19440049.2017.1339235.

5 Mercea P. et. al, 2018. Modelling migration of substances from polymers into drinking water. Part 1 - Diffusion coefficient estimations, Polymer Testing 65: 176-188.

6 Mercea P. et. al, 2019. Modelling migration of substances from polymers into drinking water. Part 2 - Partition coefficient estimations, Polymer Testing 76: 420-432.

7 Welle F, 2013. A New Method for the Prediction of Diffusion Coefficients in Poly(ethylene terephthalate). J. APPL. POLYM. SCI. 2013, DOI: 10.1002/APP.38885.

8 Welle F, 2014. Activation energies of diffusion of organic migrants in cyclo olefin polymer. Intern. J. Pharmaceutics 473 (2014), 510-517; DOI: 10.1016/j.ijpharm.2014.07.029.

carcinogenic, reproductive toxic, endocrine or neurotoxic) of a migrating substance based on existing data such as scientific literature and toxicological studies or based on structural properties, or if an accumulation of the substance in the human body is suspected (see also below: literature search and under paragraph 6.7 Other toxicity), toxicological data may be required for these endpoints even if the transfer is still below the appropriate level.

Measured migration or calculated theoretical maximum migration in mg/kg food (simulant)	Toxicological issues to be addressed
< 0,05	- Absence of genotoxicity
0,05–5	- Absence of genotoxicity - Oral, subchronic toxicity - Evidence that there is no accumulation in humans
5–60	- Absence of genotoxicity - Uptake, distribution, metabolism and excretion - Oral, subchronic toxicity - Oral, chronic toxicity/carcinogenicity - Reproductive and developmental toxicity

The following general instructions for submitting studies must be observed:

- The studies conducted must be carried out in accordance with the OECD guidelines or an internationally recognised method and under the requirements of Good Laboratory Practice (GLP). If data are already available from studies that were not conducted according to such a guideline (especially older studies), the quality and scope of the studies should be reviewed. If the studies are of high quality and comparable in scope to current guidelines, they can replace guideline-compliant studies after a case-by-case assessment.
- For an assessment, the complete original studies must always be submitted. A study summary is not sufficient.
- The submitted studies must be in German or English. For studies from other language areas, certified translations must be prepared.
- The applicant must have the right to pass on the toxicological studies submitted and declare this in writing to BfR.
- The test substance used must be sufficiently well characterised, especially with regard to identity, purity, stability or particle size distribution (for particulate substances).
- In *in vitro* studies, it must always be considered whether the substance applied for could change under physiological conditions (e.g. formation of reaction products at low pH). The stability of the tested compound under conditions after oral uptake must be proven by theoretical considerations or experiments. For expected reaction products, the necessary *in vitro* studies must also be submitted.
- In an *in vivo* study, the oral route of absorption shall be used. Studies using other routes of administration may provide additional information on the toxic properties of the substance under investigation. However, they can only replace an oral study in individual cases and entail additional requirements.
- The applicant shall conduct a literature search on the substance(s) applied for as well as on impurities or reaction products that transfer to food (simulants) and include the results with the application. The search should focus on relevant toxicological

endpoints, in particular mutagenicity, carcinogenicity, reproductive toxicity, neurotoxicity and endocrine effects. The databases and keywords or search inputs used, the number of references found and the date of the search should also be documented.

- If several studies with different results on a toxicological endpoint are available, all studies must be submitted by the applicant. The same applies to data from the literature. The evaluation is then carried out according to the "weight of evidence" principle.
- For animal welfare reasons, the following points should always be checked when selecting studies and the parameters collected.
    - Can several questions (toxicological endpoints) be tested with one study, for example by a combined study on chronic toxicity and carcinogenicity (OECD Guideline 453)?
    - Is a study necessary or already covered by data from another study? For example, a subchronic study (OECD 408) does not always need to be conducted if data from a chronic study are available (OECD 452, 453) and all parameters of the subchronic study have been tested.

Notes on the individual questions are given below.

6.1 Genotoxicity:

According to the EFSA Note for Guidance, this question should be addressed by means of two *in vitro* tests (except for nanomaterials, see below).

- *In vitro* gene mutation test in bacteria (AMES test) according to OECD Guideline 471
- *In vitro* micronucleus test in mammalian cells according to OECD guideline 487

These ensure adequate testing of the test substance for mutagenic, clastogenic and aneugenic properties. Other tests may be suitable to a limited extent.[9]

In the case of positive or inconclusive results in the *in vitro tests, in vivo* tests must usually be carried out to enable an unambiguous evaluation. For example, the following tests are suitable as a supplement:

- transgenic rodent gene mutation assays according to OECD Guideline 488 for suspected mutagenicity *in vitro*
- *In vivo* comet assay according to OECD Guideline 489, in case of suspected mutagenicity or structural chromosome damage *in vitro.*
- *In vivo* micronucleus test according to OECD guideline 474, if clastogenic or aneugenic properties are suspected *in vitro.*

In the case of submitted *in vivo* studies, proof must be provided that the investigated substance is sufficiently systemically available and has reached the respective target organ (e.g. by examining the concentration in the blood/serum, ADME studies or similar).

For nanomaterials, the EFSA guidance document is[10] relevant. The following guidance should also be observed:

- the AMES test is usually not suitable because nanomaterials usually cannot penetrate the cell wall of bacteria.
- There should always be evidence that the test substance has entered the cells or reached the target organ.

[9] Compare https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2379 and https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5113

[10] Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health, https://doi.org/10.2903/j.efsa.2018.5327.

6.2 Subchronic toxicity

This question should be addressed with the help of a subchronic study after oral intake (e. g. a 90-day study according to OECD Guideline 408). Significantly shorter studies, such as 28-day studies (e. g. according to OECD Guideline 407) are insufficient and unsuitable for a toxicological assessment.
The subchronic study does not have to be performed if data from longer studies (e.g. chronic studies according to OECD Guideline 452 or 453) are already available which cover the scope of OECD Guideline 408 with regard to the toxicological parameters investigated.

6.3 Enrichment in humans

For organic chemical compounds, a value for the common logarithm of octanol-water partition coefficient ($LogP_{OW}$) of < 3 is usually considered sufficiently likely to prevent accumulation of the substance in humans.
For inorganic compounds (e.g. salts), the $LogP_{OW}$ value is not meaningful in terms of possible accumulation in humans.
In the case of a $LogP_{OW}$ value > 3 and for inorganic substances, the applicant should plausibly demonstrate that no accumulation takes place in humans or that no health risks arise from this, even in the livelong perspective.
Appropriate methods depend on the substance under investigation and can be, for example, ADME studies (see section 6.4) or studies according to the IPCS guidelines or the RFDA Red Book II[11].

6.4 Absorption, distribution, metabolism, excretion (ADME)

If available, data on all four toxicokinetic properties (absorption, distribution, metabolism and excretion) of a substance should be provided. These data should be generated according to OECD guidelines. Information from other scientific studies with a different main focus or on partial aspects of toxicokinetics may also help to clarify this issue.

6.5 Chronic toxicity/carcinogenicity

For animal welfare reasons, these two questions should ideally be addressed together, e.g. according to OECD Guideline 453. In order to test the endpoints individually, studies according to OECD Guideline 451 or 452 are suitable.

6.6 Reproductive toxicity

This question should be addressed with a single- or multi-generation study, e.g. according to OECD guidelines 415, 416 or 443. Screening studies, e.g. according to OECD Guidelines 421, 422, may provide indications of reproductive toxicity. A developmental toxicity study in another species (OECD Guideline 414) may also be necessary.

6.7 Other toxicity

Phosphoric or phosphonic acid esters must be tested for neurotoxicity if a migration of > 50 µg/kg food is present, for example according to OECD Guideline 424. If indications of neurotoxicity are found for other substances in the chronic or subchronic studies, a corresponding study should also be carried out additionally. The necessity should always be examined and justified on a case-by-case basis.

[11] IPCS, Environmental Health Criteria 70, Principles for the safety assessment of food additives and contaminants in food, 1987.
IPCS, Environmental Health Criteria 57, Principles of toxicokinetic studies, 1986.
FDA, Redbook II, Guidance for Industry and Other Stakeholders Toxicological Principles for the Safety Assessment of Food Ingredients, 2007.

The absence of endocrine disrupting properties should be demonstrated by searches in databases and the literature, regardless of the level of migration. Necessary are the searches in

- the EU list of possible endocrine disrupters (SEC (2007) 1635) https://ec.europa.eu/environment/chemicals/endocrine/documents/index_en.htm
- the REACH registration dossier
- the opinions of international assessment bodies (e.g. WHO)
- the US databases (Toxcast, EDSP) https://www.epa.gov/endocrine-disruption

Furthermore, an up-to-date literature search for evidence of endocrine disrupting properties shall be performed and the absence of endocrine disrupting activity or human relevance shall be substantiated by the applicant.

Any other relevant information available, for example on immunotoxicity, must also be provided to enable a comprehensive assessment.

6.8 Read-across, weight of evidence, *in silico*, QSAR

Particularly from the point of view of animal protection, it should always be considered whether alternative approaches make the conduct of a study unnecessary. Information already available on similar compounds or on compounds that form similar toxicologically relevant metabolites (read-across) or information from several studies, each of which individually provides too little information (weight of evidence), should be used. If data on several similar compounds are available, models for the quantitative determination of a possible structure-activity relationship (QSAR) can also be used. Internationally recognised guidelines exist for all three of these approaches[12] and must be followed.
In silico tools, e.g. for the prediction of genotoxicity, can be used as a support in individual cases - especially for low-migrating NIAS, reaction, decay and degradation products as well as impurities, for which toxicological data are usually not available and are difficult to generate due to the lack of reference substances. In particular, *in silico* tools may be suitable for screening for structural features that raise suspicion of genotoxicity and for predicting toxicokinetic and physicochemical properties (for example, $LogK_{OW}$ value). However, toxicological tests on the intentionally used substances cannot be replaced in this way. In any case, the *in silico* tools used must be well documented and validated. All parameters used in the application of the *in silico* tools must also be sufficiently documented to make the predictions made transparent and verifiable. It must be demonstrated that the test substance is covered by the training database (validated prediction range) of the tool.

7. Further notes

7.1 Justification of confidentiality

Claims for confidentiality of information must be substantiated in accordance with the Administrative Guidance for the preparation of applications for the safety assessment of substances to be used in plastic Food Contact Materials, Annex C. According to Article 20 of Regulation (EC) No 1935/2004, the following information cannot be marked as confidential:

- name and address of the applicant
- chemical name of the substance (name and, if available, CAS No. and EC No.)
- information of direct relevance to the assessment of the safety of the substance
- the method or methods of analysis for official controls.

[12] ECHA 2011. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.4: Evaluation of available information.
ECHA 2017, Read-Across Assessment Framework (RAAF).
OECD 2014, Guidance on grouping of chemicals, second edition (ENV/JM/MONO(2014)4).
ECHA 2008, Guidance on Information Requirements and Chemical Safety Assessment. Chapter R6. QSARs and grouping of chemicals.

7.2 Name, CAS No.

The name must comply with the nomenclature rules of IUPAC and clearly describe the chemical structure and identity of the substances. If the assignment of the CAS No. to the substances and their structure cannot be made by means of generally, publicly and free of charge accessible search tools, a corresponding proof is required. For example, a report of the CAS Inventory Expert Service is suitable for this purpose. Name and CAS No. cannot be marked as confidential according to 7.1.

7.3 Manufacturing process

The manufacture of the substance shall be presented, as information on impurities and reaction and degradation products can be deriverd from this. If the purity of the starting materials may have an influence on the purity of the substance, the purity of the starting materials and the impurities shall be indicated. Alternative production processes shall be indicated and any other impurities resulting from them shall be mentioned.
The variability between manufacturing batches shall be reported and it shall be shown that the batches used for migration experiments and toxicological studies cover this variability.

7.4 Impurities and reaction products

Impurities and reaction products (including oligomers and degradation products) occurring during manufacture and application of the substance applied for must be identified and quantified. They can be partially derived from the chemistry of the manufacturing/application process, but must be analytically verified and quantified as well as checked for completeness. A comprehensive analysis ("*non-targeted screening*" or "*general unknown screening*") with methods adapted to the substance type and matrix should also detect unexpected substances. The required detection limit results from the toxicological specifications. Especially if a LC-MS(/MS) method is used, the mere comparison of base peak chromatograms (BPCs) or total ion chromatograms (TICs) is not sufficient.
For points 2.2.4 (hydrolysis) and 2.2.5/2.2.6 (decomposition/transformation) of the Note for Guidance, relevant possible reactions in the manufacturing process, during storage and use (e.g. irradiation, pH-value) as well as reactions with the food (during preparation/heating) and in the digestive tract have to be considered in addition to the behaviour under thermal stress. The latter should be seen in connection with the general notes on toxicology from point 6

7.5 Method for official controls

As described in 5.1.8 and 6.5 and in Annex 1 to Chapter IV of the EFSA Note for Guidance 2008, a method for the determination of the substance in the finished product and/or food that can be used by official controls shall be provided. This method shall be described as a validated test procedure (SOP) according to the applicable standards. It is not permissible to label this method as confidential.

7.6 Traceability, raw data

All information must be documented in a comprehensible manner. For chemical analysis, this includes selectivity, detection limits, determination limits, linearity of the method, and, if applicable, the specification of measurement uncertainties and calculations. At least exemplary typical chromatograms or spectra of standards, samples and blanks should be provided with clear labelling. In the case of analyses, the date of the measurement must be included. Raw data required for calculation (peak areas etc.) are to be provided in their **entirety** and should be in copyable table format (Excel, see also specific requirements listed below). The electronic versions must not be created or protected in a way that prevents searching and copying (e.g. texts or tables must not be inserted as pixel graphics).

The P-SDS should be used to provide a summary of the results. A reference to the annex with the respective data and raw data, indicating the page on which the relevant information is located, is required. It should be refrained from combining the data of different studies in one annex.

Analysis reports shall be clearly structured and shall contain at least the following elements:

- Detailed table of contents,
- List of figures and tables,
- Summary of the analyses and the most important results,
- clear assignment of the codes used to the samples measured,
- precise description of the methods and
- Results including a discussion of the same.

- Only chromatograms, spectra, tables and the like necessary for immediate understanding should be found in the main body of the report. Reference should be made to further figures or tables.
- Put further data in an annex to the report. Each figure or table should be accurately described and numbered.
- Non-commented, automatically generated analysis reports are not acceptable.
- Finding information must be easy for the auditor. For this purpose, the data must be structured accordingly and references must be inserted at relevant places. The documents must be searchable. Text must not be inserted as a nonsearchable graphic (simple scan). Raw data must be kept and, if necessary, made available to the BfR.

The method description should include:

- Device description and analytical parameters,
- all measurement and validation parameters (e.g. linearity, LOD/LOQ, recovery) and their determination (data on this largely in the appendix),
- information on the production of the standards.

Verification of the calculations: All calculations must be verifiable by the BfR. This includes in particular:

- the production of standards (weights and dilutions),
- calculation of LODs/LOQs,
- recoveries,
- calibrations and
- analysis results.

In order to enable a verification with reasonable effort, all raw data and pipetting schemes for the calculation of the parameters given above must be available in an Excel file.

7.7 Reference material

In deviation from the requirements of the EFSA Note for Guidance, the following address should be chosen for the shipment of the reference material:

Federal Institute for Risk Assessment
National Reference Laboratory for

"Substances intended to come into contact with food".
Max-Dohrn-Str. 8-10
D - 10589 Berlin

The substance (250 g) should be packed in inert containers, e.g. made of glass with PTFE lid seal, and information on stability and storage conditions must be enclosed. The packaging must ensure that the chemicals arrive at BfR intact. The safety data sheets must be sent electronically in advance (by e-mail to: nrl-fcm@bfr.bund.de).

Appendix 1: Tabular overview of the results (Overview of substances)

An Excel version of the table can be found at https://www.bfr.bund.de/cm/349/template_substance_overview.xlsx. The Excel version is to be filled in, the presentation here is for information only.

Substance name	CAS No., EC No.	SMILES	Structure	Calculation under the assumption of complete transfer, starting from the input quantity used in the process		Calculation assuming complete transfer, based on the content in the food contact material (point 6. DATA ON THE RESIDUAL CONTENT of the Note for Guidance).		Measured or modelled migration (point 5 MIGRATION DATA ON THE SUBSTANCE of the Note for Guidance)		Existing limitations, e.g. according to Reg. 10/2011	Comments
				Content in the formulation [mg/kg] *	Content in the food at - complete transfer [mg/kg]	Analytically determined content in the finished food contact material - [mg/kg]	Content in food at 100 % transfer of the content in the material [mg/kg].	Measured or modelled migration [mg/kg]			
								in simulants	in food		
1. polymer/oligomers:											
Monomer(s)											
Oligomeric fractions <1000 Da											
By-products and impurities											
Catalysts/initiators/others (e.g. decomposition products)											
2. non-polymeric substances:											
Substance(s)											
By-products and impurities											
Catalysts/initiators/others (e.g. decomposition products)											
3. reactive substances (catalysts/ initiators/ inhibitors/ stabilisers):											
Substance(s)											
By-products and impurities											
Decomposition/ reaction products											

* For substances whose quantity was determined analytically in the formulation (e.g. oligomers in a resin), this quantity must be indicated here and this must be marked under remarks.

ANNEX I

Special instructions for applying for the inclusion of substances in BfR recommendations XXXVI, XXXVI/1, XXXVI/2 or XXXVI/3 ("paper recommendations")

A. Basic considerations and procedures for determining the transfer of substances from paper

A gravimetric test of the overall migration or the dry residue of extracts is generally not useful for paper, as its amount is too much determined by released fibres and is thus of little or no significance with regard to an applied substance (e. g. a paper finishing agent).

In principle, the applicant should base his considerations on a ratio of surface area of paper to mass of food that takes into account the typical or usually foreseeable (unfavourable) applications. If no information on the actual use is available, the information according to DIN EN 645 is followed and a basis weight of 300 g/m² is assumed, and thus a ratio of 13.33 dm²/kg food is assumed. If the convention used in the plastics sector is used, i.e. that 6 dm^2 of packaging are in contact with 1 kg of food, this must be proven by means of application examples and the application for less favourable conditions must be restricted accordingly if necessary. Also with regard to the weight per unit area, typical or usually foreseeable (unfavourable) applications are to be assumed. If there are no indications for the actual application, a basis weight of 300 g/m^2 is to be assumed. **All assumptions made shall be justified in a comprehensible manner.**

B. Transfer of substances to food

In general, the considerations listed under 5 and the hierarchy of model systems apply. Special considerations for the application for substances for the production of paper and board are listed below.

Calculation assuming complete transfer, starting from the content in the paper:

As a rule, a test paper with a commercially available composition and the maximum application quantity of the substance applied for must be produced in the course of the application. If necessary, an enrichment of the substance in the process water must be taken into account. The amount of the substance applied for on the test paper must be determined analytically. If extraction methods are used, the completeness of the extraction must be proven. Subsequently, assuming complete transfer from the paper, the content in the foodstuff is calculated. For the calculation, a basis weight of 300 g/m^2 (if necessary, conversion of the results to 300 g/m^2, see point A) is to be assumed for the use of the substance in the paper pulp. If the substance is used in the coating, the most unfavourable application quantities are to be used for the calculation. For comparability with the results of the water extract, a surface/volume ratio of 13.33 dm²/kg foodstuff is to be assumed (calculation from 40 g paper per kilogram foodstuff and 300 g/m^2 basis weight of the paper).

When producing the test paper, care should be taken to ensure that it is as close to reality as possible with regard to the influence of the process water and, if applicable, accumulations/depletions of the substance to be applied for after a longer process time. Ideally, the paper is produced in a real paper machine with at least several hours of substance use in

order to cover the influence of increasing substance concentrations until equilibrium/ saturation in the process water is reached.
If this is not possible, the influence of the substance concentrations in the process water must be considered. This can be done, for example, by repeated sheet formation with batchwise addition of the substance in the laboratory with recirculation of the water used. Based on existing empirical values for the equilibrium adjustment of the water at the laboratory leaf former, the first 14 laboratory leaves formed should be discarded. From the 15th laboratory leaf onwards, the leaves should be dried and used to examine the residual substance content. A sufficiently large number of samples should be taken. At least three approaches of the laboratory leaf formation process are recommended. For information on the enrichment in the laboratory leaf circulation water, the course of the turbidity measurement or also COD determinations (chemical oxygen demand) of the water after leaf formation can be recorded. The use of a real process water of a paper mill in the laboratory leaf former can also be used as an alternative. At the very least, the change in substance concentrations in the water circuit of a paper machine and their influence on the quantity remaining in the paper and thus the expected mass transfers must be discussed.

Migration measurement in simulants

In addition to the test options described in 5.5.1.1 migrates as defined in this document can also be produced using the following convention methods:

- Determination of the transfer of paper and board by the application of modified polyphenylene oxides (MPPO) (DIN EN 14338)
- Cold water extract according to DIN EN 645
- Hot water extract according to DIN EN 647
- Organicsolvent extract according to DIN EN 15519

It is assumed that the transfer measured in the simulant corresponds to the transfer into the food. There should be no further conversion.
In the application, under 2.1.4 Solubility, the solubility of the substance in the simulants used shall also be stated.

C. Test conditions for the individual recommendations

In general, the information given under point 5 must be followed. Special considerations for the application for substances for the production of paper and board are pointed out below.
For all extraction and migration experiments, paper produced with the maximum intended input quantity must be used without pre-treatment. During the investigations, it may be useful to additionally examine the untreated paper in order to identify which substances or signals do not originate from the use of the substance applied for, but from the paper itself.
Due to the above considerations, the extraction agents/simulants/test food listed below are only to be understood as examples for which the applicant has to check whether they actually represent the 'worst case' or whether an alternative should be chosen. In this context, solubility considerations as well as recovery experiments are usually important aids. **If it can be proven that the transfer measured with a simulant or extraction solvent represents the worst case, the sole test with the same is sufficient.**

Papers according to BfR recommendation XXXVI

Migration calculation based on convention methods:

- cold water extract according to DIN EN 645
- organic solvent extract (isooctane/95 % ethanol) acc. to DIN EN 15519 or
- migration trials following the requirements of Regulation (EU) No 10/2011
- Determination of the transfer of paper and board by the application of modified polyphenylene oxides (MPPO) (DIN EN 14338), if applicable.

Paper according to BfR recommendation XXXVI/1

Migration calculation based on convention methods:

- Hot water extract according to DIN EN 647 and cold water extract according to DIN EN 645 [13]
- organic solvent extract with isooctane/95 % ethanol, according to DIN EN 15519 (only if required due to the polarity of the food) Migration tests are not foreseen in this case, as the papers are extracted in the course of their use.

Paper according to BfR recommendation XXXVI/2

Migration calculation based on convention methods:

- Hot water extract (DIN EN 647) and cold water extract according to DIN EN 645[13]
- organic solvent extract (isooctane/95 % ethanol) according to DIN EN 15519) or migration attempts:
- 2 h at 175 °C using modified polyphenylene oxides (MPPO) as simulant (DIN EN 14338), alternatively:
- 20 min at 220 °C with test dough acc. to DIN 10955, section 11.2.5.4

If the papers or boards are used exclusively in microwave ovens, the migration tests shall be carried out at 150 °C for 30 min.

Thermostability:
For substances to be included in Recommendation XXXVI/2, thermostability testing is required. The substance applied for (without paper matrix) shall be tested by thermogravimetry as follows: A suitable sample quantity is heated to 220 °C and then left at this temperature for 2 hours. Then the sample is further heated to 250 °C and left there for 10 minutes. For microwave applications, the sample is heated to 150 °C and then left at this temperature for 30 minutes. The heating rate should be 10 °C per minute; the test is carried out under the influence of atmospheric oxygen (no nitrogen purge). The accuracy of the method used shall be stated. The thermogravimetric test shall include the decomposition point; heating to a temperature higher than 250 °C may be necessary. Volatile release products shall be reported qualitatively and quantitatively. The resulting decomposition products up to and including a temperature of 250 °C shall be determined qualitatively and quantitatively and included in the application. Suitable methods for this purpose are, for example, thermodesorption and purge and trap. Possible reactions with food components according to 2.2.7 of the Note for Guidance shall be discussed.

[13] Studies have shown that the hot water extract does not represent the worst case for some analytes. Therefore, for hot applications, both hot and cold water extract results should be provided.

ANNEX II

Special instructions for applying for the inclusion of substances in the BfR recommendations for plastics, silicones and elastomers of the BfR

When producing test samples, a realistic maximum layer thickness must be examined in the sense of a 'worst case'. The information in the Note before Guidance from 2008 that a maximum thickness of 250 µm is sufficient cannot be used as a basis and is incorrect for many polymers.

The Fat Reduction Factor (FRF) must not be used to correct migration results in the application.

Test samples for the application for inclusion of substances in Category III (silicone elastomers [silicone rubber]) of Recommendation XV (silicones) may only be manufactured (tempered) in such a way that they do **not** emit **less** than 0.5 % volatile organic components. This is to ensure that migration tests on these test samples represent the most severe conditions under which silicone articles according to Recommendation XV can be produced in practice.

Test samples for the application for inclusion of substances in Recommendation XXI may only be produced in such a way that they can represent the most severe conditions in the substance transfers. Possible tempering of end products, which may also be necessary (for example in peroxide cross-linking), must be taken into account when assessing the substance transfers. For these applications, the substance transfer before and after tempering should be considered. This simplifies the assessment of possible reaction pathways and the reaction and degradation products that may arise.