ADOPTED: 30 July 2008
UPDATED: 09 September 2020
doi: 10.2903/j.efsa.2008.21r

NOTE FOR GUIDANCE

FOR THE PREPARATION OF AN APPLICATION FOR THE SAFETY ASSESSMENT OF A SUBSTANCE TO BE USED IN PLASTIC FOOD CONTACT MATERIALS

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), Vittorio Silano, Claudia Bolognesi, Laurence Castle, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, André Penninks, Maria de Fátima Tavares Poças, Andrew Smith, Christina Tlustos, Detlef Wölfle, Holger Zorn and Corina-Aurelia Zugravu.

This guidance was originally adopted by the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on 30 July 2008; the last revision was endorsed by the Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) on 9 September 2020[1].

Endorsement date	**9 September 2020**
Implementation date	**27 March 2021**

The present guidance has been revised and it is republished with editorial changes. The information on submission of an application, references to confidentiality claims and the section on 'Authorisation of substance' in the chapter 'EXPLANATORY GUIDANCE OF THE 'SCF GUIDELINES FOR FOOD CONTACT MATERIALS' were deleted, as replaced by the "Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials" (EFSA, 2021) following the new provisions defined by Regulation (EC) 178/2002 ('GFL Regulation'), as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain, applicable as from 27 March 2021. The scientific content has been left unchanged and until further notice, the present scientific guidance applies.

[1] This revised version of the guidance contains new text compared to the previous version. The new text has been inserted in boxes to be easily identifiable.

Panel members in 2017: Claudia Bolognesi, Laurence Castle, Jean-Pierre Cravedi, Karl-Heinz Engel, Paul Fowler, Roland Franz, Konrad Grob, Rainer Gürtler, Trine Husøy, Sirpa Kärenlampi, Wim Mennes, Maria Rosaria Milana, André Penninks, Maria de Fátima Tavares Poças, Vittorio Silano, Andrew Smith, Christina Tlustos, Detlef Wölfle, Holger Zorn and Corina-Aurelia Zugravu.

Amendments: The initial version of the document was adopted by the former EFSA AFC Panel (Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food) on 8 June 2006. It was further updated and adopted by the same Panel on 31 July 2008. On 23 March 2017, the EFSA CEF Panel (Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids) endorsed another update of the document. The current revision of the document was endorsed by the EFSA CEP Panel (Panel on Food Contact Materials, Enzymes and Processing Aids) on 9 September 2020. For transparency reason, the version adopted on 31 July 2008 is still accessible, watermarked as "obsolete", under the 'Supporting information' tab on Wiley Online Library.

Acknowledgements: The current version of the guidance was endorsed by the EFSA CEP Panel (Panel on Food Contact Materials, Enzymes and Processing Aids – CEP Panel) on 9 September 2020. EFSA Panel Members: José Manuel Barat Baviera, Andrew Chesson Claudia Bolognesi, Pier Sandro Cocconcelli, Riccardo Crebelli, David Michael Gott, Konrad Grob, Claude Lambré, Evgenia Lampi, Marcel Mengelers, Alicja Mortensen, Gilles Rivière, Vittorio Silano, Inger-Lise Steffensen, Christina Tlustos, Henk Van Loveren, Laurence Vernis, Holger Zorn.

Suggested citation: EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2008. Note for Guidance for the preparation of an application for the safety assessment of a substance to be used in plastic Food Contact Materials. EFSA Journal 2008, 6(7):21r, 41 pp. https://doi.org/10.2903/j.efsa.2008.21r

Keywords: food contact materials, plastics, safety assessment

Question number: EFSA-Q-2006-00327

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ISSN: 1831-4732

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NOTE FOR THE READER

LIST OF MODIFICATIONS TO THE DOCUMENT undertaken in 2017

In the light of the latest experience gained by EFSA in the context of applications on food contact materials, the present guidance document, related to the preparation of an application for the safety assessment of a substance to be used in plastic materials and articles intended to come into contact with food, falling under the scope of Regulation (EC) No 1935/2004[2] and Commission Regulation (EU) No 10/2011[3], has been revised.
For transparency reason, please note that the previous version of this guidance document is still accessible, watermarked as "obsolete", under the 'Supporting information' tab on Wiley Online Library.
The following information is updated:

- The former title '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 authorisation' has been changed into: 'Note for Guidance for the preparation of an application for the safety assessment of a substance to be used in plastic food contact materials', to clarify that this document applies specifically to plastic food contact materials.
- Chapter 0 and Chapter I of the previous version of the Note for Guidance, i.e. 'General Introduction' and 'EFSA Administrative Guidance', have been removed and replaced by a separate guidance document, the **'Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials'**[4].
- Chapter II of the previous version of the Note for Guidance has also been removed from the current version of the document. It consisted of the 'Guidelines of the Scientific Committee on Food for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation'[5], the so-called 'SCF guidelines for Food Contact Materials', issued in 2001 by the Scientific Committee of Food (SCF) of the European Commission's Health & Consumer Protection Directorate-General. It has been removed because it is already publicly available at the European Commission website, where all the original opinions as adopted by the former Scientific Committee on Food can be found[6]. It should be noted that the principles described in the SCF guidelines are still valid and represent the scientific reference for applicants presenting an application for the safety assessment of a substance to be used in food contact materials.
  The only exception to the above assertion is the dataset required to assess the genotoxic potential of a substance. The core set of the three *in vitro* mutagenicity studies, as presented in chapter 8.2 of the 'SCF guidelines for Food Contact Materials' has been superseded and is no longer recommended within the present guidance. The current state of the science on genotoxicity testing is described in the 'EFSA Scientific Committee opinion on genotoxicity testing strategies'[7] issued in 2011 and its recommendations should henceforth be followed by applicants. More specifically, the Scientific Committee recommends the use of the following two in vitro tests as the first step in testing:
  - a bacterial reverse mutation assay (OECD TG 471), and
  - an *in vitro* micronucleus test (OECD TG 487).
  This combination of tests fulfils the basic requirements to cover the three genetic endpoints, i.e. gene mutations, structural and numerical chromosomal aberrations, with the minimum number of

[2] 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, OJ L 338, 13.11.2004, p. 4–17
[3] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, OJ L 12, 15.1.2011, p. 1–89
[4] EFSA (European Food Safety Authority), 2021. Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials.
[5] https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out82_en.pdf
[6] European Commission's archive of opinions adopted by the former Scientific Committee on Food available at: http://ec.europa.eu/food/sci-com/scientific-committee-food-archive_en
[7] EFSA Scientific Committee; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [69 pp.] doi:10.2903/j.efsa.2011.2379.

tests: the bacterial reverse mutation assay covers gene mutations and the *in vitro* micronucleus test covers both structural and numerical chromosome aberrations.
The assessment of genotoxicity performed in the past based on the testing strategy as described in the 2001 'SCF guidelines for Food Contact Materials', remains valid and no revaluation is needed in this respect. However, from now on, applicants are recommended to develop new data according to the most up to date requirements on genotoxicity testing, as described in the 2011 'EFSA Scientific Committee opinion on genotoxicity testing strategies' (please refer to section 'Applicability and transitional period' at the end of this document).

- Chapter III of the previous version of the Note for Guidance and has been renamed **'Explanatory Guidance of the SCF Guidelines for Food Contact Materials'**. It contains the scientific requirements to be considered when preparing an application to be submitted for evaluation to EFSA. As explained above, the genotoxicity requirements (i.e. item 7.1) have been revised in line with the recommendations of the 2011 'EFSA Scientific Committee opinion on genotoxicity testing strategies'. To increase transparency, also the toxicological data requirements (i.e. section 7) have been updated with the general principle reported in the 'SCF Guidelines for Food Contact Materials', stating that the greater the exposure to the substance through migration, the more toxicological information will be needed.
  It should be noted that in January 2016, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), adopted a 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[8].
- This opinion was neither intended to be a guidance document nor to replace the 'SCF Guidelines for Food Contact Materials', but to provide the European Commission with a scientific basis for possible future revision of the legislation on food contact materials. Nonetheless it is a scientific reference that could be considered for the safety evaluation of nanomaterials when used in the manufacture of food contact material and of non-intentionally added substances (NIAS) that may migrate, since the first topic is not covered and the second topic is only partly covered in the 'SCF Guidelines for Food Contact Materials'. In addition, the 2016 EFSA scientific opinion provides references to additional OECD test guidelines, addressing some toxicological endpoints which were not considered in the previous version of the Note for Guidance, i.e. prenatal developmental toxicity, two-generation reproduction toxicity, extended one-generation reproduction toxicity, delayed neurotoxicity of organophosphorus substances, developmental neurotoxicity. To increase awareness, references to these additional OECD test guidelines have been also added in items 7.2.3 'Reproduction/Teratogenicity' and 7.4.2 'Neurotoxicity' of the Explanatory Guidance.
- Chapter IV of the previous version of the Note for Guidance, i.e. 'Commission Explanatory Guidance on Migration Testing', has also been removed from this document, as it is going to be replaced by the 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'[9], which will be soon issued by the European Commission Joint Research Centre (JRC) and published on the European Commission's website.

Besides the above-mentioned revisions, the following updates have also been introduced to this guidance document:

- The introduction to the Explanatory Guidance has been revised.
- All references to old EU Directives have been updated to the legislation currently in force.
- The outdated reference to the 'Commission Explanatory Guidance on Migration Testing' has been replaced throughout the text with a reference to the 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'.
- A reference to the JRC 'Practical guidelines on the application of migration modelling for the estimation of specific migration' has been included in item 4.1 'Specific Migration' of the Explanatory Guidance. This document gives guidance to conservative migration modelling in support of Regulation (EU) No 10/2011.

[8] 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

[9] E. Hoekstra, E. Bradley, R. Brandsch, J. Bustos, D. Dainelli, B. Faust, R. Franz, O. Kappenstein, R. Rijk, A. Schaefer, B. Schupp, C. Simoneau, M. Vints. (2016) Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011, EUR 28329 EN, doi: 10.2788/54707

- A reference to the JRC 'Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials' has been added in item 4.1.8 'Analytical method' used for specific migration and item 5.5 'Test method' for the determination of the residual content of the substance in the food contact material.
- The list of references reported in section 9 of the Explanatory Guidance has been removed as no longer relevant.
- Annex 3 (Peroxisome proliferation studies) and Annex 5 (Definition of SCF lists) to Chapter III have been removed, as they are no longer relevant to the evaluation of substances for food contact materials.
- Annex 6 to Chapter III (Model for a petitioner summary data sheet (P-SDS)) has been removed, as it is now replaced by the **Appendix A - Technical Dossier** of the '**Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials' (EFSA 2021)**

Note that minor editorial changes are not specified in the above text.

Note: In the current (2020) update of the document, the following sections have been revised: the Explanatory Guidance of the 'SCF Guidelines for Food Contact Materials' has been amended in some sections by removing 1) references to the administrative procedure of submitting an application, and 2) references to confidentiality claims, which have been amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain, and 3) the section on 'Authorisation of substance'. This information can be found in the **Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials (EFSA 2021).**

EXPLANATORY GUIDANCE OF THE 'SCF GUIDELINES FOR FOOD CONTACT MATERIALS'

Introduction

The aim of this Explanatory Guidance is to help applicants in preparing an application for the safety assessment of a substance to be used in plastic food contact materials prior to its authorisation. This guidance amplifies and explains the information requested by the 'SCF guidelines on Food Contact Materials' by giving a more detailed description of the data needed for the safety assessment of the substance.
The below layout explains what information is expected to be contained in the technical dossier. The data requested in the first column should always be provided, either as indicated in the second column or as a statement such as 'yes', 'no', 'not applicable', 'no info', 'not relevant', etc. Justification of any deviation from this Explanatory Guidance must be given in the technical dossier.

For a complete guidance on the administrative procedure to be followed and the documentation to be provided for the safety assessment of a substance to be used in food contact materials, please refer to the **'Administrative Guidance for the preparation of applications on substances to be used in plastic food contact materials (EFSA 2021)**'.

In addition, note that:

- In accordance with the EU legislation, detailed guidelines on compliance testing have been prepared by the European Commission Joint Research Centre (JRC). These guidelines have not been included in this document but are described in the JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011', which will be soon published on the European Commission's website.
- A reference to the JRC 'Practical guidelines on the application of migration modelling for the estimation of specific migration' has been included in item 4.1 'Specific Migration'. This document provides guidance to conservative migration modelling in support of Regulation (EU) No 10/2011.
- A reference to the JRC 'Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials' has been added in item 4.1.8 'Analytical method' used for specific migration and item 5.5 'Test method' for the determination of the residual content of the substance in the food contact material.
- Section 7, related to the toxicological data requirements, has been updated in line with the general principle described in the 'SCF Guidelines for Food Contact Materials', stating that the greater the exposure to the substance through migration, the more toxicological information will be needed.
- Item 7.1, related to genotoxicity requirements, has been updated in order to reflect the current state of the science on genotoxicity testing as described in the 2011 'EFSA Scientific Committee opinion on genotoxicity testing strategies'.
- References to additional OECD test guidelines have been added in items '7.2.3 Reproduction/Teratogenicity' and '7.4.2 Neurotoxicity', to address some reproduction toxicity and neurotoxicity endpoints that were not considered in the previous version of the Note for Guidance.

Data requested		Guidance for providing the data requested
1.	**IDENTITY OF SUBSTANCE**	
1.1	**Individual substance:**	Answer 'yes' or 'no' If 'no' go to 1.2, if 'yes' give information requested in 1.1.1 to 1.1.11 as complete as possible.
1.1.1	**Chemical name:**	Give chemical name of substance.
1.1.2	**Synonym(s):**	Set out synonyms, if any.
1.1.3	**Trade name(s):**	Set out trade name(s), if any.
1.1.4	**CAS Nr:**	Set out CAS number, if any.
1.1.5	**Molecular and structural formula:**	Give molecular and structural formula.
1.1.6	**Molecular weight:**	Give molecular weight.
1.1.7	**Spectroscopic data:**	Give spectroscopic data which allow identification of the substance, e.g. FTIR, UV, NMR and/or MS. *Ref:*
1.1.8	**Manufacturing details:**	Set out production process, including starting substances, production control and reproducibility of the process. If known, indicate any alternative production process and product that can be used, and whether such products have the same characteristics. *Ref:*
1.1.9	**Purity (%):**	Set out percentage purity. Set out how the purity was established. Supporting documentation (e.g. chromatograms) should be provided. The substance will be evaluated for the stated level of purity. *Ref:*
1.1.10	**Impurities (%):**	Set out: - identity and typical range of percentage of impurities - origin of the impurities (e.g. starting substance, side reaction product, degradation product) - individual impurity levels, - the analytical method(s) to determine the impurities. Supporting documentation (e.g. chromatograms) should be provided. If there might be some concern about impurities, migration and/or toxicity data on these impurities might be requested, and specifications set by authorities.
1.1.11	**Specifications:**	Where appropriate, submit a proposal for a specification

		(e.g. level of purity, nature and percentage of impurities, type of polymer to be used) to be included in Commission Regulation (EU) No 10/2011, as amended. *Ref:*
1.1.12	**Other information:**	Set out any other information that may be relevant for evaluation. *Ref:*
1.2	**Defined mixture:**	Answer 'yes' or 'no' If 'no' go to 1.3, if 'yes' give information requested in 1.2.1 to 1.2.13 as completely as possible. This section only deals with 'process mixtures', obtained from a reproducible process and where the detailed composition can be easily determined (e.g. mixture of isomers). 'Synthetic mixtures', made up by mixing individual components are not considered here.
1.2.1	**Chemical name:**	Give chemical name of mixture, if any.
1.2.2	**Synonym(s):**	Set out synonyms, if any.
1.2.3	**Trade name(s):**	Set out trade name(s), if any.
1.2.4	**CAS Nr:**	Set out CAS number(s), if any.
1.2.5	**Constituents:**	Set out chemical name(s) of constituents of the mixture.
1.2.6	**Proportions in the mixture:**	Set out proportions of substances in the mixture. *Ref:*
1.2.7	**Molecular and structural formula:**	Give molecular and structural formula of each component including isomers.
1.2.8	**Molecular weight (Mw) and range:**	Give molecular weight (weight averaged molecular mass) and molecular weight range. *Ref:*
1.2.9	**Spectroscopic data:**	Give spectroscopic data which allow identification of the mixture, e.g. FTIR, UV, NMR and/or MS. *Ref:*
1.2.10	**Manufacturing details:**	Set out production process, including starting substances, production control and reproducibility of the process. If known, indicate any alternative production process and product that can be used, and whether such products have the same characteristics. *Ref:*
1.2.11	**Purity (%):**	Set out percentage purity. Set out in what way the purity was established. Supporting documentation (e.g. chromatograms) should be provided. The substance will be evaluated for the stated level of purity. *Ref:*

1.2.12 Impurities (%):

Set out:
- identity and typical range of percentage of impurities,
- origin of the impurities (e.g. starting substance, side reaction product, degradation product)
- individual impurity levels,
- analytical methods to determine the impurities. Supporting documentation (e.g. chromatograms) should be provided.

If there might be some concern about impurities, migration and/or toxicity data on these impurities might be requested, and specifications set by authorities.

Ref:

1.2.13 Specifications:

Where appropriate, give a proposal for a specification to be included in Commission Regulation (EU) No 10/2011, as amended.

Ref:

1.2.14 Other information:

Set out any other information that may be relevant for evaluation.

Ref:

1.3 Non-defined mixture:

Answer 'yes' or 'no'
If 'no' go to 1.4, if 'yes' give information requested in 1.3.1 to 1.3.16 as complete as possible.
Non-defined mixtures are mixtures which may vary from batch to batch, but which have a composition within certain specifications. Typical examples of non-defined mixtures are products derived from natural sources. Their composition will depend on the origin of source, climate and treatment. Also, technical processes like ethoxylation, epoxidation or hydrogenation may create a large number of individual components.

1.3.1 Chemical name:

Give description as complete as possible.

1.3.2 Synonym(s):

Set out synonyms, if any.

1.3.3 Trade name(s):

Set out trade name(s), if any.

1.3.4 CAS nr:

Set out CAS number(s), if any.

1.3.5 Starting substances:

Set out substances or raw materials used in manufacturing the mixture.

1.3.6 Manufacturing details:

Set out production process, production control and reproducibility of the process.
If known, indicate any alternative production process and product that can be used, and whether such products have the same characteristics.

Ref:

1.3.7 Substances formed:

Set out substances formed during the process.

Ref:

1.3.8 Purification by:

Set out details of purification of the end product.

Ref:

1.3.9	**By-products:**	Give qualitative and quantitative information on by-products, if any. *Ref:*
1.3.10	**Molecular and structural formula:**	Give molecular and structural formula. For non-defined mixtures this information may be complicated. In some cases, the information requested could be described as e.g. 'oil of natural origin' with range of fatty acids and further treatment, if any.
1.3.11	**Molecular weight (M_W) and range:**	Give Mw (weight averaged molecular mass) and molecular weight range. *Ref:*
1.3.12	**Purity (%):**	Set out percentage purity. Set out how the purity has been established. Supporting documentation (e.g. chromatograms) should be provided. The substance will be evaluated for the stated level of purity. *Ref:*
1.3.13	**Impurities (%):**	Set out: - identity and typical range of percentage of impurities, - origin of the impurities (e.g. starting substance, side reaction product, degradation product) - individual impurity levels, - analytical methods to determine the impurities. Supporting documentation (e.g. chromatograms) should be provided. If there might be some concern about impurities, migration and/or toxicity data on these impurities might be requested, and specifications set by authorities. *Ref:*
1.3.14	**Spectroscopic data:**	Give spectroscopic data which allow identification of the substance, for example FTIR, UV, NMR and/or MS. *Ref:*
1.3.15	**Specifications:**	Where appropriate, give a proposal for a specification to be included in Commission Regulation (EU) No 10/2011, as amended.
1.3.16	**Other information:**	Set out any other information that may be relevant for evaluation. *Ref:*
1.4	**Polymer used as additive:**	Answer 'yes' or 'no' If 'no' go to 2, if 'yes' give information requested in 1.4.1 to 1.4.19 as complete as possible. Polymeric additive means any polymer and/or prepolymer and/or oligomer, which may be added in plastics in order to achieve a technical effect, but which cannot be used as such for the manufacture of finished materials and articles. It includes also polymeric substances which may be added to the medium in which

polymerisation occurs.

1.4.1 Chemical name: Give chemical name of substance, if any.

1.4.2 Synonyms: Set out synonyms, if any.

1.4.3 Trade name(s): Set out trade name(s), if any.

1.4.4 CAS Nr: Set out CAS number, if any.

1.4.5 Starting substances: Set out monomers and/or other starting substances.

1.4.6 Manufacturing details: Set out production process, production control and reproducibility of the process.
If known, indicate any alternative production process and product that can be used, and whether such products have the same characteristics.
Ref:

1.4.7 Additive(s): Set out additives used, if any.

1.4.8 Structure of polymer: Give structure of polymer.

1.4.9 Weight averaged molecular mass: Give weight averaged molecular mass.
Ref:

1.4.10 Number averaged molecular mass: Give number averaged molecular mass.
Ref:

1.4.11 Molecular mass range: Give molecular mass range and a distribution curve.
Curve of the distribution of the molecular masses (see figure below). This should be obtained by gel permeation chromatography (GPC) or by another validated method.

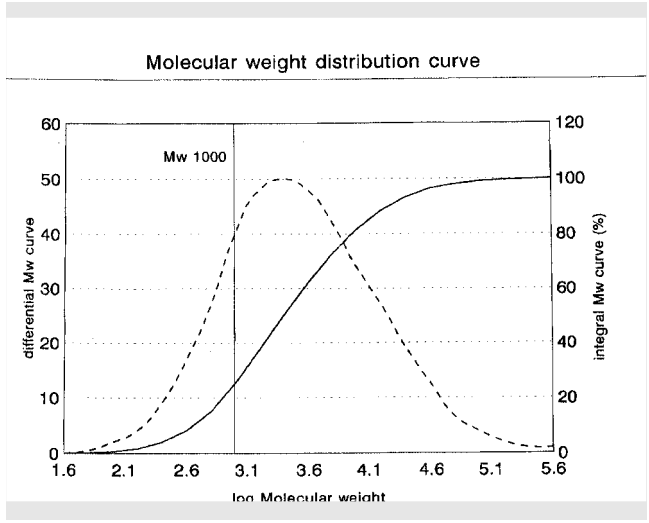
- The GPC calibration supplied should include as standards samples of the same polymer, having their molecular mass accurately determined by an adequate technique (their molecular mass should lie around 1,000 Da). Determine the weight averaged molecular mass in weight (M_W) and the number averaged molecular mass (M_n).

- If standards of the same polymer are not available, then polystyrene standards should be used. An absolute value of M_W or M_n should then be determined by an adequate technique. The abscissa of the GPC molecular mass distribution curve should then be corrected by the factor:

$$\frac{M_n \text{ (absolute value)}}{M_n \text{ (GPC value relative to PS)}} \quad \text{or} \quad \frac{M_W \text{ (absolute value)}}{M_W \text{ (GPC value relative to PS)}}$$

On the integrated molecular mass distribution curve (determined according the above-mentioned guidelines) determine the point corresponding to abscissa 1,000 Da

(true value): this gives the percentage of polymeric additive with molecular mass less than 1,000 Da.



figure

Ref:

1.4.12 Constituents with molecular mass <1,000 (%):

Set out percentage constituents with molecular mass < 1,000 Da. Check this by analysis of the constituents < 1,000 Da by chromatography, e.g. gas chromatography (GC).

1.4.13 Viscosity, if available:

Give intrinsic and/or relative viscosity, if any.

Ref:

1.4.14 Melt flow index, if available:

Give melt flow index, if any.

Ref:

1.4.15 Density (g/cm^3):

Give density, if any.

Ref:

1.4.16 Spectroscopic data:

Give spectroscopic data, which allow identification of the subject substance, for example FTIR, UV, NMR and/or MS.

Ref:

1.4.17 Residual monomers (mg/kg):

Set out monomers as well as individual monomer contents. See also section 5 (i.e. Data on residual content of substance in the food contact material).

Ref:

1.4.18 Purity (%):

Set out percentage purity.
Set out how the purity was established. Supporting documentation (e.g. chromatograms) should be provided.
The substance will be evaluated for the stated level of purity.

Ref:

1.4.19 Impurities (%):

Set out:

- identity and typical range of percentage of impurities,
- origin of the impurities (e.g. starting substance,

side reaction product, degradation product)
- individual impurity levels,
- describe the analytical methods to determine the impurities. Supporting documentation (e.g. chromatograms) should be provided.

If there might be some concern about impurities, migration and/or toxicity data on these impurities might be requested, and specifications set by authorities.

Ref:

1.4.20 Specifications:

Where appropriate, give a proposal for the specification to be included in Commission Regulation (EU) No 10/2011, as amended.

Ref:

1.4.21 Other information:

Set out any other information that may be relevant for evaluation.

Ref:

2. PHYSICAL AND CHEMICAL PROPERTIES OF SUBSTANCE

2.1 Physical properties

2.1.1 Melting point (°C):

Give melting point.

2.1.2 Boiling point (°C):

Give boiling point.

2.1.3 Decomposition temperature (°C):

Give decomposition temperature, if any.

Ref:

2.1.4 Solubility (g/l):

Set out solubility in solvents.
If available, solubility in organic solvents should be presented as well as in food simulants.
If in migration tests a fatty food simulant is replaced by a substitute volatile simulant, then both solubility in the oil and in the substitute, simulants is required. At least a semi-quantitative estimate of solubility should be presented to make the use of substitute solvents acceptable. The solubility may be given in g/L, or it may be indicated, e.g. miscible, good, moderate, poor or insoluble, etc. The intention here is that comparative information on solubility, which is one of the parameters that may influence migration, is obtained.

Ref:

2.1.5 Octanol/water partition (log Po/w):

Set out partition coefficient, if available.
Information is obligatory in the following cases:
- Migration is > 0.05 mg/kg of food/food simulant
- Substance is requested to be subject to the Fat (consumption) Reduction Factor (FRF).

If the migration is > 0.05 mg/kg, then information on accumulation in man is requested (see Annex 3). The log $P_{o/w}$ could be a tool to decide for the need of additional data.

Lipophilic substances may be marked as appropriate to apply the FRF. Proper evidence should be provided to demonstrate the lipophilic properties of a substance. A log $P_{o/w}$ value may be one of the three criteria established to classify the substance as lipophilic. The other two are the following:

1) Migration into non-fatty simulants should not exceed 1/10 of the Specific Migration Limit (SML) of the substance or
2) Solubility in the non-fatty simulants should be less than 10% of the SML

Ref:

2.1.6 Other information related to lipophilicity: Give any other relevant information.

Ref:

2.2 Chemical properties

2.2.1 Nature: Answer 'acidic', basic' or 'neutral'.

2.2.2 Reactivity: Give information on reactivity of subject substance.

2.2.3 Stability: Give information on stability of subject substance in the polymer towards light, heat, moisture, air, ionising radiation, oxidative treatment, etc.
Provide a thermogravimetric analysis (for substances other than monomers) of the substance.
For chemicals which are not deemed to react in the polymer, the onset of degradation should in general be 10% above the max. process temperature. If this is not met, an explanation should be given why the substance can be used above or near the decomposition temperature. If any of the other parameters are relevant for authorisation of the substance, then sufficient detailed information shall be provided for a proper evaluation.

Ref:

2.2.4 Hydrolysis: Hydrolysis may simplify the petition if already evaluated chemicals are formed in high yield in body fluid simulants. If relevant, give results of hydrolysis tests carried out according to the guidelines of Annex 1. If hydrolysis tests are carried out, full details shall be provided, including the analytical method.

Ref:

2.2.5 Intentional decomposition/ transformation: Give information on intentional decomposition or transformation of substance, if any, during manufacture of a food contact material or article.
If there might be some concern about decomposition products, migration and/or toxicity data on these products might be requested, and specifications or restrictions may be set.
In this respect, a monomer is considered to be transformed into a polymer additive like scavengers will be transformed and antioxidants will be decomposed according to the intention of use. Other substances may

be decomposed, e.g. by oxidation or due to high temperature, etc.

Ref:

2.2.6 Unintentional decomposition/ transformation product(s):

Where relevant, set out unintentional decomposition or transformation products
- of the pure substance (see 2.2.3)
- formed in the material during the manufacture of a final article
- formed during various treatments likely to be applied to the finished material or article (e.g. ionising treatments).

Ref:

2.2.7 Interaction with food substances:

Give information on reaction of the substance with food substances, if any.
This item is important for making decisions on the type of restriction to be established (SML, QM or QMA). If migration tests, including recovery tests (see item 4.1.11), have been carried out, reference could be made to item 4.1. In any other situation, stability of the substance in food simulants should be provided, unless a QM or QMA limit is requested by the applicant.

Ref:

2.2.8 Other information:

Set out any other information that may be relevant for evaluation.

Ref:

3. INTENDED APPLICATION OF SUBSTANCE

3.1 Food contact material:

Set out food contact material(s) in which the substance is to be used. Provide specific examples. Information should be provided in what type of polymers the substance is intended to be used, and/or in what type of food contact material, e.g. all kinds of polyolefins, ABS used for manufacture of household machines, only in PET beverage bottles. This information may be important for estimating the real exposure.
Indication of a very restricted or a very broad field of application may influence the final authorisation and the restrictions of the substance.

3.2 Technological function:

Set out the function(s) of the substance in the production process or in the finished product. For example, monomer, co-monomer in the production of polymer X, antioxidant, antistatic agent, preservative, etc. Provide relevant information to demonstrate the functionality of the substance in the final product. If relevant, provide information on the production process.

3.3 Maximum process temperature (°C):

Set out maximum temperature in manufacturing process of polymer as well as final food contact material. (see also 2.2.3)

3.4	**Maximum percentage in formulation:**	Set out maximum percentage of the substance used in the formulation and/or related to the final food contact material (e.g. a substance added in an aqueous suspension should be related to the dry matter). The maximum percentage to achieve a technological property, as well as the level used in practice should be given, if relevant. Typically, in the case of additives, the maximum percentage will influence the migration of the substance. Materials submitted to migration testing should contain the maximum percentage indicated.
3.5	**Conditions of contact in practice**	
3.5.1	**Contact food:**	Set out the foods to be in contact with the finished products. Indicate typical foodstuffs and use for all types of foodstuff. Migration tests should be carried out accordingly.
3.5.2	**Time and temperature:**	Set out approximate time and temperature of contact in practice as well as restrictions of time and temperature. See Commission Regulation (EU) No 10/2011, as amended for further guidance.
3.5.3	**Surface to volume ratio:**	Set out the approximate ratio of dm^2 food contact materials to kg food in practice. For materials intended for general application the ratio is conventionally 6 dm^2/kg. For specific applications the ratio area/food may deviate significantly, e.g. tubing or large tanks, single portion package (see also 3.1) Information requested here should not be confused with the information requested in item 4.
3.5.4	**Other information:**	Give any other relevant information.
3.6	**Treatment of food contact material prior to use:**	Give information on treatment of food contact material prior to contact with food, e.g. sterilisation, cleaning with pressurised steam, rinsing, irradiation, e-beam or UV light treatment, etc.
3.7	**Other uses:**	Set out other uses or intended uses of the substance additional to food contact materials, if any. If the substance is used in other domains than food contact materials, only a fraction of the ADI may be allocated to food contact materials.
3.8	**Other information:**	Set out any other information that may be relevant for evaluation.

4. DATA ON MIGRATION OF SUBSTANCE

If food simulants are used, the provisions concerning the specific and overall migration set out in Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, as amended, should be followed. Further guidance can be also found in the 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011', which will be soon issued by the European Commission Joint Research Centre (JRC) and published on the European Commission's website.

4.1 Specific migration (SM):

Answer 'SM determined' or 'SM not determined'. If SM is not determined, give reasons. In general, the determination of the specific migration will be requested to estimate the worst-case migration. Based on the level of migration, the number of toxicity tests can be established. However, there are a number of exceptions where the determination of specific migration can be replaced by the determination of the content of the substance followed by worst case calculation. If it is impossible to measure specific migration because of the properties of the substance, e.g. polymeric additives, the overall migration can be used to demonstrate worst case migration of the substance. All experiments required in specific migration testing should be performed in triplicate.
If migration modelling is applied, useful guidance can be found in the JRC Technical Report "Practical guidelines on the application of migration modelling for the estimation of specific migration"[10].

Ref:

4.1.1 Substance:

Set out substance(s) determined.
Information on migration of decomposition products (e.g. antioxidant) and/or impurities – if any – may be required as well.

Ref:

4.1.2 Test sample:

The test sample should always represent the worst-case situation. This means the highest concentration of additive or co-monomer should be present. Also, the thickness of the test sample should represent the worst-case situation. If the test sample is intended to represent a range of materials of different brands or grades, it should be assured that the material selected represents the worst-case situation in the migration testing. If the substance is used in different kinds of polymers, in principle each type of polymer should be tested. However, if it is properly argued, only migration tests with the polymer representing worst case can be acceptable.

Ref:

[10] E.J. Hoekstra, R. Brandsch, C. Dequatre, P. Mercea, M.R. Milana, A. Störmer, X. Trier, O. Vitrac A. Schäfer and C. Simoneau; Practical guidelines on the application of migration modelling for the estimation of specific migration; EUR 27529 EN; doi:10.2788/04517

4.1.2.1 Chemical composition: Set out the chemical composition of the test sample. Information should be provided particularly on the initial concentration of the substance, but also on the total composition of the test specimen, as this may influence the final migration of the substance.

4.1.2.2 Physical composition: Set out the physical composition of test sample, such as homogeneous material or multilayer material. In case of a multilayer material, it should be indicated in which layer the substance is present. If this is not the direct food contact side, also information on the top layers is needed.

4.1.2.3 Density, melt flow index of polymer: Set out density and melt flow index (if relevant) of the polymer containing the substance. This information is required for mathematical modelling. In multilayer constructions also the density of the barrier layers shall be given.

4.1.2.4 Dimensions of test sample: Set out dimensions of test sample.
Test sample is the sample manufactured for the purpose of the migration study. Provide information on shape, e.g. bottle, film, sheet, etc., and the thickness of the test sample. For laminates, the total thickness and the thickness of each relevant layer should be indicated. For articles with inhomogeneous thickness, the thickness at various places should be given. The dimensions of an article should be set out (height, length, width and/or diameter).

4.1.2.5 Dimensions of test specimen: Describe briefly the part or section of the test sample from which the test specimen was taken particularly in case of inhomogeneous materials (e.g. bottle).
Set out spatial dimensions of test specimen (length, height, width, diameter).
Calculate the total area of the test specimen. In case of two-sided contact (see 4.1.5), also calculate the total area of both sides. If the test specimen does not come into contact completely with the simulant (with use of one side migration cells) then calculate the actual contact area.

4.1.3 Treatment of test sample prior to testing: Set out to what treatment the food contact material was subjected prior to testing, e.g. cleaning, washing, etc. The treatment should be representative of the use in practice.

4.1.4 Test food(s)/food simulant(s): Set out foodstuff(s) or food simulant(s) used in migration testing. Commission Regulation (EU) No 10/2011, as amended, should be followed for the selection of the food simulant. Especially when olive oil is replaced by substitute food simulants, this document should be studied carefully. The JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011' should be also taken into account. Data on solubility as requested in item 2.1.4 shall also be provided in those cases. Replacement of olive oil by substitute simulants is only acceptable in cases of technical problems. Therefore, the

necessity of the use of substitute simulants should be clarified, preferably supported by analytical data. Olive oil should not be replaced for convenience only. Arguments will be considered for validity. Poor analytical chemistry or lack of facilities may not appear acceptable arguments for replacement of olive oil by substitute simulants.
In the special case of migration of metal ions where ion exchange is the driving force, migration experiments should also be performed in the following simulants: 40 mM sodium acetate buffer at pH 5 and 50 mM sodium phosphate buffer at pH 7.

4.1.5 Contact mode:

Set out whether the sample was tested on one or on two sides and in which way contact with the simulants was achieved, e.g. cell, pouch, total immersion etc. If tested on two sides, set out whether one or both sides of the test specimen are used in the calculation of the contact area.

4.1.6 Contact time and temperature:

Set out the duration of the test and test temperature. Time temperature combinations should be determined in accordance with Annex V to Regulation (EU) No 10/2011.
In case of short contact times (≤ 2 hours) at high temperature (≥ 100°C), describe the temperature profile over the test period.

4.1.7 Surface to volume ratio:

Set out dm^2 test sample per kg food or L simulant. Give the actual contact area and the volume of simulant. Calculate from these data the actual surface to volume ratio applied in the migration test. Conventionally the ratio is 6 dm^2/kg simulant. For analytical reasons it may be necessary to deviate from that ratio, which in principle is acceptable. However, it should be considered whether using a different ratio of area to volume could influence the migration due to saturation of the simulant.

4.1.8 Analytical method:

Set out the principle of the analytical method used and submit a copy in standard format.
Useful guidance can be found in the JRC 'Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials'[11] and in the JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'.
The technical dossier should contain, e.g. actual data concerning the preparation of calibration solutions, typical chromatograms, calibration curves, correlation coefficients and all other relevant data needed for a proper evaluation of the method and the migration data provided. The method may be used by enforcement laboratories and should, therefore, use generally available equipment. Use of very sophisticated methods should be justified.

[11] Bratinova S., Raffael B., Simoneau C. (2009) Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials. 1st edition 2009. Publication Office of the European Union, Luxembourg, JRC Scientific and Technical Report, EUR 24105 EN

Ref:

4.1.9 Detection/ determination limit:

Give the detection and/or determination limit of the method and set out the way the detection limit was established. Detection limits are particularly important when migration is not detectable or near the detection limit. Where relevant, visual information such as typical chromatograms, calibration curve and blank values should be provided.

Ref:

4.1.10 Precision of test method:

Give the repeatability (r) of the method at the migration level. For example, repeatability of the method can be obtained from the standard deviation of triplicate migration experiments or from recovery experiments.

Ref:

4.1.11 Recovery:

Set out the percentage of substance recovery as determined in recovery experiments under time-temperature conditions of the migration tests. To obtain data on the suitability of the analytical method as well as the stability of the substance in the food simulants, recovery experiments (triplicate) shall be performed with the food simulants used spiked with the substance at a level of interest (e.g. 50 μg/kg) or at the actual level of the migration values. The spiked food simulants shall be kept under the same conditions of time and temperature, in the same or equivalent containers as used in the migration experiments. Provide all actual data to allow proper evaluation of the results, such as the method of standard addition (solvent used, volume added), amount of substance added to a known volume of simulant (x μg/y mL), storage condition, etc.
If low recovery values are obtained, reasons for this should be explained.
Results of the recovery test may influence the type of restriction to be established.

Ref:

4.1.12 Other information:

Set out any other information that may be relevant for evaluation.

Ref:

4.1.13 Results:

Give all individual migration data obtained, blank and recovery data inclusive. Preferably the data should be presented in a table, which should contain sufficient details to follow the way the final results are obtained, e.g.:

- test conditions of time and temperature
- simulant
- contact area
- volume of food simulant used in the test
- actual concentration of the substance in the simulant as obtained from the migration experiment
- migration in the food simulant expressed in mg/dm²
- migration in the food simulant using the conventional factor of 6 dm²/kg or any other relevant ratio
- amount of substance added in the recovery tests.

Ref:

4.2 Overall migration (OM):

Answer 'determined', 'not determined'.
In general, the determination of the OM is not required for petitioning of an additive or a monomer. The overall migration may be used as a replacement for specific migration in those cases where the specific migration is impossible to measure because of the properties of the substance, e.g. polymeric additives. The overall migration may be used to demonstrate worst case migration of the substance.
In special cases the CEF Panel may require OM data, e.g. when larger amounts of oligomers are suspected (see item 4.3). For the determination of OM, refer to the JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'.

Ref:

4.2.1 Test sample:

Set out what food contact material sample was subjected to testing, e.g. composition, shape (bottles, film, cups, tins, etc.), thickness and dimensions. For selection of test samples, etc., see 4.1.2. Where relevant use the same grade of test material in specific and overall migration testing. However, there may be reasons to take different grades of material. Where the overall migration of one grade gives highest results while from another grade the specific migration is the highest, then different test samples could be used.

Ref:

4.2.2 Treatment of sample prior to testing:

Set out to what treatment food contact material was subjected prior to testing.

4.2.3 Food simulant(s):

Set out food simulant(s) used in testing.
Commission Regulation (EU) No 10/2011, as amended, should be followed for the selection of food simulants. The JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011', should be also taken into account. The necessity of the use of substitute test medium should be explained, preferably supported by some analytical data.

4.2.4 Contact mode:

Set out whether the sample was tested on one or on two sides. Set out in which way contact with the simulants was achieved, like cell, pouch, total immersion etc. If tested on two sides, set out whether one or both sides of the test specimen are used in the calculation of the contact area.

4.2.5 Contact time and temperature:

Set out duration of test and test temperature in °C. Time temperature combinations should be determined in accordance with Annex V to Regulation (EU) No 10/2011.
In case of short contact times (≤2 hours) at high temperature (≥100°C), describe in acceptable manner or demonstrate maintenance of the temperature over the

test period.

4.2.6 Surface to volume ratio:

Set out area of test sample in dm^2/L simulant.
Conventionally the ratio is 6 dm^2/kg simulant. The actual ratio in the migration tests may deviate.

4.2.7 Test method:

Set out analytical methods used. Reference to valid CEN methods (see item 4.2) should be given, where relevant. Any deviation from those methods should be reported. If other methods are used to determine the overall migration, then a detailed description of the analytical method should be provided.

4.2.8 Other information:

Set out any other information that may be relevant for the evaluation.

4.2.9 Results:

Give all individual migration data obtained, if relevant, blanks inclusive. The data should preferably be presented in a table, which should contain sufficient details to follow the way the final results are obtained, e.g.:

- test conditions of time and temperature (in °C)
- simulant
- contact area (dm^2)
- volume of food simulant used in the test (mL)
- migration in the food simulant expressed in mg/dm^2
- migration in the food simulant using the conventional factor of 6 dm^2/kg or any other relevant ratio.

Ref:

4.3 Quantification and identification of: a) migrating oligomers and b) reaction products derived from monomers and starting substances and additives:

Answer 'determined', or 'not determined'. Where it is not determined, a justification should be given.
Experimental data show that in polymers the migration of oligomers (M_w < 1,000) or reaction products occurs, and in some cases, high levels were found. Therefore, there is a need for information on:

(a) the migration of oligomers from polymers produced from monomers or which are produced by means of polymerisation aids that influence the molecular structure or molecular weight of the polymer.
(b) the migration of reaction products from polymers produced from monomers or additives.

In the first instance, there is a need for information on the identity and level of substances that migrate as a consequence of the use of a new monomer or additive (see also 2.2).
Tests with olive oil may not be suitable for identification purposes. Substitute simulants or alternative test media may be more convenient for identification purposes.
In principle, the identity of the migratable substances may be required, however in some cases a simple characterisation by identification of the functional groups may be sufficient.

Ref:

4.3.1 Test sample:

The test sample composition and its thickness should always represent the worst case. In general, the highest

concentration of the substance, and the largest thickness, should be used. If the substance is intended to be used in a range of materials of different polymers or grades, then each type of material should be tested. However, if it is properly argued, only tests with the material representing the worst case may be acceptable.

Ref:

4.3.1.1 Chemical composition:

Set out chemical composition of the test sample. Information should be provided on the initial concentration of the substance(s), and also on the total composition, as this may influence the final migration of the substance(s).

4.3.1.2 Physical composition:

Set out physical composition of test sample, such as homogeneous material, multi-layer material, etc.
In the case of a multi-layer material, it should be indicated in which layer the substance(s) is present. If this is not the direct food contact side, then relevant information should also be given on the top layers.

4.3.1.3 Density, melt flow index of polymer:

Set out density and melt flow index (if relevant) of the polymer containing the substance(s).
This information is required for mathematical modelling. The density of the barrier layers should also be given in multilayer constructions.

4.3.1.4 Dimensions of test sample:

Set out dimensions of test sample.
Test sample is the sample manufactured or used for the study. Provide information on shape, e.g.: bottle, film, sheet, etc. and thickness. For laminates, the total thickness and the thickness of each relevant layer should be indicated. For articles with non-homogeneous thickness, the thickness at various places should be given. The dimensions of an article should be set out (height, length, width and/or diameter).

4.3.1.5 Dimensions of test specimen:

Describe briefly the part or section of the test sample from which the test specimen was taken. Particular attention should be paid to this step-in case of variable thickness materials (e.g. bottle).
Set out spatial dimensions of test specimen (length, height, width, diameter).
Calculate the total area of the test specimen. In case of two-sided contact (see 5.3.1.4), also calculate the total area of both sides. If the test specimen does not come into contact completely with the simulant, then calculate the actual contact area.
In case of extraction, the weight of the test sample may suffice.

4.3.2 Treatment of test sample prior to testing:

Set out to what treatment the food contact material was subjected prior to testing, e.g. cleaning, washing etc. Treatment of a test sample should be representative of use in practice.

4.3.3 Test food(s)/food simulant(s)/extraction

Set out foodstuff(s) or food simulant(s) or extraction solvent(s) used in migration testing.

solvent(s):	For quantitative determinations, the use of food simulants selected according to Commission Regulation (EU) No 10/2011 as amended should be followed. Identification or characterisation of migratable substances may be possible in aqueous food simulants. In general, use of olive oil may not be feasible for various reasons. The use of volatile simulants or extraction solvents may be required to allow identification or characterisation of the migratable substances.
4.3.4 Contact mode:	Set out whether the sample was tested on one or on two sides. Set out in which way contact with the simulants was achieved, e.g.: cell, pouch, total immersion etc. If tested on two sides, set out whether one or both sides of the test specimen are used in the calculation of the contact area. Set out conditions of extraction, if relevant.
4.3.5 Contact time and temperature:	Set out test duration and temperature.
4.3.6 Surface to volume ratio in migration tests:	Give the actual contact area and the volume of simulant used in the migration experiment. Calculate their ratio expressed as dm^2/kg food simulant. In principle, the ratio should be equivalent to the ratio occurring in real use. If this ratio is not known, then the conventionally 6 dm^2/kg simulant may be used. For analytical reasons, it may be necessary to deviate from that ratio, which in principle is acceptable. However, it should be carefully considered whether or not using a higher ratio of area to volume, could influence the final migration due to saturation of the simulant, which may occur with substances poorly soluble in the simulant used. In extraction experiments, this most likely will not occur.
4.3.7 Analytical method:	Set out the principle of analytical method(s) used and submit a full copy of the method in the technical dossier. Follow the description of item 4.1.8. Identification or characterisation of migratable substances usually require application of various sophisticated and complementary techniques. The analytical methods applied should be described in the technical dossier in such detail to allow appropriate evaluation of the results. This requires information on chromatographic, mass spectrometric systems, or other means of isolation or detection. Chromatograms, spectra, etc. should be provided with a proper legend. Information or conclusions to be deduced from such documents should be accompanied by an explanatory text. Details should be given on the quantitative gravimetric analysis method. When using quantitative chromatographic methods, all details of the method that may be relevant for the evaluation of the results should be provided, e.g. actual data concerning the calibration procedure, typical chromatograms or spectra, calibration curves, correlation coefficients, etc.

Ref:

4.3.8 Detection/ determination limit:

Give detection and/or determination limit of the method and set out the way the detection limit was established for quantitative determinations. Where relevant, visual information such as typical chromatograms, calibration curve, blank values should be provided.
An indication on the detection limit should also be provided in quantitative analyses.

Ref:

4.3.9 Recovery:

Set out percentage recovery of substance as determined in recovery experiments under time-temperature conditions of migration test.
Recovery experiments as required in specific migration testing may or may not be possible, as no reference substances may be available. If there are proper arguments, then the recovery tests are not required.

Ref:

4.3.10 Other information:

Set out any other information that may be relevant for evaluation.

Ref:

4.3.11 Results:

Describe the migratable substance(s) that have been characterised or identified and give their migration levels (expressed in mg/6 dm^2). The presentation of the results of the characterised or identified migratable substance(s) may not be a straightforward issue. Any conclusions drawn from the investigations will need to be justified with some clear reasoning and explanation.

Ref:

5. DATA ON RESIDUAL CONTENT OF SUBSTANCE IN THE FOOD CONTACT MATERIAL

5.1 Actual content:

Answer 'actual content determined' or 'actual content not determined'. The need for the determination of the actual or residual content of the substance in the test material depends on the type of substance and the data provided in the specific migration determination. For guidance, the following examples are given:

- monomer (case 1)

Full data on specific migration are provided. Determination of residual content is not required.

- monomer (case 2)

Specific migration is not determined, but calculation of migration based on residual content and assuming 100% migration is provided. Determination of residual content is required. Full details concerning the method and results shall be provided.

- monomer (case 3)

Worst case migration is based on the amount of monomer initially added to the polymerisation process, while assuming 100% migration

Determination of residual content is not required. However, a properly described method for the determination of the residual content shall be provided for enforcement purposes.

- additive

Migration of additive is determined by specific and/or overall migration. The presence of the additive at the intended level in the actual test material used in migration experiments (see section 4) should be demonstrated by means of analytical data. In general, it is sufficient to demonstrate by analytical experiments the presence of the additive at the intended level. In this situation, validation of the analytical method and extensive description of the analytical method is of less importance. Nevertheless, sufficient information should be provided to make the data provided transparent and acceptable.

- monomer or additive

Determination of the specific migration of monomer or additive is not possible because of, e.g. instability of the substance in food simulants, or because a QM limit is more appropriate. The determination of the actual content should be described in full detail according to standard format. In addition, the method should be validated, and, where relevant, visual information (e.g. chromatograms) should be added.

Ref:

5.2 Substance:

Set out substance.

5.3 Test sample:

Where relevant, the test sample shall be equivalent to the test sample used in the migration experiments. In other situations, the sample shall represent a worst-case situation. If the test sample is intended to represent a range of materials of different brands or grades, then it should be assured that a material is selected that will represent the worst-case situation. If the substance is used in different kinds of polymers then, in principle, each type of polymer should be examined for the residual content of the substance. However, if it is properly argued only determination of the residual content in a polymer representing the worst case can be acceptable. Criteria of selection will depend on the substance and the manufacturing process.

Ref:

5.3.1	**Chemical composition:**	Set out chemical composition of the test sample. Information should particularly be provided on the initial concentration of the substance, but information on the total composition is also required as the composition of the test specimen may influence the applicability of the analytical method and/or the residual content.
5.3.2	**Physical composition:**	Set out physical composition of test sample, such as homogeneous material, multilayer material. In case of multi-layer material, it should be indicated in which layer the substance is present. If this is not the direct food contact side, then also relevant information on the top layers shall be given.
5.3.3	**Density, melt flow index of polymer:**	Set out density and melt flow index (if relevant) of the polymer containing the substance. This information is required for mathematic modelling. In multilayer constructions, also the density of the barrier layers shall be given.
5.3.4	**Dimensions of test sample:**	Set out dimensions of test sample. The test sample is the sample manufactured for the purpose of the determination of the residual or actual content of substance. Provide information on shape, e.g. bottle, film, sheet, etc., and thickness. For laminates the total thickness and the thickness of each relevant layer should be indicated. For articles with in-homogeneous thickness, the thickness at various places should be given. The dimensions of an article should be set out (height, length, width, diameter).
5.3.5	**Dimensions of test specimen:**	Set out dimensions or weight of test specimen. The test specimen is the actual part of material submitted to the residual content determination. Set out actual dimensions (height, length, width, diameter) or weight of the test specimen. If a subsample is taken from in-homogeneous materials (e.g. bottle), then set out which part was taken.
5.4	**Treatment of sample:**	Set out treatment of the test sample, if not included in the test method.
5.5	**Test method:**	If relevant, follow the description of item 4.1.8. The technical dossier shall contain the following information: actual data concerning the preparation of calibration solutions, typical chromatograms, calibration curves, correlation coefficients and all relevant data needed for a proper evaluation of the method as well as the data related to the residual content. Useful guidance can be found in the JRC 'Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials' and in the JRC 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'. The method of determination may be used by enforcement laboratories in order to enforce restriction

set for the substance. Therefore, the method should use generally available equipment. Use of very sophisticated methods should be justified.
Where relevant, visual information such as typical chromatograms, calibration lines, etc. should be included.

Ref:

5.5.1 Detection/ determination limit:

Give detection and/or determination limit of method and set out the way the detection limit was established. Detection limits are particularly important when a substance is not detectable or at the level of the detection limit. Where relevant visual information such as typical chromatograms, calibration curve, blank values should be provided.

Ref:

5.5.2 Precision of test method:

Give repeatability (r) of method at residual content level. For example, repeatability of the method can be obtained from the standard deviation of the triplicate determination or from recovery experiments.

Ref:

5.5.3 Recovery:

Set out percentage recovery of substance as determined in recovery experiments. To obtain data on the suitability of the analytical method, recovery experiments (triplicate) shall be performed by standard addition of the substance to the polymer sample at a level of interest or at the level of the actual content. Also, the use of similar test material not containing the substance may be allowed. The spiked samples shall be treated in the same way as the test samples itself. Where relevant, visual information should be provided. If low recovery values are obtained, reasons for this should be provided.

Ref:

5.5.4 Other information:

Give any other relevant information.

Ref:

5.6 Results:

Give individual test results, including blank and recovery data. Preferably the data should be presented in a table, which should contain sufficient details to follow the way the final results are obtained.

Ref:

5.7 Calculated migration (worst case):

Set out calculation of migration of substance assuming total migration. In case, worst case calculation is acceptable an analytical method for analysis has to be provided. See also the 'Technical guidelines for compliance testing of plastic food contact materials in the framework of Regulation (EU) No 10/2011'.

Ref:

5.8 Residual content versus specific migration:

Give the relationship between residual content and specific migration, if determined.

Ref:

6. MICROBIOLOGICAL PROPERTIES OF SUBSTANCE

This section focuses on the use of antimicrobial substances incorporated into food contact materials. Biocidal products are defined in Commission Regulation (EU) No 528/2012[12] concerning the making available on the market and use of biocidal products, as amended, as 'any substance or mixture, in the form in which it is supplied to the user, consisting of, containing or generating one or more active substances, with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action, any substance or mixture, generated from substances or mixtures which do not themselves fall under the first indent, to be used with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action'.
According to art. 3 (1)(g) of the same Regulation, a harmful organism is understood to be 'an organism, including pathogenic agents, which has an unwanted presence or a detrimental effect on humans, their activities or the products they use or produce, on animals or the environment'.

This section provides information to applicants regarding documentation to be supplied in order to permit the assessment of the public health implications, i.e. safety and efficacy including the microbiological effects of the use of an antimicrobial substance incorporated into food contact materials. Deviations are allowed provided that an appropriate justification is given.

It is not possible to give more specific guidance as to the methods to be used, as no validated methodology has been agreed at international level. Furthermore, different approaches may have to be followed for different substances depending on their intended use.

It should be noted that any effect of the biocidal active substance incorporated into the food contact material on the microbial flora of the food is strongly dependent on the contact time of the food contact material with the food (dose-time relation). This should be taken into account when assessing the effect of the **antimicrobial substance** on the microbial flora.

The evaluation of the microbiological data may lead to a restriction of use or of migration. If there is also another restriction based on toxicology, the lower should apply.

Substances with antimicrobial properties, which are intended to be incorporated into food contact materials will be evaluated on a case by case basis. Applicants shall provide all data required in items 1-6 of this Note for Guidance. Toxicological data shall be provided for new substances or substances not evaluated before by the EFSA-CEF panel. Active ingredients evaluated before will NOT need new toxicological data, provided the carrier system is inert and/or already approved and does not actively contribute to the antimicrobial properties of the food contact material. A typical example is the use of silver based antimicrobial agents where different supports for the silver ions may be used.

It should be emphasised that the use of the **antimicrobial substance** should not replace the need for good hygiene practices.

6.1	**Is the substance used as an antimicrobial**	**Answer 'yes' or 'no'.** If 'no' go to section 7, if 'yes' go to 6.2

[12] Commission Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products, OJ L 167, 27.6.2012, p. 1–123, repealing Commission Directive 98/8/EC of 16 February 1998 concerning the placing of biocidal products on the market.

agent?

6.2	**What is the intended microbiological function?**	Set out the technological function of the biocide. If the **antimicrobial substance** is used: a) as a 'protection agent' during production process or storage of products to be used in the manufacture of the final article, go to 6.2.1 b) to reduce the microbiological contamination on the surface of the finished food contact material (FCM) and thereby improve hygiene in food preparation areas, go to 6.2.2 *Ref:*
6.2.1	**Protection agent during production process or storage of products:**	An **antimicrobial** substance may be added to protect from microbial spoilage the products to be used in the manufacture of the final article during production process or storage, e.g. an aqueous emulsion or process water containing these products. In this case, it should be argued from Minimum Inhibitory Concentration (MIC) values, migration data and/or concentrations in the final product that there could be no antimicrobial activity on the surface of the finished article. Alternatively, it could be demonstrated using an appropriate method e.g. JIS Z 2801[13] (adapted to use a wider range of microorganisms). If this is demonstrated, go to section 7.
6.2.2	**Means of reducing microbial contamination on the surface of a FCM**	An antimicrobial substance may be added to an FCM to reduce the numbers of microorganisms on its surface and in turn to reduce the possibility of cross contamination. In this case, all information requested below should be provided.
6.2.2.1	**Intended applications of use**	Describe as far as possible the intended applications. Information should be provided on whether it is intended to be used for industrial food processing applications, consumer use (including catering) or both. Information should also be provided, whether each application is intended for 'repeated use' or 'single use'.
6.2.2.2	**Other information**	Give any information on the intended use other than those mentioned under 6.2.2.1 and in section 3 if it may be useful for the risk assessment of the biocide.
6.3	**Spectrum of microbiological activity:**	Provide data on the spectrum of activity against various food-associated microorganisms, including pathogens. Any insensitive genera or species known or identified should be included.

[13] Japanese Industrial Standard / Antimicrobial products – Test for antimicrobial activity and efficacy (Japanese Standards Association – 4-1-24, Akasaka, Minato-ku, Tokyo, 107-8440 JAPAN)

Ref:

6.4 Level of activity:

Provide information on MICs of the pure biocidal substance or preferably its active component, e.g. silver ions, for the microorganisms likely to be exposed to the substance. The concentration of the microorganisms and the nature of the test medium in which they are exposed to the antimicrobial substance should be described.

Include any dose-time-response information if available, e.g. varying doses of antimicrobial substance for a constant time or a single concentration of antimicrobial substance for varying times. Describe the nature of the test medium in which the microorganisms are exposed to the biocide.

Document the possibility of resistance arising to the antimicrobial substance in the sensitive population or cross-resistance to other antimicrobials developing.

Ref:

6.5 Possible consequences of the use of the antimicrobial substance:

Describe any possible encouragement to favour selective overgrowth of the flora on the surface of the food contact material containing the biocidal substance(s) by organisms that are insensitive to the biocidal substance(s).

Ref:

6.6 Efficacy:

Efficacy strongly depends on migration of the antimicrobial substance to the surface of the material, and therefore on the type of polymer and on its antimicrobial substance content. On the other hand, migration should not be so high that it causes preservative effect on food (see item 6.8). Consequently, efficacy testing should be performed with polymers mentioned in 3.1, especially using that giving the highest and that giving the lowest migration (e.g. LDPE and PET respectively). The concentration of the antimicrobial substance in these test materials should not exceed that indicated in 3.4 and 4.1.2.1.

Provide data to demonstrate the efficacy under the intended conditions of use describing the testing methodology that demonstrates this efficacy.
When the biocide is to be used at low temperatures, e.g. in chill rooms, refrigerators, efficacy should be demonstrated at these temperatures.
However, when this is technically impossible, e.g. in large scale industrial applications, provide data obtained from experiments that simulate the intended conditions of use.

An alternative approach may rely for instance on comparison of predicted migration values with MICs, taking into account intrinsic and extrinsic conditions. The model should be properly validated.

Ref:

6.7	**Efficacy upon repeated use:**	Information should be provided to describe the behaviour of the biocidal surface after, for example, repeated cleaning procedures. Preferably, demonstration of efficacy under in-use conditions could be done using microbiological tests or by establishing the concentration of the active substance. *Ref:*
6.8	**Demonstration of the lack of antimicrobial activity against microbes in/on the food:**	Describe the evidence for absence of any effect on the microbiological flora in/on the food including comparison with data obtained from use of the same/comparable FCM not containing the biocidal substance(s). This should cover the worst case, which could include: - the most sensitive microorganism(s), - the highest release level of the biocidal substance(s) or FCM with the highest concentration applied for, - foodstuffs spiked with the biocidal substance(s) at concentrations exceeding the observed or calculated migration levels. This consideration includes: - comparison of the observed or calculated migration levels with MIC values, - information on interaction of the biocidal substance(s) with food constituents which may lead to the inactivation of the biocide. *Ref:*
6.9	**Other information:**	Set out any other information that may be relevant for evaluation. *Ref:*
6.10	**Information on claim or disclaimer in accordance with the requirement of the relevant Regulation:**	The claim should be consistent with the data described above on efficacy and activity.
6.11	**Information on authorisation as biocidal product in the frame of Commission Regulation (EU) No 528/2012:**	Supply information if the substance is listed in Annex I of Commission Regulation (EC) No 528/2012 or if it is a constituent of biocidal products authorised under Article 55(2) of Commission Regulation (EC) No 528/2012 or if it is a constituent of biocidal products allowed under the transitional measures or subject to the 10-year work programme provided for in Article 89 of Commission Regulation (EC) No 528/2012.

7. TOXICOLOGICAL DATA

A complete report of the toxicity studies performed should be provided. The studies should be performed following prevailing EU or OECD guidelines or other internationally agreed methods and should be in compliance with Good Laboratory Practice, as better specified below.
The substances tested should be the commercial substances for which the authorisation is requested. Especially, the percentage of purity and the identity of impurities should be the same as those of the substances to be used in practice. In any case, the substances used in any toxicological experiment should be described properly and their samples tested must be traceable. In the absence of specifications on the identity (see Section 1) of the substances tested, a justification should be provided.

The general principle for developing the toxicological data as reported in the 2001 'SCF Guidelines on Food Contact Materials' should apply, i.e. the greater the exposure through migration, the more toxicological information will be required:

(a) In case of high migration (i.e. 5 - 60 mg/kg/food), a full data set is needed to establish the safety.
(b) In case of migration between 0.05 and 5 mg/kg food, a reduced data set may suffice.
(c) In case of low migration (i.e. <0.05 mg/kg food), only a limited data set is needed.

In determining the appropriate extent of the data set required, the migration values should not be regarded as absolute limits but as indicative values.

(a) Full data set comprises:
- At least two *in vitro* genotoxicity tests, in line with the testing strategies of the EFSA Scientific Committee recommendations on genotoxicity testing strategies[14]:
  i) A bacterial reverse mutation test
  ii) An *in vitro* mammalian cell micronucleus test
- A 90-day oral toxicity study
- Studies on absorption, distribution, metabolism and excretion
- Studies on reproduction and developmental toxicity
- Studies on long-term toxicity/carcinogenicity

Under certain circumstances the extensive set of tests as described above may not be required and only the tests indicated below may have to be provided.
Reduced data sets (b) and (c) comprise:

(b) In cases where migration is in the range from 0.05 to 5 mg/kg of food / food simulant, the following data are needed:
- At least two genotoxicity tests as indicated above
- A 90-day oral toxicity study
- Data to demonstrate the absence of potential for accumulation in man

(c) In cases where migration is below 0.05 mg/kg of food / food simulant the following data are needed:
- At least two genotoxicity tests as indicated above

[14] EFSA Scientific Committee; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [69 pp.] doi:10.2903/j.efsa.2011.2379.

7.1 Genotoxicity

In line with the EFSA Scientific Committee recommendations on genotoxicity testing strategies,[15] the two *in vitro* genotoxicity assays described in items 7.1.1 and 7.1.2 should be performed. The combination of these two tests fulfils the basic requirement to cover the three genetic endpoints with the minimum number of tests: the bacterial reverse mutation assay covers gene mutations and the *in vitro* micronucleus test covers both structural and numerical chromosome aberrations.
In case of positive results obtained from the *in vitro* genotoxicity tests, further *in vivo* genotoxicity tests may be required.
Consistent with the recommendations of the EFSA Scientific Committee on genotoxicity testing strategies, the *in vivo* tests described in items 7.1.3, 7.1.4 and 7.1.5 would be suitable for following up substances that test positive in the *in vitro* basic battery. These EFSA Scientific Committee recommendations should be consulted for further details of the testing strategy.

7.1.1 Bacterial reverse mutation assay:

According to the OECD Guideline 471[16].

Ref:

7.1.2 *In vitro* mammalian cell micronucleus test:

According to the OECD Guideline 487[17].

Ref:

7.1.3 *In vivo* micronucleus test:

According to the OECD Guideline 474[18].

The *in vivo* micronucleus test covers the endpoints of structural and numerical chromosomal aberrations and is an appropriate follow-up for *in vitro* clastogens and aneugens.

Ref:

[15] EFSA Scientific Committee; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379, 69 pp. https://doi.org/10.2903/j.efsa.2011.2379
[16] OECD (1997), Test No. 471: Bacterial Reverse Mutation Test, OECD Publishing, Paris.
[17] OECD (2010), Test No. 487: In Vitro Mammalian Cell Micronucleus Test, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264091016-en
[18] OECD (2014), Test No. 474: Mammalian Erythrocyte Micronucleus Test, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264224292-en

7.1.4 *In vivo* Comet assay:

According to the OECD Guideline 489[19].

The *in vivo* Comet assay evaluating DNA primary lesions is an indicator test sensitive to substances that cause gene mutations and/or structural chromosomal aberrations *in vitro*. The assay can be applied to any tissues from which single cell suspensions can be prepared. It is also suitable for the detection of DNA damage at the first site of contact.

Ref:

7.1.5 Transgenic rodent gene mutation assays:

According to the OECD Guideline 488[20].

Transgenic rodent assays can detect point mutations and small deletions and are without tissue restrictions. The combination of tests assessing different endpoints in different tissues in the same animal, or the incorporation of such testing within other repeated-dose toxicity studies that will be conducted anyway, should be considered.

Ref:

7.1.6 Other information:

Include any other information that may be relevant for evaluation of the genotoxicity of the substance (e.g. chemical reactivity of the substance, structural alerts and 'read-across' from structurally related substances, data on bioavailability, metabolism, toxicokinetics, target organ specificity, any relevant published data on the genotoxicity of the substance).

7.2 General toxicity

7.2.1 Repeated dose 90-day oral toxicity study:

According to the OECD guideline 408.[21]

Ref:

7.2.2 Combined Chronic Toxicity/Carcinogenicity:

According to the OECD guideline 453.[22]

Ref:

7.2.3 Reproduction/teratogenicity:

According to the EC Methods B.34–B.35 and the OECD guidelines 421 and 422.[23],[24]

Ref:

[19] OECD (2014), Test No. 489: In Vivo Mammalian Alkaline Comet Assay, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264224179-en

[20] OECD (2011), Test No. 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264122819-en

[21] OECD (1998), Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents, OECD Publishing, Paris.

[22] OECD (2009), Test No. 453: Combined Chronic Toxicity/Carcinogenicity Studies, OECD Publishing, Paris.

[23] OECD (1996), Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264070981-en

[24] The following OECD guidelines have also been developed to assess additional reproduction toxicity endpoints:

- OECD (2001), Test No. 414: Prenatal Development Toxicity Study, OECD Publishing, Paris.

7.2.4	**Other information:**	Set out any other information that may be relevant for evaluation, e.g. acute or subacute (28 days) toxicity[25], dermal and inhalation effects should be provided when available. *Ref:*

- OECD (2001), Test No. 416: Two-Generation Reproduction Toxicity, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264070868-en
- OECD (2011), Test No. 443: Extended One-Generation Reproductive Toxicity Study, OECD Publishing, Paris.DOI: http://dx.doi.org/10.1787/9789264122550-en

[25] OECD (2008), Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264070684-en

7.3	**Metabolism**	
7.3.1	**Absorption, distribution, biotransformation and excretion:**	Give any relevant information when available. *Ref:*
7.3.2	**Accumulation in man:**	To assess the potential for this, consider the approaches listed in Annex 3. As detailed guidelines for methodology are absent the relevant sections of existing EU guidelines on veterinary drugs, additives in animal nutrition and human drugs may be consulted. Also, IPCS (EHC 70[26] & EHC 57[27]) as well as the FDA Red Book II[28] may provide guidance. *Ref:*
7.3.3	**Other information:**	Set out any other information that may be relevant for evaluation. *Ref:*
7.4	**Miscellaneous**	
7.4.1	**Effects on immune system:**	Give relevant information, if any. *Ref:*
7.4.2	**Neurotoxicity:**	Phosphoric and phosphorous acid esters should be tested for neurotoxicity, if migration exceeds 0.05 mg/kg food/food simulants. According to OECD guideline 424.[29],[30] *Ref:*
7.4.3	**Other information:**	Set out any other information that may be relevant for evaluation. *Ref:*

[26] IPCS, Environmental Health Criteria 70, Principles for the safety assessment of food additives and contaminants in food, 1987.
[27] IPCS, Environmental Health Criteria 57, Principles of toxicokinetic studies, 1986.
[28] FDA, Redbook II, Guidance for Industry and Other Stakeholders Toxicological Principles for the Safety Assessment of Food Ingredients, 2007.
[29] OECD (1997), Test No. 424: Neurotoxicity Study in Rodents, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264071025-en
[30] The following OECD guidelines have also been developed to assess additional neurotoxicity endpoints:
- OECD (1995), Test No. 418: Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264070905-en
- OECD (1995), Test No. 419: Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264070929-en
- OECD (2007), Test No. 426: Developmental Neurotoxicity Study, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264067394-en

Annex 1

MEASUREMENT OF HYDROLYSIS OF PLASTICS MONOMERS AND ADDITIVES IN DIGESTIVE FLUID SIMULANTS

Contents

INTRODUCTION

For the protection of human health, plastic food contact materials shall be in compliance with Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, as amended, with regard to composition and migration of constituents to foodstuffs coming into contact with these materials.

Constituents that may migrate to foodstuffs comprise residual monomers and other starting substances, residual process chemicals and additives as well as breakdown products and impurities of these substances.

Certain constituents may hydrolyse when ingested. The method described in this Guideline allows determination of the extent of hydrolysis, especially of esters, in order to assess whether the constituents break down into innocuous substances.

1. SCOPE

The method can be used to measure the extent of hydrolysis of monomers and additives *in vitro*, using standard digestive fluid simulants for saliva, gastric juice and intestinal fluid.
The method does not describe the analytical procedures required for the determination of the parent constituent and its hydrolysis products in the simulants.

2. PRINCIPLE

The test substance (monomer or additive) is dissolved in an appropriate solvent. An aliquot of the solution is transferred to the digestive fluid simulant, which is maintained at 37°C with continual agitation. After a specified time period the concentrations of both parent constituent and hydrolysis products are determined in the simulant, whereupon percentage hydrolysis is calculated.

3. REAGENTS

NOTE: All reagents should be of recognised analytical quality unless otherwise specified.

3.1. Chemicals

3.1.1. Water, distilled or deionised

3.1.2. Sodium bicarbonate ($NaHCO_3$)
3.1.3. Sodium chloride (NaCl)
3.1.4. Sodium taurocholate?
3.1.5. Potassium carbonate (K_2CO_3)
3.1.6. Sodium hydroxide standard solution, 0.2 M
3.1.7. Hydrochloric acid standard solutions, 2 M and 0.1 M
3.1.8. Potassium dihydrogen orthophosphate (KH_2PO_4)
3.1.9. Porcine pancreatin extract, activity equivalent to 8x SUP specification
3.1.10. Dispersing solvents, one of:
- acetonitrile
- N,N-dimethylacetamide
- 1,4-dioxane
- ethanol
- methanol
- propan-2-ol
- tetrahydrofuran
- water

3.2. Digestive fluid simulants

3.2.1. Saliva simulant:
Dissolve 4.2 g of sodium bicarbonate ($NaHCO_3$), 0.5 g of sodium chloride (NaCl) and 0.2 g of potassium carbonate (K_2C0_3) in 1 L of water. The pH of the solution should be approximately 9.

3.2.2. Gastric-juice simulant:
Dilute 0.1 M hydrochloric acid standard solution to a concentration of 0.07 M. The pH of the solution should be 1.2 $\pm$ 0.1.

3.2.3. Intestinal-fluid simulant:
NOTE: Care should be taken to ensure that the simulant is prepared in the order given.

Dissolve 6.8 g of potassium dihydrogen orthophosphate (KH_2PO_4) in 250 ml of water, transfer to a 1 L volumetric flask and add 190 mL of 0.2 M sodium hydroxide (NaOH). Add 400 mL of water and shake briefly to mix. Weigh 10.0 g of pancreatin extract into a 250 mL beaker. Add a little water, and stir to make a stiff, homogenous paste. Gradually dilute the paste with small portions of water, stirring well after each dilution, to give approximately 150 mL of a lump-free solution. Transfer the solution to the volumetric flask, rinsing the beaker and funnel with water. Add 0.5 g of sodium taurocholate, gently shake the flask and make the volume up to the neck of the flask. Adjust the pH of the solution to 7.5 $\pm$ 0.1 with 0.2 M sodium hydroxide (NaOH). Make the volume up to the mark with water and shake thoroughly to mix.

4. APPARATUS

NOTE: An instrument or item of apparatus is listed only where it is special, or made to a particular specification, usual laboratory equipment being assumed to be available.

4.1. Glass vials, 100 mL or 125 mL, with crimp-on type PTFE/silicone rubber septa.

4.2. Crimping and decapping pliers.

4.3. Device for mechanical agitation of the simulant, e.g. a flask shaker, or a magnetic stirrer bar for use with a stirrer plate, situated in a cabinet or water bath controlled to a temperature of 37 $\pm$ 1°C.

5. SAMPLES

NOTE: The test substance should be of similar purity as the substance used in food contact materials.

5.1. Preparation of stock solutions

Weigh out the required weight of the test substance to the nearest 0.1 mg into a 10 mL volumetric flask and dissolve in a suitable dispersing solvent such as one listed in section 3.1.10. Make the volume up to the mark and shake the flask thoroughly to mix.

NOTE: The solvent selected must completely dissolve the test substance and must not chemically react with it.

The final concentration of solvent (other than water) in the digestive fluid simulant should not exceed 0.1% (v/v).
The concentration of the test substance in the digestive fluid simulant should be selected such as to enable determination of the substance down to 5% of the amount added to the simulant. Anyhow, that concentration should not be lower than the maximum likely human intake predicted from migration studies.

6. PROCEDURE

6.1. Hydrolysis equation

Set out the hydrolysis equation, using the following model expression:
PC => HP-1 + HP-2 (+ HP-3 +.... HP-N), in which:
PC = parent constituent
HP = hydrolysis product

6.2. Selection of simulants

Select simulants to be used in the test such that the analytical effort is kept to the minimum, e.g. a test with intestinal fluid simulant is often sufficient to demonstrate hydrolysis of esters. So, if the test substance is an ester, a test with intestinal fluid simulant should be carried out first. If complete hydrolysis is demonstrated, it is not necessary to perform tests with other simulants.

6.3. Performance of hydrolysis test

Transfer for each test 100 mL of the digestive fluid simulant to a glass vial using a measuring cylinder. Crimp-seal the vial with a PTFE-silicone rubber septum. Commence shaking the vial or stirring its contents and equilibrate the simulant at 37 $\pm$ 1°C.

NOTE: As for analytico-technical reasons each substance in the hydrolysis equation selected for determination has to be assessed in a separate hydrolysis test and each of the determinations has to be carried out in triplicate, the number of glass vials needed for the test amounts to thrice the number of combinations of substances (be it parent constituent or hydrolysis product) to be determined, specified time period and simulant.

Subsequently add a suitable aliquot of the stock solution (25 to 100 µL) to the simulant, using a 100 µL syringe. Inject the solution through the septum, below the surface of the simulant, and continue agitation or stirring for the duration of the test. Take the duration of the test from the following table:

- saliva simulant 0.5 h
- gastric-juice simulant 1, 2 and 4 h
- intestinal-fluid simulant 1, 2 and 4 h

NOTE: If gastric-juice simulant or intestinal-fluid simulant is used for the test, a test for one hour should be performed first. If complete hydrolysis is demonstrated, it is not necessary to perform tests for two and four hours.

6.4. Analysis of hydrolysates

After termination of the hydrolysis test, determine the hydrolysis products in the hydrolysate. Use an appropriate analytical method and calculate percentage hydrolysis from the results.

NOTE It is insufficient to only measure disappearance of the parent constituent. A case-by-case selection should be made about which hydrolysis products need be measured in order to permit a judgement about mass balance.

Suitability of the analytical methods should be demonstrated by performing tests with standard addition of the hydrolysis product(s) of interest set out in the CEN standard format.

7. TEST REPORT

The test report should conform to the CEN standard format.

Annex 2

POLYMERIC ADDITIVES

Components with a molecular mass above 1,000 Dalton (Da) are very unlikely to be absorbed by the gastro-intestinal tract and thus are not considered to present a toxicological risk. The value of 1,000 Da was chosen because it takes into account the effect of the shape of the molecule, which has an important influence on the likelihood of absorption of substances in the molecular mass range 600-1,000 Da. Below 600 Da, most substances are absorbed and the rate of absorption is determined by factors other than size and shape of the molecule.

Since only the fraction of the polymeric additive with molecular mass below 1,000 Da is regarded as toxicologically relevant a distinction has been made between polymeric additives with a weight averaged molecular mass (Mw) below 1,000 Da and those with Mw above 1,000 Da. For polymeric additives with Mw above 1000 Da, the fraction with molecular mass below 1,000 Da will vary, and a case-by-case consideration of the specification will determine whether further data are required.

The following data should be supplied:

I) Data according to the 'Explanatory Guidance to the SCF Guidelines for Food Contact Materials' on:

- paragraph 1.4 "Identity"
- paragraph 2 "Properties"
- paragraph 3 "Use"

II) Genotoxicity data on the monomer(s) according to the 'Explanatory Guidance to the SCF Guidelines for Food Contact Materials'.

IIIa) For those additives with Mw less than 1,000 Da: migration and toxicity data on the polymeric additive itself, according to 'SCF Guidelines' with the exception that mutagenicity studies on the polymeric additive itself are not required.

IIIb) For those additives with Mw above 1,000 Da: data, including migration and toxicity, may be required on the polymeric additive itself once the CEF Panel has examined the specification; especially for those additives containing a significant fraction with molecular mass below 1,000 Da.

In deciding whether further data are needed, the CEF Panel will take into account both the size of the fraction with molecular weights below 1,000 Da and the proportion of the additive in the plastic.

N. B. As regards the migration, the level of the migrated fraction with molecular mass less than 1,000 Da should preferably be supplied. However, if the applicant(s) is (are) unable to determine this or decides (decide) not to determine the migrated fraction with molecular mass less than 1,000 Da, the total migration of the polymeric additive will be attributed to the fraction with molecular mass less than 1,000 Da.

These guidelines apply to polymeric additives in general. The CEF Panel will however consider any scientific arguments put forward by applicants for deviation from the guidelines. For example, in cases of additives made using hydrogenation, or additives in which residual monomers have been removed from the final product, not all the data mentioned in the guidelines may be required.

If relevant toxicological data are available, they may be submitted because they may support evaluation.

Annex 3

ACCUMULATION IN MAN

This Annex focuses on accumulation in man and not on bioaccumulation in general. Many experts are familiar with the term 'bioaccumulation' as it relates to the fate of a chemical in the environment. It covers e.g. the behaviour in aquatic organisms and potential for accumulation through the food web.

In the case of food contact materials, the interest centres on the potential for direct accumulation in mammalian tissues and not on biomagnification through the food chain. However, normally a log $k_{O/W}$ value below 3 would be considered sufficient evidence for the lack of accumulative potential in the mammalian body, unless special considerations, e.g. chemical structure, give cause for concern. On the other hand, a log $k_{O/W}$ of 3 and higher will not by itself be proof of accumulation as a substance may not be absorbed or be metabolised to substances with no accumulation potential. In these circumstances other evidence for the absence of accumulative potential is needed.

It is not possible to give definitive guidance as to the methods to be used, as different approaches must be followed for different substances according to their chemical structures and physical properties. If it can be shown by appropriate kinetic studies (absorption distribution, metabolism, excretion (ADME)) after oral exposure that the biological half-life excludes accumulation, this would be considered sufficient evidence. Furthermore, the use of appropriately radioactively labelled substances and autoradiography can demonstrate the existence/absence of an accumulative potential of a substance.

Guidelines describing in detail the procedures for such studies do not appear to exist, but some relevant information may be found in existing EU guidelines on veterinary drugs, additives in animal nutrition, and human drugs. Also, IPCS (EHC70 and EHC57) as well as the FDA Red Book II could be useful sources on possible methodology.

In principle, accumulation is undesirable but not automatically associated with any toxic effects. In cases where accumulation potential has been demonstrated or its lack not demonstrated, it remains the responsibility of the applicant to provide evidence that any accumulation found will not be associated with toxic effects even after long-term exposure.