15:40 - 16:10:

SAFETY ASSESSMENT OF SUBSTANCES/MIXTURES FROM RENEWABLE BIOLOGICAL RESOURCES

Regional seminar on 'Food Contact Materials and Safety Requirements applicable to Recycled Plastic', 26th June 2023

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EUROPEAN FOOD SAFETY AUTHORITY

OUTLINE

- Context
- Considerations
- Proposal

Disclaimer: the content of this presentation is not an official position and does not necessarily represent the position of EFSA. To consult the opinions of EFSA Panel on food contact materials, enzymes, and processing aids (CEP), see www.efsa.europa.eu

CONTEXT

APPLICATIONS ON PLASTIC FOOD CONTACT SUBSTANCES

Assessment of plant-based additives (fillers) in plastics has triggered further discussions and considerations.

- Plants are made of complex mixture with variability in the nature and the level of constituents. A fraction 'may' not be identified and/or quantified and/or LoD > TTC of 0.15 µg/kg food (0.0025 µg/kg bw pd). This uncharacterised fraction makes the assessment more complex and uncertain.
- Plants are natural and may be food or close to food. This may waive the need for some or all tox data and simplify the assessment.

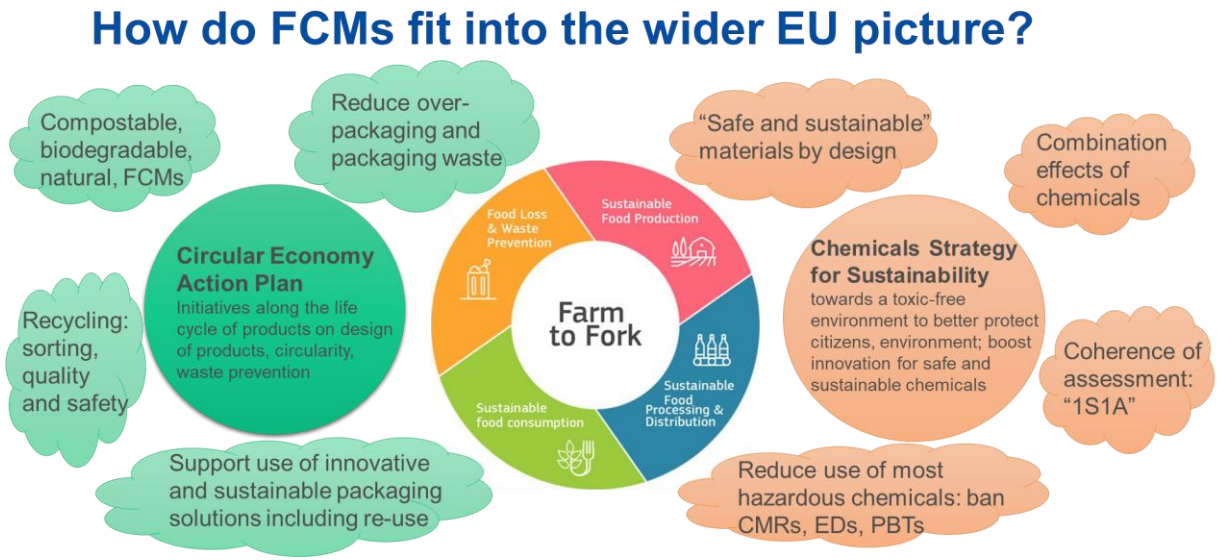
STATUS AND OBJECTIVE

- Assessment of submitted applications by EFSA FCM Working Group (WG) and EFSA CEP Panel (‘from 2015’ -on).
- CEP Panel made a proposal in March 2022 for Scientific Committee (SC) work program 2022-24.
- **Discussions at FCM WG since April 2022**:
  - The aim is to collect and analyse experiences and approaches in EFSA, and to clarify FCM WG views and propose FCM principles to the SC for starting its cross-cutting work in 2024.
  - Preparation of an EFSA Technical Report by 2023.

REVISION OF THE FCM FRAMEWORK LEGISLATION

EC possible options for FCM rules. Shifting the focus onto the final material and **refocus on broader material types**; e.g.

- Synthetic organic type materials (plastics, rubbers, coatings, inks, adhesives)
- Natural organic type materials (paper, wood, fibres, plant-based)
- Inorganic based materials including metals
- Recycled materials
- Active FCM



CONSIDERATIONS

CONSIDERATIONS FOR THE SAFETY ASSESSMENT

- EFSA Scientific Committee (SC) cross-cutting Guidance (especially on mixtures, genotoxicity, TTC).
- FCM Guidelines (EC SCF) and Note for Guidance (EFSA).
- Recent FCM opinions on plant-based additives for plastics.
- Experience/Guidance from:
  - other sectors (novel food (NF), botanicals, enzyme (ENZ), feed additives (FEED), smoke flavourings (SMK)) to learn and understand how they deal with similar assessment; and from
  - other EU and USA Institutions.

EFSA SC GUIDANCE ON MIXTURES

- Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 2019;17(3):5634, 77 pp. https://doi.org/10.2903/j.efsa.2019.5634

Abstract

This Guidance document describes harmonised risk assessment methodologies for combined exposure to multiple chemicals for all relevant areas within EFSA's remit, i.e. human health, animal health and ecological areas. First, a short review of the key terms, scientific basis for combined exposure risk assessment and approaches to assessing (eco)toxicology is given, including existing frameworks for these risk assessments. This background was evaluated, resulting in a harmonised framework for risk assessment of combined exposure to multiple chemicals. The framework is based on the risk assessment steps (problem formulation, exposure assessment, hazard identification and characterisation, and risk characterisation including uncertainty analysis), with tiered and stepwise approaches for both whole mixture approaches and component-based approaches. Specific considerations are given to component-based approaches including the grouping of chemicals into common assessment groups, the use of dose addition as a default assumption, approaches to integrate evidence of interactions and the refinement of assessment groups. Case studies are annexed in this guidance document to explore the feasibility and spectrum of applications of the proposed methods and approaches for human and animal health and ecological risk assessment. The Scientific Committee considers that this Guidance is fit for purpose for risk assessments of combined exposure to multiple chemicals and should be applied in all relevant areas of EFSA's work. Future work and research are recommended.

- Statement on the genotoxicity assessment of chemical mixtures. EFSA Journal 2019;17(1):5519, 11 pp. https://doi.org/10.2903/j.efsa.2019.5519

Abstract

The EFSA Scientific Committee addressed in this document the peculiarities related to the genotoxicity assessment of chemical mixtures. The EFSA Scientific Committee suggests that first a mixture should be chemically characterised as far as possible. Although the characterisation of mixtures is relevant also for other toxicity aspects, it is particularly significant for the assessment of genotoxicity. If a mixture contains one or more chemical substances that are individually assessed to be genotoxic *in vivo* via a relevant route of administration, the mixture raises concern for genotoxicity. If a fully chemically defined mixture does not contain genotoxic chemical substances, the mixture is of no concern with respect to genotoxicity. If a mixture contains a fraction of chemical substances that have not been chemically identified, experimental testing of the unidentified fraction should be considered as the first option or, if this is not feasible, testing of the whole mixture should be undertaken. If testing of these fraction(s) or of the whole mixture in an adequately performed set of *in vitro* assays provides clearly negative results, the mixture does not raise concern for genotoxicity. If *in vitro* testing provides one or more positive results, an *in vivo* follow-up study should be considered. For negative results in the *in vivo* follow-up test(s), the possible limitations of *in vivo* testing should be weighed in an uncertainty analysis before reaching a conclusion of no concern with respect to genotoxicity. For positive results in the *in vivo* follow-up test(s), it can be concluded that the mixture does raise a concern about genotoxicity.

EC SCF GUIDELINES, 2001

8.4.3 Foodstuffs/Food ingredients

These can be used as monomers, as starting substances or as additives and will require only the data requested in sections 1 and 3.

8.4.4 Food additives

Those already evaluated by the SCF will, in the first instance, only require the data requested in sections 1, 3 and 6.

EFSA FCM NOTE FOR GUIDANCE, 2008

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.
1.3.10	**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.

FCM No. 9: acids, C2-C24, aliphatic, linear, monocarboxylic from natural oils and fats, and their mono-, di- and triglycerol esters (branched fatty acids at naturally occurring levels are included)

APPLICATIONS: FCM WG & CEP PANEL ASSESSMENTS

Additives (fillers) derived from plants; amongst those assessed by the FCM WG:

- Untreated woodflour and fibres
- Ground sunflower seed hulls
- Bleached cellulose pulp from softwood

UNTREATED WOOD FLOUR AND FIBRES (CEP PANEL, 2019)

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.

3.2. Criteria for future evaluations of wood and similar materials from plant origin as additives for plastic for food contact applications

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, 2008). Specifically, the following aspects should be considered:

- species;
- possible variability related to age, growth conditions and geographical origin;
- treatment during cultivation/storage;
- manufacturing from the source material into the additive: physical and mechanical processing, chemicals used in this process;
- substances used together with the additive to produce the plastic material, e.g. coupling agents;
- 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;
- migration of substances resulting from using the additive, comparing samples made with and without the additive;
- toxicological data covering the migrating substances detected in this analysis.

FROM OTHER AREAS: NF, BOTANICAL, ENZ, FEED, SMK 1/2

- Uncharacterised fraction adds complexity and uncertainties.
- Identification incl. botanicals, variability/specifications, process are key.
- Analysis and assessment of substances of concerns that are defined as known hazardous substances (natural constituents or pollutants or plant protection products or storage or process contaminants).
- Thorough compositional characterisation “as fully as possible”, uncharacterised fraction “as low as possible”. Based on expert judgement, literature, compendium, process, history of use, available tox information.

FROM OTHER AREAS: NF, BOTANICAL, ENZ, FEED, SMK 2/2

- A waiver for tox data requirement is considered:
  - Edible food considering history of safe use, exposure.
  - Qualified Presumption of Safety (QPS) principle may help for substances derived from natural sources by using microorganisms listed by EFSA to have the QPS status.
- Tox data requirement can be significant (e.g. NF, FEED).
- Application of EFSA SC Mixture guidance: i.e. Component Based Approach (CBA) for identified chemicals (*in silico*, literature, read across, CRAMER, TTC; studies) and Whole Mixture Approach (WMA) for the uncharacterised fraction.

FROM OTHER EU AND USA INSTITUTIONS

- **US FDA** GRAS classification and **ECHA** UVCB of limited help.
  - GRAS approach in its modern implementation does not offer any specific ‘shortcuts’.
  - Information obtained on UVCB composition is considered by ECHA not sufficient for the Chemical Safety Assessment (a large fraction of the substance being unknown expected to be addressed by the repeatability of the process and assessment like SC approach on mixture).

PROPOSAL

MAIN ELEMENTS OF FCM WG CONSENSUS 1/3

- (Mixtures from) natural sources are not safe *per se*.
- Uses and assessment of natural complex mixtures triggers additional uncertainties especially regarding the uncharacterised fraction.
- Identity and composition are key. Variability is critical for the representativity.
- The FCM tiered approach for the toxicological data requirement depending on the migration levels should be followed.
- All components <1,000 Da must be assessed individually (CBA) or as a mixture (WMA) acc. to EFSA SC Guidance documents, i.e. a combined approach that provide a defined frame and methodology, while identifying the limitations and uncertainties especially regarding the uncharacterised fraction.

MAIN ELEMENTS OF FCM WG CONSENSUS 2/3

- It can be that neither the available data from the compositional analysis nor from those of 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/day.
- Not to assess substances of concern already present in food(s), but compare their exposure with that from food, potentially applying an allocation factor.
- **Waiving part(s) or all the toxicological data requirements** for substances **produced by QPS microorganism** or **derived from edible food sources** (plants, animals) is acceptable.

MAIN ELEMENTS OF FCM WG CONSENSUS 3/3

- **Waiving for substances derived from edible food sources** should consider:
  - the "history of safe use" and possible adverse effect; the presence and exposure of substances of concern; the exposure 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;
  - the substances should not be changed; if changed under conditions 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 to the consumed food, the tox data requirements could be waived. The chemical modifier(s) should be assessed.
  - If the waiving is not justified for all or for part of the mixture, the migrating substances not covered should be assessed acc. to FCM tiers and tox data requirements.

POSSIBLE CONCEPTUAL FRAMEWORK

As a pre-requisite: non-toxicological data should be provided on:

- **Identity of the source**: needs to be clearly described incl. scientific (Latin) name (binomial name, i.e. genus, species, subspecies or variety), part of the plant uses, geographical origin (see Guidance on Botanicals).
- **Composition**: Compendium + literature (incl. possible substance(s) of concern) + comprehensive compositional analysis of the LMWF - with e.g. a combination of GC-MS-(FID) & LC-MS – and incl. targeted analysis of substances of concern (constituents or contaminants or pesticides residues). Possible variability related to age, growth conditions, geographical origin, and batch to batch needs to be addressed (≥5). Specification needs to be informed.
- **Production / manufacturing process**: from cultivation to the use (e.g. treatment during cultivation/growth and storage, extraction, chemical synthesis, thermal treatment, fermenting agents, coupling agents, presence of nanoparticles, enzymatic treatment).
- **Physicochemical properties**: as in EFSA Note for Guidance.
- **Intended uses**: as in EFSA Note for Guidance.
- **Migration potential**: of the LMWF resulting from the use of the substance (comparing samples made with and without the substance); possible exception for Category III. Residual content of the substance added/used in the FCM article.

THREE CASES FOR TOX DATA REQUIREMENT

- Case I: the substance originates from a food or food ingredient
- Case II: the substance originates from a non-consumed part of a food plant or animal
- Case III: Assessment - following FCM tiers - of the LMWF of the mixture/substance itself and of migrating LMWF not present in the substance itself

CASE I: FROM A FOOD OR FOOD INGREDIENT

- Comparison with edible part
  - In line with SCF, 2001; EFSA NfG; ENZ, NF
  - Examples: citrus seeds/endocarp/skin cups, waste coffee grain cups, chitin and chitosan

Case I: Does the substance originate from a **food or food ingredient**?

↓ Yes

Is the food (ingredient) chemically (modifier, oxidation) or significantly physically (T, process) modified?

No ↓

I.A. Tox testing waived but information on exposure from diet and on reported safety/adverse effect/history of safe use

↓ Yes

I.B. Chemical comparison with the not modified food (ingredient) -> assessment of the chemical modifier/modification **plus** the new LMWF peaks acc. to Case III

CASE II: NON-CONSUMED PART OF A FOOD PLANT OR ANIMAL

- A **part of a plant derived from food production (Cat II)** could be defined "food grade" (meeting the requirements for food):
  1. 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).
  2. It is expected 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) via comparison of the compositions.
  3. Examples: ground sunflower seed hulls, coffee husk cups

Case II: Does the substance originate from **non-consumed part of a food plant or animal**?

↓ Yes

Tox testing waived if **similar/equivalent composition to the consumed part(s)**.

❑If equivalent ⇔ I.A. comparison of exposures (acceptable level tbd) and reported safety/adverse effect/history of safe use)

❑If not equivalent -> **either** assessment of the new LMWF substances ⇔ I.B.

CASE III: ASSESSMENT FOLLOWING FCM TIERS OF THE LMWF

- Considering FCM tiers, EFSA SC guidance on mixtures, LMWF; example: cellulose bleached pulp

Case III: **following FCM tiers, assessment of the LMWF of the mixture/substance itself and of migrating LMWF not present in the substance itself**

Based on a combination of WMA for the uncharacterised/unidentified fraction and CBA for identified substances

a. Genotoxic potential of the identified components should be assessed individually (CBA) using all available data (info from studies (published & not published) -> Read Across -> in silico ((Q)SAR,…).

b. Genotoxic potential of the unidentified components should be tested on the 'unidentified' fraction separated from the rest of the mixture if possible, otherwise WMA on the entire mixture. *Negative result to be assessed on case-by-case basis due to limitation on the sensibility of the approach*.

c. For endpoint other than genotoxicity -> WMA and CBA (incl. CRAMER classification).

   ADME study not requested on the mixture "due to difficult interpretation of toxicokinetic studies, considering that a substantial part of the tested material may remain unidentified". For migration > 5ppm, an ADME studies is required for the main components of the mixture (CBA). For 0.05 < migration < 5ppm, a way forward is proposed next slide.

d. Possible comparison with other dietary source of exposure.

ASSESSMENT OF POTENTIAL FOR ACCUMULATION IN HUMAN AND ADME *STILL UNDER DISCUSSION*

Accumulation is undesirable but not automatically associated with any toxic effects (EFSA NfG, 2008)

❑ FCM tier 2: 0.05 ≤ migration < 5 mg/kg food: based on the evaluation of repeated tox studies (i.e. 90-d)

If no adverse effects observed at high doses (e.g. Limit Test in OECD TG 408) and/or information shows limited concerns for accumulation (e.g. e.g. easy dissociation in natural constituents in the diet or human body, low absorption, fast hydrolysis, etc.) -> no further assessment

If adverse effects are observed and/or 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 component based approach (CBA) should be applied.

- Toxicologically relevant constituents of the mixture should be evaluated for their ADME properties.
- Supporting information from *in vitro* and *in silico* tools could be provided in order to evaluate relevant physico-chemical intrinsic properties and kinetic parameters. Some constituents might be considered of ”low priority” based on low levels of exposures and a proper justification.

If this is not sufficient, 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.

❑ FCM tier 3: migration ≥ 5 mg/kg food: based on full data set

-> an ADME study is required for the main components of the mixture (CBA)

Thank you for your attention

Any questions?

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