Technical Report

waAPPROVED: 15 October 2023
doi: 10.2903/sp.efsa.2023.EN-NNNN

Principles that could be applicable to the safety assessment of the use of mixtures of natural origin to manufacture food contact materials

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Abstract

This report describes work to establish principles and procedures that could be applicable to the safety assessment of the use of mixtures of natural origin in the manufacture of food contact materials (FCM). There is increasing interest in the use of substances obtained from renewable biological resources (non-fossil) to manufacture materials and articles intended for food contact. They may be single substances or simple well-defined mixtures, but more commonly they are complex mixtures with a substantial fraction that is uncharacterised. The source materials are plant biomass and (to a lesser degree) animal biomass. Natural compounds and/or complex mixtures are assessed in several sectors under the EFSA remit dealing with regulated chemicals, including novel foods, food enzymes, botanicals, food and feed additives, food flavours and FCM. These sectors have been consulted to learn from their experience. Waiving part of the data requirements for substances derived from edible food sources (e.g. food as such or the non-eaten parts, and or food ingredients) seems acceptable. Substances that migrate and give rise to concern (based on their chemical, physical or toxicological properties), but are already present in the diet, should not be (re-)evaluated, but rather, their exposure from FCMs should be compared with that from the diet. All other components and impurities in the mixture, should be assessed using the established FCM guidelines and cross-cutting EFSA guidance documents. The report concludes with recommendations on several topics that have a cross-cutting character and which may benefit from further considerations and developments by the EFSA Scientific Committee.

Key words: natural, mixture, safety assessment, whole mixture approach (WMA), component-based approach (CBA), biobased, food contact materials

Requestor: EFSA internal mandate
Question number: EFSA-Q-2023-00256
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Acknowledgements: EFSA wishes to thank the following for the support provided to this scientific output: EFSA staff members: Bernard Bottex, Eirini Kouloura, Yi Liu, Paola Manini and Carla Martino; ECHA staff members: Dorota Burchard-Sosnowska, Evelin Fabjan and Ronan Nicolas; the EFSA CEP Panel members other than those already members of the FCM WG: José Manuel Barat Baviera, Andrew Chesson, Pier Sandro Cocconcelli, David Michael Gott, Marcel Mengelers, Alicja Mortensen, Inger-Lise Steffensen, Henk Van Loveren, Laurence Vernis and Holger Zorn; and the EFSA FCM Network.

Suggested citation: EFSA (European Food Safety Authority), Barthélémy E, Bolognesi C, Castle L, Crebelli R, Di Consiglio E, Franz R, Grob K, Hellwig N, Lambré C, Lampi E, Merkel S, Milana MR and Rivière G, 2023. Principles that could be applicable to the safety assessment of the use of mixtures of natural origin to manufacture food contact materials. EFSA supporting publication 2023:EN-NNNN. 3 pp. doi:10.2903/sp.efsa.2023.EN-NNNN

ISSN: 2397-8325

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1 Introduction

1.1 Background and terms of reference

In view of,

- the applications submitted to EFSA for the assessment of plant-based additives (fillers) used to manufacture plastics,
- the revision by EC of the Food Contact Materials (FCM) framework legislation (Farm to Fork Strategy) that intends to give importance to natural organic material types (plant- and animal-based), notably in the context of the Circular Economy Action Plan (including support to innovative and sustainable packaging solutions), and the Chemicals Strategy for Sustainability (including safe and sustainable materials by design),
- the assessment of substances from natural sources in several EFSA regulated sectors, such as novel foods, botanicals, enzymes, food and feed additives and smoke flavours,
- the proposal made in March 2022 by the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) to the EFSA Scientific Committee (SC) to clarify and prepare a guidance for the assessment of "natural" materials and food components for use in FCM,

it is requested to the FCM WG and EFSA to prepare a technical report and to present their views on the principles to assess natural mixtures from natural sources (for instance from renewable biological resources) used to manufacture any of the different groups of FCM (Annex I Reg. 1935/2004). This report should serve as background document for the SC.

2 Data and Methodologies

The starting point for this activity was existing EFSA Scientific Guidance considered to be relevant to the safety assessment of the use of mixtures of natural origin. These included both sectorial and cross-cutting guidance documents from the Scientific Committee. These published guidance documents were taken together with practical experience gained during the assessment of substances of natural origin used to manufacture plastics and in other EFSA regulated sectors, such as novel foods, botanicals, food enzymes, food and feed additives and smoke flavours. Experience and assessments from US-FDA and ECHA related to natural compounds and/or complex mixtures were also considered.

The principles extracted from that learning exercise and subsequently the draft Technical Report were discussed by the EFSA FCM Network (November 2022 and April 2023 and October 2023)[1]. The CEP Panel was consulted[2] on the draft principles (March and June 2023) and on the draft Technical Report in July 2023. The draft principles were presented to stakeholders in the CEP Plenary meeting open to observers in June 2023.

The work was also presented for discussion and feedback at the 15th Biennial International Symposium on Worldwide Regulation of Food Packaging and at the EU-funded Regional (ASEAN) Seminar on 'Food Contact Materials and Safety Requirements', both held in June 2023.

The comments received from all parties during these consultations were considered in the preparation and finalisation of this EFSA Technical Report.

[1] https://www.efsa.europa.eu/en/events/8th-meeting-fcm-network; https://www.efsa.europa.eu/en/events/9th-meeting-fcm-network; https://www.efsa.europa.eu/en/events/10th-meeting-fcm-network.

[2] https://www.efsa.europa.eu/da/events/35th-plenary-meeting-cep-panel; https://www.efsa.europa.eu/en/events/36th-plenary-meeting-cep-panel-open-observers.

Based on this information, discussions and consultations, considerations and principles that could be applicable for the safety assessment of mixtures of natural origin used to manufacture FCM as well as specific data requirements are proposed.

3 Assessment

3.1. Context

There is increasing interest in the use of substances obtained from renewable biological resources (non-fossil) to manufacture materials and articles intended for food contact. Substances from renewable biological resources may offer low- or zero-carbon alternatives to synthetic substances based, e.g., on petroleum (oil). Their natural origin may also confer biodegradability/composability attributes. The source materials are plant biomass and (to a lesser degree) animal biomass. The biomass may come from food production species, either as such or as agri-food wastes, or from non-food species.

Being derived from renewable biological resources, such substances might be considered synonymous with 'natural' and 'safe' (or at least 'safer') than their synthetic counterparts, but this is not necessarily the case.

In this report, the term 'substance' is used with reference to what substances are (or that could be) used to manufacture FCM, since this is the terminology used in that specific area in preference to alternatives such as e.g. "compound", "chemical" etc. Substances from renewable biological resources may be single substances or well-defined mixtures of identified substances, but more commonly they are complex mixtures – in ECHA terminology called UVCB substances (Unknown or Variable Composition, complex reaction product, or Biological materials). These UVCB substances of biological origin may be obtained directly and be chemically unchanged, using physical processes, such as extraction, enrichment and purification. However, the production process may also result in modification of the constituents, either unintentionally or intentionally, to make the product more suitable for its intended use in the FCM. Microorganisms may be used to transform the biomass into the FCM substances or more conventional conversion processes may be used. As a consequence, the composition may deviate from the components in/from the biomass source material, which itself is likely to have a composition that is not fully known/defined and which may be variable.

Natural compounds and/or complex mixtures are assessed in several sectors under the EFSA remit dealing with regulated chemicals, including novel foods, food enzymes, botanicals, food and feed additives, food flavours and FCM.

Recent examples coming from the FCM sector are biobased materials intended to be used as additives/fillers in plastics, i.e. unmodified wood flour and wood fibres, ground- and chemically-modified sunflower seed hulls, and bleached cellulose softwood pulp. Another example is the substance PHBH (poly((R)-3-hydroxybutyrate-co-(R)-3-hydroxyhexanoate; EFSA CEF Panel, 2018), which is a biobased and biodegradable plastic produced by fermentation of palm oil and/or palm oil fatty acid distillate as the carbon source, by using a genetically modified microorganism (*Cupriavidus necator*). These examples along with other examples from the FCM sector and other EFSA sectors confirm that a particular characteristic of the substances under evaluation is their compositional complexity, variability, and the presence of an uncharacterised fraction.

3.2. Current principles and guidance for assessing food contact materials substances

The Guidelines of the Scientific Committee on Food (EC, 2001) for the presentation of an application for safety assessment of a substance to be used in FCM prior to its authorisation, while not explicitly listing natural substances, cover the use of foodstuffs and food ingredients as monomers, starting substances

or additives. In addition, food additives already evaluated by the SCF may be used for the manufacture of FCM. For foodstuffs and food ingredients, only data on the identity of the substance (including all relevant information concerning the substance itself, its impurities, breakdown and reaction products) and on the intended use are needed. For food additives intended to be used in FCMs, additional data on the migration of the substance and its impurities, breakdown and reaction products are needed. Therefore, for the submission of the application, no toxicological data are requested on foodstuffs, food ingredients and food additives as such.

The FCM WG EFSA Note for Guidance was originally adopted by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) in 2008 (EFSA CEF Panel, 2008), updated and endorsed by the CEF Panel and then the CEP Panel in 2017 and 2020, respectively. That Guidance details the data requirements for the assessment of new substances used to produce (plastic) FCM. The data required for the evaluation of natural substances are covered by the category 'non-defined mixtures', which includes products derived from natural sources, as typical examples of non-defined mixtures. Non-defined mixtures are described therein as "mixtures which may vary from batch to batch, but which have a composition within a certain specification". For the evaluation of non-defined mixtures, such as products from natural sources, data on substance characterisation, e.g. structural formulae and molecular mass distribution are required and one should consider the origin of the source, the climate and treatment(s), as well as technical processes possibly modifying the mixture. Furthermore, data are required for the fraction with a molecular mass below 1,000 Da, being the fraction of toxicological interest, and on non-intentionally added substances (NIAS; e.g. impurities, degradation products, by-products from production). In accordance with the SCF Guidelines, unless the substance is a foodstuff, a food ingredient or a food additive, toxicological data are required – as for any other substances – according to a tiered approach based on the migration level.

Cross-cutting Guidance from the EFSA Scientific Committee apply to the FCM sector. In particular, the Guidance documents or Statements on the following subjects are used:

- the Threshold of Toxicological Concern (TTC) (EFSA SC, 2019a),
- the genotoxicity strategy (EFSA SC, 2011),
- the clarification on some aspects of genotoxicity assessment (EFSA SC, 2017),
- aneugenicity (EFSA SC, 2021c),
- technical requirements for regulated food and feed product applications to establish the presence of small particles, including nanoparticles (EFSA SC, 2021b),
- risk assessment of nanomaterials (EFSA SC, 2021a).

When considering the uncharacterised fraction of chemical mixtures, the Statement on the genotoxic assessment of chemical mixtures (EFSA SC, 2019b) and the Guidance on harmonised methodologies for human and animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019c), are of particular importance. In fact, the EFSA CEF Panel already highlighted in 2016 that the testing of mixtures might be a useful tool to address genotoxic potential where the identification and evaluation of a large number of reaction products and impurities is not feasible (EFSA CEF, 2016a). The EFSA CEF Panel stressed that this testing assumes sufficient sensitivity for detecting genotoxic substances. This is in line with the opinion of the SC that recommends further fractionation to remove toxicologically irrelevant components from the mixture (e.g. high-molecular-weight polymers), to minimise the dilution of the components of interest in the tested sample, or to remove highly toxic components that may prevent testing adequately high doses of the mixture because of overt toxicity (EFSA SC, 2019b). While the SCF guidelines and the EFSA Note for Guidance (EFSA CEF Panel, 2008) cover, in principle, also the assessment of substances derived from natural sources, their assessment deserves further clarification, update and coherence with other sectors within EFSA.

3.3. Case studies of safety assessment of natural substances used as additives in the manufacture of FCM

3.3.1. 'Wood flour and fibres, untreated' (FCM No 96) for use in plastic FCM

In the generic assessment of wood flour and fibres used as fillers, the CEP Panel (EFSA CEP, 2019) clarified that "wood cannot be considered inert *per se* owing to the many low molecular weight substances it contains, and when migrating into food, the safety of these constituents must be assessed". The CEP Panel highlighted the differences in the chemical composition of wood species and emphasized that the safety of these materials must be evaluated on a case-by-case basis. The CEP Panel set out criteria for future evaluations of wood and similar materials from plant origin intended as additives for plastics for food contact applications. These criteria complement the EFSA Note for Guidance (EFSA CEF Panel, 2008), providing more detailed guidance for the assessment of such additives. They are reported below:

"Seeing the variability in composition and the possible presence of toxic substances in some woods, the safety of wood and similar materials from plant origin as additives for plastic FCM should be evaluated as for any other additives following the EFSA Note for Guidance (EFSA CEF Panel, 2008). Specifically, the following aspects should be considered:

a. species;
b. possible variability related to age, growth conditions and geographical origin;
c. treatment during cultivation/storage;
d. manufacturing from the source material into the additive: physical and mechanical processing, chemicals used in this process;
e. substances used together with the additive to produce the plastic material, e.g. coupling agents;
f. comprehensive analysis of the low molecular weight constituents below 1,000 Da (1,500 Da for poly- and per-fluoro compounds; EFSA, 2016), including contaminants;
g. migration of substances resulting from using the additive, comparing samples made with and without the additive;
h. toxicological data covering the migrating substances detected in the analysis."

3.3.2. Ground sunflower seed hulls (FCM No 1060) for use in plastic FCM

Ground sunflower seed hulls were assessed twice by EFSA for use as filler in plastics. The two assessments provided toxicological clarifications and new considerations.

In the first evaluation (EFSA CEF, 2016b) on the safety of use in plastic intended for contact with dry foods, no toxicological data were requested on the additive as such, because, owing to the high molecular mass of the polymeric material, it is not expected to migrate and to be absorbed by the cells used in genotoxicity tests. The CEF Panel focused its toxicological assessment on the potential migration of impurities and reaction and degradation products of low molecular mass (<1,000 Da).

In the second assessment, carried out in 2021[3] for the extension of use in plastics intended for contact with all other food types (EFSA OpenEFSA portal, 2023), the EFSA FCM WG focused on the possible migration of the Low Molecular Weight Fraction (LMWF). In line with the EFSA SC Guidance on the use of the Threshold of Toxicological Concern (TTC) approach in food safety assessment (EFSA SC, 2019),

[3] The mandate was withdrawn in 2022 after a first assessment and a request for additional information by the EFSA Working Group on Food Contact Materials.

the EFSA FCM WG clarified that the use of the TTC concept should be restricted to chemically defined substances lacking toxicological data. The substances identified and showing structural alerts for genotoxicity and/or present above the appropriate TTC would need to be further assessed. As a new alternative way forward, the EFSA FCM WG considered to compare the exposure of the substances migrating from the proposed uses of the sunflower seed hulls in the FCM to the exposure via the diet.

3.3.3. Bleached cellulose pulp for use in plastic FCM

Bleached cellulose pulp, consisting of cellulose fibres and hemicellulose obtained from pine and spruce wood, was assessed for its use as additive in plastics (EFSA CEP Panel, 2022). That opinion strengthens the implementation of the above-mentioned criteria (3.3.1) and brings further considerations on the assessment of such plant-based additives.

As for the assessment of the ground sunflower seed hulls (3.3.2Ground sunflower seed hulls (FCM No 1060) for use in plastic FCM), no toxicological data were provided for the bleached cellulose pulp itself, as no migration into food was expected. The assessment of the CEF Panel focused on the potentially migrating LMW components, highlighting that they must be assessed individually or as a mixture according to EFSA Guidance documents (EFSA CEF Panel, 2008; EFSA SC, 2019a,b). The safety of the detected and identified substances was addressed individually and adequately. However, not all possibly migrating substances were identified or were even amenable to the analytical methods applied. Furthermore, the detection limits of the applied methods were too high to ensure the detection of genotoxic substances at a migration leading to a human exposure above the relevant TTC. This led the CEP Panel to note that the single component approach may be inadequate for the evaluation of complex mixtures containing a substantial fraction of unidentified components. In such cases, the whole mixture approach from the EFSA Scientific Committee (EFSA SC, 2019a,b) could help.

Moreover, the surface of the additive was modified by a coupling agent to improve the compatibility with the intended plastic host matrix. The need to provide data and assess the safety of the coupling agent used together with the substance was reiterated in line with the above-mentioned criteria (3.3.1).

3.4. Assessing regulated substances from natural sources in other EFSA sectors

In the remit of EFSA, also other sectors face the need to assess substances of natural origin. The approaches used by the following sectors were taken into consideration: botanicals, novel foods[4], food enzymes, smoke flavourings, and food and feed additives. Taken together, these approaches show that the information required is similar and comprises, principally, identity and nature of the source material, then, for the substance, chemical composition and associated variability, information on existing assessments (or history of safe uses), exposure and, finally, toxicological data. The quality and quantity of the data requested in the different sectors may differ as well as the general understanding of some principles.

A difficulty encountered by all sectors is to estimate the risk related to the uncharacterised fraction. There is a consensus that the presence of unidentified components adds complexity and uncertainties to the assessment and demonstration of the safe use(s). It is common that this uncharacterised fraction is required to be "as low as possible" (e.g. novel food, feed additives). The acceptability of what is 'low enough' is based on experts' judgement, considering the data available, such as the literature, manufacturing process(es), history of use and toxicological information.

[4] Food or ingredient that has not been consumed to a significant degree by humans in the EU before 15 May 1997.

Another commonality is to consider the so-called "substances of concern" for which the coverage may vary in the different EFSA sectors. They are, *a priori*, known to occur or considered likely to occur, based on the source materials used or the production method applied. The substances of concern are hazardous (e.g. genotoxic, carcinogenic, reprotoxic, neurotoxic) natural constituents (e.g. cyanogenic glycosides) or chemical and biological contaminants (from environment, during storage, from the process; e.g. heavy metals, natural toxins, heat-induced furan and acrylamide) or pesticides residues. In many cases, they are known from common expert knowledge and may be identified systematically using the published literature and the existing databases, such as the EFSA compendium of botanicals (EFSA, 2018a). Commonly, targeted chemical analysis is performed, but their assessment varies, depending on the sector (see Appendix A – Considerations on the assessment of the so-called substances of concern in sectors other than Food Contact Materials).

In most sectors, toxicological data on substances of natural origin are requested following a tiered approach that may be based on the level of exposure (or migration in the case of FCM) or on the results of the studies generated at a lower tier (in the case of novel foods). It is understood that in all cases guidelines and guidance documents published by EFSA should be followed. A component-based approach (CBA) is applied for identified chemicals (using testing and/or non-testing methods[5]). A whole mixture approach (WMA) is applied for the uncharacterised fraction. In special cases, toxicological data requirements may be waived.

- For **food enzymes**, toxicological data may be waived when the enzyme is derived from edible parts of plants or animal tissues intended to be or reasonably expected to be ingested by humans[6] or for some enzymes produced from an edible part of an animal (EFSA CEP, 2021, section 4.1). The following criteria must be met: i) a documented consumption of the concerned plant parts or animal tissues in the EU or elsewhere, ii) safety is established through published toxicity testing or safety established through comparable exposure via the use as food enzymes vs. the intake of the source in regular diet, iii) no hazard is introduced during the enzyme manufacturing process.
- A waiver is also applied for enzymes produced by a microorganism for which the "qualified presumption of safety" (QPS) status is granted at strain level (EFSA CEP, 2021). The QPS approach has initially been designed for microorganisms deliberately added to food and feed (EFSA SC, 2007). The approach foresees the possibility to be extended to sub-taxonomic groups (e.g. species subspecies) without the need for further assessment, when the safety at a sufficiently high taxonomic level is concluded (e.g. family or genus taxonomic units: species for bacteria, yeast, fungi, protists/microalgae and families for viruses). The QPS approach provides a generic pre-assessment of the safety of a given microorganism. Safety concerns are highlighted as "qualifications" which should be addressed at the food/feed product level (EFSA BIOHAZ Panel, 2022).
- The possibility of applying the QPS approach to plants has been explored by the EFSA Scientific Committee as part of its activities on how to assess the safety of botanicals (EFSA SC, 2014). Unfortunately, because of the high variability of the composition of plants (among same species, depending on the growing conditions and places, the plant part considered, extraction/preparation process, etc.), it has not been possible to allocate QPS status at sufficiently high taxonomic level to justify the resources needed to create a QPS list for plants. In the absence of such a list, the QPS option is currently unavailable for the assessment of natural products, including those used in or as FCM.

[5] The safety assessment of the use of mixtures of natural origin to manufacture food contact materials could be supported by the application of New Approach Methodologies (NAMs). EFSA started various projects to promote the implementation of NAMs in regulatory risk assessment. The main objective is to promote a comprehensive chemical risk assessment to fill data gaps while fostering the transition towards a mechanistic-based risk assessment (EFSA, 2023). Once the implementation of NAMs for the assessment of regulated products is ready and accepted, this could apply in principle to any areas, including FCM.

[6] Evidence may be a book description, cooking recipes, or better consumption data.

- The guidance for data submission for new **food additive** applications (EFSA, 2012) includes considerations for substances derived from botanical sources. A cornerstone in setting out requirements for a description of the plant source of the additive is the EFSA Guidance on botanicals and botanical preparations (EFSA SC, 2009). According to this Guidance, data on the constituents that are characteristic of the food additive (chemical fingerprinting) should be provided. The evaluation by the Panel of known impurities and substances of concern takes into account whether the source material is a food, e.g. comparing exposure with that from the diet, as in the case of methanol from the intake of pectin present in the regular diet. Otherwise, the evaluation relies on a tiered approach to toxicity assessment using the WMA, applied to a sample of the additive representative of the actual material of commerce, meeting the proposed specifications and manufactured as described in the application.
- **Traditional foods** from third countries consisting of botanicals and botanical preparations (EFSA NDA Panel, 2021a) may benefit from a "presumption of safety", provided an adequate body of knowledge exits[7] (EFSA SC, 2009). In this case, the assessment is based on data submitted by the applicant and retrieved from the literature on the identity, production process, composition, specifications, experience of continued use of the traditional food for more than 25 years in at least one third country, on the proposed/requested conditions of use, and on other information available, such as reported adverse effects (e.g. allergenicity). The assessment relies on the proximate compositional analysis[8], the results from the analysis of the substances of concern and the reported adverse effects (e.g. EFSA, 2022a, b, c). There may be toxicological studies available from the literature that cover some concerns on chronic effects (e.g. EFSA 2021a,b). However, in general, it is understood that the history of safe use, including the possible reported adverse effects, is more prone to address acute than chronic effects (e.g. carcinogenicity), which are, therefore, not covered other than by the considerations of substances of concern.
- The toxicological data for the assessment of **novel foods** consisting of botanicals and botanical preparations are required by default. As a first tier, toxicological testing refers mainly to the request of the battery of genotoxicity testing, a 90-day sub-chronic toxicity study and data on absorption. Part or all of these data may not be needed if appropriate justification is provided (EFSA NDA Panel, 2021b). This is the case for some whole foods, novel foods composed largely by macronutrients, botanicals novel food products consisting of edible plant parts (e.g. edible Chuta kernels, EFSA NDA Panel, 2022) and plant-based preparations from consumed plants (e.g. mung bean protein, EFSA NDA Panel, 2021c) and from non-consumed plant parts, the composition of which is similar to other part(s) consumed as food. This assessment also relies on the body of evidence from the product characterisation, the quality and outcome of the analytical data on the composition and the presence of substance(s) of concern as detailed in the guidance on novel foods (EFSA NDA Panel, 2021b).

While a waiver may be possible, toxicological data requirements may still be significant. For instance, for novel foods, the first tier requires experimental data on genotoxicity, absorption and subchronic toxicity.

Overall, the approach for assessing substances of natural origin shows similarities over the different sectors of EFSA. The assessment of substances consisting of foodstuffs, food ingredients or more generally recognised to be consumed, do not require additional toxicological information other than those that may be already available. However, some harmonisation is needed when assessing mixtures of natural origin: e.g. the acceptable proportion of the non-identified fraction and the approaches to conclude in case of assessing genotoxic and/or carcinogenic effects (margin of exposure, TTC).

[7] This corresponds to the level A of the general framework proposed in the EFSA guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. The term "presumption of safety" from this Guidance is, however, not further used nor reported in the sector of botanicals.

[8] i.e. Ash, moisture, protein, fat, carbohydrates.

3.5. Other USA and EU assessments

It was explored whether the "Generally Recognised As Safe" (GRAS) principle established by the US-FDA and the assessments carried out by US-FDA (for food contact substances) and ECHA (under REACH) have specific considerations for complex mixtures originating from synthetic or natural sources.

The GRAS principle was established by the US-FDA for substances used in food before 1958. Nowadays, the recognition of safety via GRAS requires the same quantity and quality of scientific evidence as required to obtain approval of the substance to be used as a food additive (a substance used to make FCM is termed an indirect food additive by the US FDA). The US FDA assesses the claims submitted and decides on the inclusion in the GRAS notices inventory. It is important to highlight that a non-fully known/characterised fraction may be defined by the manufacturing process. FDA provides guidance on the factors to be considered when determining whether a significant change in a manufacturing process affects the safety status of a food substance (GRAS or otherwise) already on the market. Since in its modern implementation the GRAS approach does not offer natural compounds any specific waiver for toxicological data requirements, it was not considered further in this Technical report.

The term UVCB stands for unknown or variable composition, complex reaction products or of biological materials and is used by ECHA for substances falling under REACH that are complex reaction products obtained from well-defined production processes. For declared/claimed UVCB, Industry should report all constituents ≥10%. All other known constituents and all constituents contributing to the classification and labelling information (C&L) and the assessment of persistence, bioaccumulation and toxicity (PBT) should be individually reported (REACH legal text (Annex VI.2) and the 'SID guidance'). This can still leave a large fraction of the UVCB substance being unknown[9]. Although the exact composition may remain unknown (= U) or only partially known, the composition from batch to batch can be rather consistent (so not Variable). This is important to partly overcome the uncertainties on the composition and for allowing 'testing a representative sample' using the WMA. Consideration of the production process and the variability amongst batches is important. This echoes the approach of the EFSA SC on the assessment of mixtures. In specific cases, where a potential risk is identified based on potential hazard and exposure, studies on specific constituents can be requested under the REACH substance evaluation process. Since the UVCB approach does not offer natural compounds any specific waiver for toxicological data requirements, it was not considered further in this Technical report.

3.6. Considerations and principles that could be applicable

3.6.1. General principles assumed

Based on the above considerations, the general principles below are assumed:

- In the general FCM context, substances of either synthetic or natural origin are single compounds or mixtures that are defined or non-defined. In the context of natural compounds, a 'substance' is most likely to be a non-defined (complex) mixture used as a starting substance or an additive to manufacture any FCM group type (e.g. plastics, rubber, silicones, etc.).
- Substances from natural sources cannot be assumed to be safe *per se*. Many foods are known to contain hazardous components. The acceptable level of exposure to such substances from their use in FCM is to be decided by risk managers.
- The uses and assessment of complex mixtures derived from natural sources trigger additional uncertainties regarding the safety of the uncharacterised fraction.

[9] According to ECHA, based on the current information requirements, the information on the composition of UVCB provided by registrants is considered often not sufficient for the Chemical Safety Assessment and for Regulatory risk management. Update of the standard information requirements arise currently under discussion.

- Batch to batch variability is critical, notably for the representativeness of the substance for which compositional analysis is performed and/or that is tested in the toxicity studies.
- The FCM tiered approach/principle for the toxicological data requirement depending on the migration levels[10] (EFSA CEF Panel, 2008) should be followed.
- The assessment of NIAS in FCM is demanding. Comprehensive chemical analysis for all potential unknowns at migration at or above 0.15 µg/kg food (corresponding to the lowest TTC tier[11]) is often technically unfeasible. Harmonisation (or at least coherence) with other EFSA approaches in other sectors of EFSA is needed.
- No toxicological data are needed on particles used as additive when demonstrated to be firmly embedded in the FCM matrix (EFSA CEF, 2016b; EFSA CEP Panel, 2022), because they are not expected to migrate.
- All migrating components < 1,000 Da must be assessed individually (CBA) or as a mixture (WMA) according to EFSA Guidance documents (EFSA CEF Panel, 2008; EFSA SC, 2019a,b). The guidance documents on mixtures (SC, 2019b,c) provide a defined and agreed frame and methodology, while identifying the limitations and uncertainties especially regarding the uncharacterised fraction.
- When assessing identified migrating chemicals following the CBA, all available data can be used (e.g. published or unpublished studies, read across, *in silico* tools, TTC for CRAMER classes, TTC for DNA-reactive mutagens and/or carcinogens applicable to NIAS only).
- In common to the assessment of products of natural origin, including foods, it can be that neither the available data from the compositional analysis nor from the whole mixture toxicity tests are of sufficient sensitivity to rule out exposure to highly toxic substances at levels of concern, including genotoxic substances above 0.15 µg/person per day.
- Substances of concern that migrate, but that are already present in the diet, should not be (re-) evaluated, but rather their exposure from FCMs should be compared with that from the diet estimated for the general population[12] and should not lead to more than a minimal increase of the exposure to consumers via the diet. This could apply to any other substances that consumers can be exposed to via the diet.
- Waiving part of the data requirements for substances derived from edible food sources (i.e. food, food ingredient) or produced by QPS microorganisms is accepted by EFSA. Animal forage and feed cannot benefit of data waiver, as it cannot be considered equivalent to food or food ingredient[13].

3.6.2. Waivers for toxicological data requirements

It is proposed to waive toxicological data requirements for:

A. *Substances that are consisting or derived from edible food sources (i.e. food or food ingredients from plants or animals)* provided that the following criteria are observed/met:

[10] The meaning of the numerical values may need to be revisited in the context of mixtures as to whether it refers to e.g. the sum of all the LMWF, of the compounds with structure similarity, or to any single peaks/compounds.

[11] The EFSA Scientific Committee concluded that a threshold of 0.15 µg/person per day would provide sufficient protection against (genotoxic) carcinogenic and heritable effects when it can be ruled out that the compounds are part of the exclusion category. This threshold of 0.15 µg/person/day, for a person of 60 kg body weight, corresponds to 0.0025 µg/kg bw per day. Considering that a person consumes 1 kg of packed food, it corresponds to 0.15 µg/kg food.

[12] Comparison can be made with results from total diet studies carried out in EU countries or with estimates based on the results of monitoring plans. This Technical report does not propose a methodology. A methodology should be discussed and set in coherence with other sectors, considering the question of highly exposed individuals.

[13] To be considered as food, any materials including animal forage and feed should be assessed and authorised on the EU market either as traditional food or as novel food following the related regulations and guidance.

- the "history of safe use" and possible adverse effect should be reported;
- the presence of known or demonstrated substances of concern should be reported and should be at a level which does not lead to more than a minimal increase of the exposure to consumers via the diet (see 3.6.3 for more details). The acceptance level should be agreed with risk managers, including when an HBGV is already reached or exceeded due to dietary sources, and be coherent with other sectors;
- The exposure of consumers to the uncharacterised fraction in a food used for making FCMs should be as low as possible compared to the exposure to the same fraction in food, since it is unknown whether it contains hazardous substances;
- the substances that are derived from edible food sources should not be intentionally or unintentionally changed, e.g. by the use of chemical modifiers, thermal or oxidative stress during production of the food contact substance (e.g. an additive) or during the manufacture of the FCM;
- if the substance/mixture is chemically changed under conditions that are not comparable to those applied to consumed foods, or if the substance originates from a non-consumed part of a food plant or animal, the chemical composition could be compared to the consumed food. If the composition is sufficiently similar (case-by-case expert judgement) to the consumed food, the toxicological data requirements could be waived.

If the waiving of data requirements is not justified for all or for parts of the mixture, then the migrating substances not covered should be assessed in accordance with the FCM tiers and toxicological data requirements (EFSA Note for Guidance, EFSA CEF Panel, 2008). The chemical modifier(s) should be assessed in all cases.

B. *Substances derived from natural sources by using microorganisms in the production process that may benefit from application of the QPS principle*.
If the microorganism is listed by EFSA to have the QPS status, toxicity testing is waived, since QPS microorganisms do not produce toxic metabolites. *A priori,* there is no safety concern, independently of the biomass/carbon source used to produce the substance, unless the biomass/carbon source by itself raises concern for the presence of toxic contaminants or constituents.

3.6.3. Consideration of substances of concern

The so-called substances of concern are identified as a commonality amongst various sectors of regulated products in EFSA (see 3.4). For the purpose of the assessment of mixtures of natural origin to manufacture FCM, the substances of concern are substances known *a priori* to be present or likely to be present and they give reasons for concern due to their chemical, pharmacological or toxicological properties (constituents or contaminants, from environment, storage, process or pesticides residues). They are identified from existing databases (e.g. the EFSA compendium of botanicals (EFSA, 2018a), the Commission Regulation (EC) No 2023/915 on maximum levels of contaminants in foodstuffs[14]), data submitted in applications, literature or expert knowledge. They may be constituents of the mixture derived from natural sources or impurities or contaminants of the substance/mixture. Three situations can be envisaged.

1. If the source material for the intended food contact substance is a food and if the substance of concern also occurs in foodstuffs, then exposure arising from the use of the proposed food contact applications should be compared[12] with the existing dietary exposure, and any additional exposure

[14] Commission Regulation (EC) No 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0915&qid=1695052740821.

should be not more than minimal. In case a HBGV has been set and has been reached or exceeded due to exposure from the diet, the risk manager should consider the additional risk as part of the authorisation process. Acrylamide or trans fatty acids could be examples.

2. If the source material is not a food consumed by the EU population, (e.g. part of a food crop that is not normally eaten or a non-food crop), and if the substance of concern is also found in the normal diet, again exposure arising from the use in the proposed food contact applications should be compared[13] with the existing dietary exposure and any additional exposure should not be more than minimal. An example could be the cyanogenic glycosides found in some edible fruits, but that are concentrated in the stones/pips which could potentially be used as the source material for FCM applications.

3. If there is a substance of concern in the mixture that does not occur in the normal diet and if the substance is a component of the food contact mixture, a standard safety assessment according to the existing guidelines should be applied. If it is an impurity or a contaminant that migrates from the proposed food contact applications, alternative approaches may be applied, such as the TTC.

   The distinction between components of a mixture and impurities/contaminants of a mixture is vexed. The recent "Chemicals Strategy for Sustainability" (CSS) proposes a 'generic approach to risk management' for the most harmful chemicals. This approach is intended to 'ensure that consumer products do not contain chemicals that cause cancers, gene mutations, affect the reproductive or the endocrine system, or are persistent and bioaccumulative' (EC, 2020a). It is expected to be implemented in the regulatory context of FCMs, as outlined in the EC's inception impact assessment on the revision of EU rules on FCMs (EC, 2020b). This means that it could be a policy decision not to permit the intentional use of recognised hazardous substances to make FCMs, unless an argument is made for "essential use". In the sector of the FCM, the distinction between components and impurities of a mixture corresponds to the 'intentional' and 'non-intentional' uses and what have become known as IAS and NIAS, respectively.

   Also relevant in this context is the framework within which the TTC concept is applied. 'The TTC approach should not be used for substances for which EU food/feed legislation requires the submission of toxicity data' (EFSA SC, 2019a). Plastic FCMs are subject to such data requirements. The EFSA Scientific Committee concluded that a threshold of 0.15 µg/person per day would provide sufficient protection against (genotoxic) carcinogenic and heritable effects when it can be ruled out that the compounds are part of the exclusion category (EFSA SC, 2012). Therefore, no genotoxicity data may be needed for NIAS if exposure is below 0.15 µg/person per day, but this assessment approach is not applicable for substances used intentionally to make FCMs.

   So, for any substance of concern that may be identified as present in and/or migrating from the intended food contact application, it will be necessary to be able to discriminate between impurities/contaminants and constituents of a mixture derived from a natural source. It seems not possible to simply set a numerical threshold to discriminate whether a substance can be considered as an unavoidable impurity/contaminant or as a characteristic constituent of the mixture (EFSA SC, 2019b). To discriminate unavoidable impurities from characteristic and necessary constituents, specific aspects of the manufacturing process should be considered along with information on the intended function of the mixture when used to make an FCM.

3.6.4. Presence of small particles including nanoparticles

As mentioned in section 3.4, the cross-cutting Guidance from the EFSA Scientific Committee on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (EFSA SC, 2021b) and on risk assessment of nanomaterials (EFSA SC, 2021a) apply to the FCM sector independently of the source. This should include substances from renewable biological origin containing or consisting of particles used to manufacture FCM. If, however,

the substance is derived from an edible source not changed with regards to particle size, the requirement to establish the presence of small particles, including nanoparticles, is likely to be waived.

3.7. Specific data requirements

3.7.1. Non-toxicological data requirement

Natural substances can have a great variability in their composition and in their constituents, but also in by-products and impurities. Considering the data currently requested in the EFSA Note for Guidance on non-defined mixtures (EFSA CEF Panel, 2008), in the criteria set in the EFSA opinion on wood (EFSA CEP Panel, 2019) and considering the data requested in the other EFSA sectors, the following non-toxicological data are required as a pre-requisite for the evaluation of all natural substances/mixtures:

- Identity of the source: the scientific (Latin) name (binomial name, i.e. genus, species, subspecies or variety), the part of the plant used and the geographical origin (see Guidance on Botanicals; EFSA SC, 2009). The nomenclature should follow the European Pharmacopeia.
- Composition should be characterised, whereby the LMWF is of particular interest. A comprehensive compositional analysis of the LMWF using, e.g., a combination of GC-MS-(FID) and LC-MS should be provided. This could include a fingerprinting analysis for comparison with the source material, if that is a food or a food ingredient. The comparison should be capable of detecting and identifying any newly-formed substances, formed intentionally, e.g. by chemical modification, or unintentionally, e.g. by thermal or other manufacturing processes used. The analytical methods used should have sufficient coverage, selectivity and sensitivity to allow sound conclusions at toxicologically relevant levels of composition/migration/exposure.
- Substances of concern (as defined under 3.6.3) should be identified from the compositional analysis, general knowledge, or retrieved from the literature or existing databases (e.g. the EFSA compendium of botanicals), then quantified using targeted analysis.

  The batch-to-batch composition may be subject to fluctuations/variability related to, e.g., geographical origin, growth conditions, age and manufacturing, and needs to be addressed. Therefore, information on cultivation and treatment prior to use is of interest and should be specified. Especially, information about cultivation and growth conditions, storage, extraction, chemical synthesis, thermal treatment, fermenting agents, coupling agents, presence of nanoparticles, enzymatic treatment, etc. could be necessary. Batch-to-batch variability should be investigated by the comprehensive analysis of representative batches. Information on how and when these batches were produced and why they were selected to be representative, should be provided.
- Proposed specifications need to be described to adequately define the mixture.

In addition to the above-mentioned data, which are specifically required for the evaluation of natural substances, data on physicochemical properties (incl. information on the stability, reactions and fate of the substances/mixture as such, in the plastic during manufacture and in the food following migration) and the intended use, data on the migration potential of the LMWF resulting from the use of the substance (comparing samples made with and without the substance), data on the residual content of the substance added/used in the FCM article, that are requested via the EFSA Note for Guidance (EFSA CEF Panel, 2008), are also required here.

3.7.2. Potential for accumulation in human

Due to the uncharacterised fraction of the substance, the assessment of the potential for accumulation in humans, including the interpretation of absorption, distribution, metabolism and excretion (ADME)

studies performed on the whole mixture, is challenging. A possible way forward is proposed for the two situations that - in accordance with the EFSA Note for Guidance - require the potential for accumulation in human to be addressed: when the migration is between 0.05 and 5 mg/kg food (no ADME study required) and when it is above 5 mg/kg food (ADME study/ies required). It is of importance to note that accumulation is undesirable, but not automatically associated with a toxic effect (EFSA CEF Panel, 2008).

In case of migration between 0.05 – 5 mg/kg food, data to demonstrate the absence of potential for accumulation in man, usually log K_{ow}, are required. However, log K_{ow} of the mixture may be difficult or not feasible to determine. In this case, the evaluation of the results of the 90 days repeated dose toxicity study/ies performed on the whole mixture, together with a well-substantiated justification based on the available data, may be sufficient to draw conclusions on the potential for accumulation of the mixture and/or components of the mixture.

- In case no adverse effects are observed at high doses in the 90-day study (i.e. by the Limit Test in OECD TG 408 or the highest dose to be applied limited by the maximum injected volume, as indicated in the EFSA Scientific Guidance for the submission of dossiers on Food Enzymes (EFSA CEP Panel, 2021) and as applied for genotoxicity testing of the mixtures) and/or the information submitted shows limited concerns for accumulation (e.g. easy dissociation in natural constituents in the diet or human body, low absorption, fast hydrolysis, etc.), the accumulation potential of the mixture could be excluded.
- If some adverse effects that are not an indication of accumulation are observed in the 90-day study, and/or if there are indications of an accumulation of the test item, itself or as derivatives (e.g. accumulation of pigments), and the information/data submitted on the ADME properties is not sufficient to support the lack of potential for accumulation in human, a CBA should be applied as follows.

  The toxicologically relevant constituents of the mixture should be evaluated/characterised for their ADME properties (EFSA ANS Panel, 2012; EFSA NDA Panel, 2021b). Toxicologically relevant constituents are - according to the EFSA ANS Panel Guidance for submission for food additive evaluations (EFSA ANS Panel, 2012) - "generally considered to be the major components and those other components with known or demonstrable biological or toxicological activity and should be determined on a case-by-case basis with a scientific justification" [15]. Supporting information from *in vitro* and *in silico* tools could be provided to evaluate relevant physico-chemical intrinsic properties and kinetic parameters. Some constituents might be considered of"low priority" based on low levels of exposure and a proper justification.

  If the submitted information is not considered sufficient to support the lack of accumulation in humans of the toxicologically relevant constituents of the mixture, either restrictions in use could ensure that their migration is lower than 0.05 mg/kg food or ADME study/ies could be performed. In some cases, instead of ADME study/ies on all toxicologically relevant constituents of the mixture, representatives of each class of constituents could be evaluated.

In case of migration above 5 mg/kg food, ADME study/ies are required for the toxicologically relevant constituents of the mixture.

3.7.3. Allergenicity

In principle and in coherence with other sectors, potential allergenicity should be considered for all source materials from biological origin, i.e. plant and animal biomass as well as microorganisms. Food

[15] Toxicologically relevant constituents include substances of concern (known a priori to give reasons for concern). Those not occurring in the normal diet or occurring but with a migration from FCM increasing exposure more than minimally should follow a standard safety assessment, including to address the potential for accumulation when required by the FCM tiered approach.

allergens are mostly proteins (EFSA NDA Panel, 2021b) and "trace amounts of food allergens transferred to food could, in principle, present a hazard for sensitised individuals" (EFSA CEP, 2021). Hence, when substances used to manufacture FCMs are or contain proteins, known or suspected allergens or are extracted from matrices that contain allergens, the allergenic potential of FCM needs to be assessed. For instance, whey, casein, collagen, chitin and chitosan are known to be food allergens and used to produce packaging materials, edible films and coatings (Etxabide, A. *et al.*, 2017; FERA, 2019; Tanpichai S. *et al.*, 2022).

The incomplete deproteinisation of chitin may lead to the presence of allergenic proteins in the final material, such as tropomyosin (UK COT, 2021). Therefore, while there is, as yet, no recognised threshold for allergenicity, the assessment should also consider the effect of the manufacturing process of the FCM, of the combination with other materials and of the foodstuff(s) in contact, as they may alter allergenicity, i.e. by revealing allergenic or destroying epitopes (FERA, 2019).

The allergenicity may be very low, if any, if the material is not made of or does not contain proteins, or if there is no migration of the proteins under the intended uses. Cross-linking of proteins, which has been used to produce gelatine and casein edible films (Chambi and Grosso, 2006), may also be considered to lead to a reduction or elimination of the allergenicity of food proteins, including for whey and soy protein isolate as well as casein (Damodaran and Li, 2017; Li and Damodaran, 2017; Quintieri *et al.*, 2017).

4 Conclusion

The use of substances/mixtures of natural origin to manufacture FCM should be seen in the context of wider societal aims towards a more circular and sustainable economy. This technical report outlines the principles and the data requirements to assess mixtures from natural sources (for instance from renewable biological resources) to be used to manufacture FCM and articles. It was prepared using case studies from the plastic FCM sector and by consultation with the CEP Panel and the FCM Network. It has gathered information from other EFSA sectors, where materials of natural origin are assessed, and has taken into consideration the applicable EFSA cross-cutting guidance documents.

In the context of natural compounds, a 'substance' is most likely to be a non-defined (complex) mixture used as a starting substance or an additive to manufacture any FCM group type (e.g. plastics, rubber, silicones, etc.).

Substances/mixtures from natural sources cannot be assumed to be safe *per se*. A particular characteristic is their compositional complexity, variability and frequently the presence of an uncharacterised fraction.

The FCM tiered approach for the toxicological data requirement depending on the migration levels (EFSA CEF Panel, 2008) should be followed. All migrating components <1,000 Da must be assessed individually using the CBA and/or as a mixture using the WMA. This requires knowledge of the composition of the substance/mixture and the identity and level of all substances migrating to food from the intended use of the FCM.

A common requirement in all the relevant EFSA sectors is that a mixture should be characterised and that the uncharacterised/unidentified fraction should be 'as low as possible'. Comprehensive chemical analysis for all constituents and impurities that have the potential to migrate, with the capacity to identify and detect substances at a concentration commensurate with the lowest TTC tier (i.e. migration at 0.15 µg/kg food, corresponding conventionally to 0.0025 µg/kg bw per day) is often technically unfeasible. Similarly, the sensitivity, limitations and uncertainties inherent in the WMA to toxicity testing, especially regarding the uncharacterised fraction and low-level constituents/impurities, are well recognised. This gap between the capability of current non-targeted methods for chemical analysis and the sensitivity of current toxicological tests when applied to mixtures, is partly filled by targeted analysis for known

substances of concern. This capability gap is not unique to mixtures from natural sources, but more evident, given their likely UVCB nature. Harmonisation (or at least coherence) in establishing rules and levels for 'as low as possible' with other approaches in other sectors of EFSA is needed.

Waiving part of the toxicity data requirements for substances derived from edible food sources can be justified. This may require a demonstration that there is no intentional or unintentional chemical transformations occurring that do not/would not also occur in foods, e.g. brought about by cooking or other processing methods.

Substances of concern that migrate and are already present in the diet should not be (re-)evaluated, but rather, their exposure from FCMs should be compared with that from the diet estimated for the general population and be minimal compared to that.

If the substance is derived from an edible source and is not (intentionally or unintentionally) transformed, the requirement to establish the presence/absence of small particles, including nanoparticles, could be waived and a conventional risk assessment approach taken.

Substances not known *a priori*, but detected and identified as IAS/NIAS by non-targeted compositional and/or migration analysis, also need to be evaluated.

Concerning allergenicity, food allergens are mostly proteins and mixtures obtained from plant and animal biomass that may contain proteins. Proteins are too large to migrate from FCMs by diffusion mechanisms, but other release mechanisms may operate. Since there is currently no recognised threshold for allergic substances, the potential risk for allergenicity must be considered case-by-case.

This report helps to establish the basis for data requirements to demonstrate the safety of using complex mixtures of natural origin for FCMs. The provision of these data and the safety assessment itself is likely to be complex. This could potentially lead to (i) a significant amount of requested studies, (ii) more time to reach a conclusion from EFSA, and (iii) specifications required on the substances/mixtures and the manufacturing process(es) used along with restrictions on the FCM applications.

5 Recommendations

In response to the terms of reference, this technical report has been prepared to help establish the principles for assessing mixtures from natural sources for possible use to manufacture of food contact materials and articles. This report is intended to serve as a background document for further work by the EFSA SC. Developments in risk assessment approaches on this topic depend in part on ensuring the applicability and possible updating of EFSA cross-cutting guidance documents. It is recommended that the following may merit particular consideration by the SC in any future work:

(i) clarification on the extent to which the unknown fraction should be 'as low as possible', since this influences the extent of the chemical characterisation of the mixture that is required, and to help ensure a consistent level of safety;

(ii) recognition and possible reconciliation of the gap between (a) the capability of non-targeted methods of chemical analysis to comprehensively elucidate the full composition of complex mixtures, (b) the sensitivity of (especially) genotoxicity tests applied to whole mixtures (with respect to the capability to detect minor unknown components) and (c) the TTC thresholds (especially the TTC value for genotoxicity);

(iii) consider the possible application of the TTC approach not only to contaminants, but also to minor constituents of complex mixtures;

(iv) establishing a consistent approach to be taken for substances of concern, general acceptance of the principle of minimal additional exposure, and the consequent acceptance of waivers of toxicological data requirements.

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Abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
CBA	Component-Based Approach
C&L	Classification and Labelling
CSS	Chemicals Strategy for Sustainability
EC	European Commission
ECHA	European Chemicals Agency
EFSA SC	EFSA Scientific Committee
EU	European Union
FCM	Food Contact Materials
FCM WG	Food Contact Materials Working Group
FCM&A	Food Contact Materials and Articles
GC-MS-(FID)	Gas Chromatography – Mass Spectrometry – (Flame Ionization Detector)
GRAS	Generally Recognised As Safe
HBGV	Health-Based Guidance Value
IAS	Intentionally Added Substances
K_{ow}	n-octanol-water partition coefficient
LC-MS	Liquid Chromatography – Mass Spectrometry
LMW	Low Molecular Weight
LMWF	Low Molecular Weight Fraction
NAMs	New Approach Methodologies
NIAS	Non-Intentionally Added Substances
OECD TG	Organisation for Economic Cooperation and Development Test Guidelines
PBT	Persistence, Bioaccumulation and Toxicity
PHBH	poly((R)-3-hydroxybutyrate-co-(R)-3-hydroxyhexanoate
QPS	Qualified Presumption of Safety
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
SCF	Scientific Committee on Food
SID	Substance Identity
TTC	Threshold of Toxicological Concern
USA	United States of America
US-FDA	United States Food and Drug Administration
UVCB	Unknown or Variable Composition, complex reaction product, or Biological materials
WMA	Whole mixture approach

Appendix A – Considerations on the assessment of the so-called substances of concern in sectors other than Food Contact Materials

When genotoxic and/or carcinogenic substances are present in botanical feed additives, their assessment is based on three possible scenarios depending on the availability of data from carcinogenicity studies in rodents and exposure: the MoE (if a $BMDL_{10}$ can be derived), the TTC, and the comparison of the intake and exposures. Their assessment may conclude to be indicative of a low concern (MoE < 10,000), low probability of adverse effects (exposure < relevant TTC value) and low probability of additional risk (in case of minimal increase of the intake via the feed use of the additive of botanical origin), respectively. Minimal increases of the exposure accepted in the assessments of feed additives are for instance < 4% (EFSA FEEDAP Panel, 2021b) and < 10% (EFSA FEEDAP Panel, 2021c).

The assessment of smoke flavouring primary products considers whether the presence of constituents, impurities or contaminants evaluated to be genotoxic *in vivo* is "unavoidable", i.e. resulting from the manufacturing process of the primary product. If the estimated exposure of these "unavoidable" genotoxic substances is below the TTC for DNA-reactive mutagens, it is concluded that there is a low probability of adverse health effects (EFSA SC, 2019). If relevant carcinogenicity data are also available, a MoE approach (EFSA SC, 2005, 2012) may be used in the case of impurities or contaminants (e.g. for PAH). Contaminants, especially PAH, are also assessed against the maximum level set in foodstuffs (according to EC Reg. 2023/915[14]) and the added exposure to consumers. Constituents, impurities or contaminants that are genotoxic (or for which genotoxicity cannot be excluded using the information available) and are "avoidable" are considered a potential safety concern.

The assessment of novel food distinguishes contaminants from naturally occurring substances of concern. Contaminants are assessed against the maximum level set in foodstuffs (according to EC Reg. 2023/915[14]). Naturally occurring substances of concern (e.g. alkaloids, furocoumarin) other than genotoxic and/carcinogenic are assessed against available HBGV - the TTC is not considered -, and if no HBGV is available, the intake and exposures are compared (similar exposure compared to other food sources is considered of no concern). The presence of (known or experimentally proved) genotoxic substances in principle would lead to a negative scientific opinion of a novel food and, thus, a non-authorisation on the market of the European Commission. Up to now none of the authorised novel food has been identified to contain genotoxic substances.
For the assessment of food enzymes, contaminants (e.g. heavy metals, pesticides, mycotoxins) are considered against regulatory limits and/or limits of quantification and/or available HBGV.

Appendix B – Case studies

In the context of the use of mixtures of natural origin to manufacture food contact materials and depending on the mixture, different assessment approaches might be appropriate. Different cases are described below.

Case 1: Substance from food or food ingredients, e.g. chitin, chitosan, citrus seeds/endocarp/skin

A. In case the substance originates from a food or food ingredient and is demonstrated to not be modified during production of the food contact substance (e.g. an additive) or during the manufacture of the FCM, the request for new toxicological data could be waived. Information should be provided on the levels of exposure of the possible substances of concern from the diet and from the use to manufacture FCM, and the possible reported potential adverse effects and/or history of safe use.

B. If the substance is chemically changed under conditions that are not comparable to those applied to consumed foods, due to e.g. thermal or oxidative stress, or to a chemical modification during production of the food contact substance (e.g. an additive) or during the manufacture of the FCM, the composition could be compared with the non-modified substance to identify the new peaks/substances.

   The migration of these new LMWF peaks/substances and the chemical modifier (if any) should be assessed in accordance with the FCM tiers and toxicological data requirements.

   In addition regarding the non-modified fraction, information should be provided on the levels of exposure of the possible substances of concern from the diet and from the use to manufacture FCM, and the possible reported potential adverse effects and/or history of safe use.

Case 2: Substance from a non-consumed part of a food plant or animal, e.g. coffee husk, ground sunflower seeds

In case the substance originates from the non-consumed part of a plant or animal derived from food production, it is expected (i) that the plant or animal meet the requirements for food for human consumption: growing, harvesting and storage of a plant, a part of which is consumed, would cover maximum permissible levels of chemical and biological contaminants (e.g. pesticides, mycotoxins, heavy metals and foodborne pathogens), and (ii) to have more knowledge on the composition of the consumed part(s) and on their history of safe uses. Consequently, the assessment could focus on the LMWF not covered by the consumed part(s), if any, via comparison of the compositions. Additionally, it should consider whether the LMWF (covered and not covered by the consumed part(s)) is changed during production of the food contact substance or during the manufacture of the FCM (case 1A or 1B). Information should also be provided on the levels of exposure of the possible substances of concern from the diet and from the use to manufacture FCM, and the possible reported potential adverse effects and/or history of safe use.

A. If an equivalent composition of the non-consumed *versus* the consumed part is proven, the request for toxicological data could be waived and the substance could be assessed according to the above Case 1.

B. If the composition is not equivalent, the assessment could focus on LMWF not covered by the consumed part(s).

Case 3: Substance originating from plant or animal that are not consumed (partly or all), e.g. cellulose bleached pulp

This case comprises mixtures, not originating from edible foods (from food plant or animal) nor from the non-consumed part of a plant or animal derived from food production, along with the migrating LMWF coming from Cases 1 and 2. The assessment must be carried out in accordance with the FCM tiers and toxicological data requirements.

The toxicological evaluation requires a careful identification, quantification and assessment of available toxicological information/data on the substances identified as potential migrants. Demonstration of the identity and stability (batch-to-batch variability, including information on possible range of variation as well as stability over time) of the mixture is necessary to ensure that the mixture tested is representative of the one to be placed on the market. If it does not conform, test material specification should be provided together with a scientific justification for using the available data in evaluating the safety of the material intended for market.

According to recommendations on genotoxicity assessment of complex mixtures and the Guidance on harmonised methodologies for risk assessment of combined exposure to multiple chemicals (EFSA SC guidance on mixture, 2019 a,b), a combination of a CBA approach for the identified substances and a WMA approach for the uncharacterised/unidentified fraction must be applied as follows.

i. Genotoxic potential of the identified components should be assessed for each individual component known and well-identified (CBA) by using all available data (studies published and unpublished, read across, *in silico* (e.g. (Q)SAR) and other NAMs). Identified substances that are not components but NIAS to which the TTC could be applied (see 3.6.3) and which show structural alerts for genotoxicity and/or present at a concentration leading to an exceedance of the appropriate TTC should be further evaluated.

   According to the EFSA Scientific Committee (EFSA SC, 2019b, see section 2.3), "...for mixtures that contain individual components that may indicate a potential concern for genotoxicity but for which the data available are not sufficient to conclude on genotoxicity, e.g. positive results in *in vitro* genotoxicity tests of an individual component, additional data would be needed to complete an assessment" (EFSA, 2011, 2017). Even if none of the identified chemical substances in a mixture raises concern for genotoxicity, the genotoxic potential of the unidentified fraction should also be evaluated to complete the assessment of the mixture. Experimental testing of the unidentified fraction should be considered as the first option or, if this is not feasible and a scientific justification is provided, testing of the whole mixture should be undertaken. Further fractionation of the test material could be considered case-by-case to remove inert, toxicologically irrelevant components from the mixture (e.g. high-molecular-weight polymers) to minimise the dilution of the components of interest in the tested sample, or to remove highly toxic components (e.g. surface active substances) that may prevent testing adequately high doses of the mixture because of overt toxicity. Moreover, if either the starting material used or the production process indicates the possible presence of genotoxicants in the unidentified fraction of the mixture, an attempt should be made to isolate and test the fraction of concern as such, if it is not possible to chemically identify and quantify the substance."

ii. For toxicological endpoints other than genotoxicity required by the FCM tiered approach, a whole mixture approach could be applied, considering the presence of insufficiently chemically defined fractions as well as all the individual components and potential interactive effects among different components. Similarly to genotoxicity testing of the mixture, fractionation of the test material could be considered case-by-case to remove inert, toxicologically irrelevant components from the mixture (e.g. high-molecular-weight polymers) to minimise the dilution of the components of interest in the tested sample. The aim is to test a mixture that represents as closely as possible the migrating species, taking into account aspects of molecular mass and any chemical changes that may occur when the substance is incorporated into FCM. The identified migrating chemicals not present in the mixture tested in the toxicological studies could be assessed using all available data (e.g. studies, literature, read across, *in silico* tools, CRAMER classes). For the assessment of the potential for accumulation in human, a possible way forward is proposed in section 3.7.2.