5.A SAFETY ASSESSMENT OF SUBSTANCES/MIXTURES FROM RENEWABLE BIOLOGICAL RESOURCES

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EFSA FCM Network on 20th April 2023

EUROPEAN FOOD SAFETY AUTHORITY

AIM OF THIS AGENDA ITEM

- To describe the FCM WG considerations and principles for safety assessment of natural compounds
- To allow for comments

APPLICATIONS ON PLASTIC FOOD CONTACT SUBSTANCES

- Assessment of plant-based additives (fillers) has triggered further discussions and considerations.
- Plants are made of **complex mixture** with variability in the nature and the level of constituents
  - A fraction is identified and (semi-)quantified
  - 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.

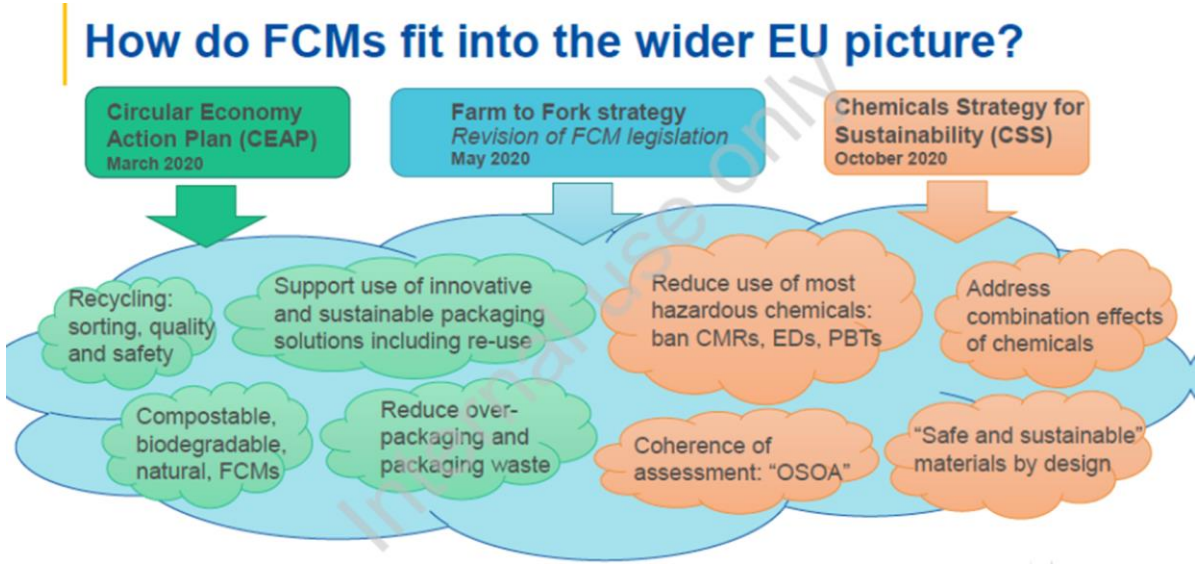
STATUS AND OBJECTIVE

- **Assessment of applications** by FCM WG & CEP Panel (from 2015 - on)
  - CEP Panel made a proposal in March-22 for SC work program 2022-24
  - Discussions at FCM WG since April 2022 incl. consultation of other EFSA sectors dealing with similar assessment (NF, botanicals, ENZ, FEED, SMK)
    - The aim is to clarify FCM WG views and propose FCM principles to the SC for starting its cross-cutting work in 2024
    - An internal mandate was approved for the preparation of a Technical Report by end 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



EFSA INTERNAL MANDATE APPROVED IN MARCH 2023

- Fit for purpose background document used as input for the Scientific Committee.
- Collecting and analysing experiences and approaches in EFSA.
- EFSA Scientific Report approved by EFSA Executive Director.
- Prepared by EFSA FCM WG and EFSA Staff.
- Published in EFSA website (if possible in EFSA Journal).
- Deadline is end 2023.

INTERNAL AND INSTITUTIONAL CONSULTATIONS

- *CEP Panel March 2023: Consultation on principles*
- *EFSA FCM Network April 2023: Consultation on principles*
- *CEP Open Panel June 2023: Presentation of the principles*
- *CEP Panel July 2023: Consultation on the draft technical report*
- *Scientific Committee September/November: Presentation and discussion*
- *EFSA FCM Network October: Consultation on the draft technical report*
- *Deadline end 2023*

CONSIDERATIONS

CONSIDERATIONS FOR THE SAFETY ASSESSMENT

- FCM Guidelines and Guidance
- Recent FCM opinions on plant-based additives for plastics
- Experience/Guidance from other sectors dealing with compounds/substances from natural sources

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 (generic)
- Ground sunflower seed hulls up to 50% (dry foods at ambient T or below…)
- Bleached cellulose pulp from softwood (pine and spruce) up to 40% (inconclusive)

Examples of other fillers types

efsa European Food Safety Authority

Mineral particles use as additives (e.g. fillers), e.g.:

- CaCO3 nano (coated & not) up to 40%
- Se nano, ZnO nano; TgO
- TiO2 surface-treated with fluoride-modified alumina up to 25%
- Chopped carbon fibers up to 40% (orga.)
- Montmorillonites clays modified (up to 4% in PLA)

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.

GROUND SUNFLOWER SEED HULLS (CEP PANEL, 2016; FCM WG, 2021)

- EFSA CEP Panel (2016):
  - No tox data were requested on the additive itself (a high molecular weight polymer is not expected to migrate and to be absorbed by the cells used in genotoxicity tests).
  - The Panel focused its toxicological assessment on the possible migration of impurities and reaction and degradation products <1,000 Da.
- EFSA FCM WG (2021):
  - As in 2016, it focused on the possible migration of the LMWF.
  - Clarified that potential migrants should primarily be assessed based on the available toxicological information and TTC should be restricted to chemically defined substances lacking toxicological data and should not be extended to unknown substances found in analytical tests. The substances identified and showing structural alerts for genotoxicity and/or present > TTC would need to be further assessed.
  - It considered as a possible way forward to compare the exposure of the substances migrating from the intended uses of the additive to the exposure via the diet.

BLEACHED CELLULOSE PULP FROM SOFT WOOD (CEP PANEL, 2022)

- No tox data were provided for the substance as its migration into food is not expected
- The process is not sufficiently specified to assume that the composition of all bleached cellulose pulp samples will be the same as the ones investigated.
- The safety of the potentially migrating substances of low molecular mass detected was addressed individually and was considered adequate.
  - LoDs not low enough to ensure absence of potentially genotoxic substances at a concentration leading to an exposure >TTC. Not all possibly migrating substances were identified or amenable to the analytical methods applied.
  - This was insufficient owing to a substantial fraction of unidentified components.
- All components <1,000 Da potentially migrating …must be assessed individually or as a mixture. The single chemical approach may be inadequate for the evaluation of complex mixtures containing a substantial fraction of unidentified components.

FROM OTHER AREAS: NF, BOTANICALS, ENZ, FEED, SMK

- Identification incl. botanicals, variability/specifications, process.
- Analysis and assessment of substances of concerns (e.g. for genotoxic and/or carcinogenic in FEED: MoE, TTC, intake comparison).
- Thorough compositional characterisation (“as fully as possible”, (SM-)F) incl. literature & compendium. Uncharacterised fraction (“as low as possible” (NF), expert judgement, literature, process, history of use, av. tox info).
- Unidentified components add complexity and uncertainties.

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

- A waiver for tox data requirement is considered (edible, history of safe use, comparison of exposure).
- QPS principles; it may help (microorganism cases) but has limitations.
- Tox data requirement can be significant (e.g. NF, FEED).
- Application of CBA for identified chemicals (*in silico*, literature, read across, CRAMER, TTC; studies).
- Application of WMA for the uncharacterised fraction.

- Commonalities and differences between the different areas.

MAIN ELEMENTS OF FCM WG CONSENSUS 1/4

- Harmonisation/coherence with other sectors is possible and needed.
- (Mixtures from) natural sources are not safe *per se*.
- Uses and assessment of natural compounds/complex mixtures triggers additional uncertainties especially regarding the safety of the uncharacterised fraction.
- All components <1,000 Da must be assessed individually or as a mixture according to EFSA Guidance documents.
- Waiving part of the data requirements for substances derived from edible food sources is acceptable. If modified, the modifier and new substances formed should be assessed.

MAIN ELEMENTS OF FCM WG CONSENSUS 2/4

- The assessment of NIAS is more conservative in FCM than in other areas, incl. FOODADD. Measuring 0.15 µg/kg food (TTC) is often technically unfeasible. The safety level could be calibrated against that for foods => possible role for risk manager to set the safety level.
- Data requirement should be the same for all food contact substances (FCS), including mixtures from natural sources (i.e. waiver could apply to all FCS falling under the same criteria).
- Feed should not be considered as food or food ingredient.

MAIN ELEMENTS OF FCM WG CONSENSUS 3/4

- Not to assess substances of concern already present in food(s), but compare their exposure with that from food, potentially applying an allocation factor (for risk managers).
  - known hazardous substances (natural constituents or pollutants or plant protection products or storage or process contaminants).
- US FDA GRAS classification and ECHA UVCB of limited help.
  - GRAS approach in its modern implementation does not offer any ‘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).

MAIN ELEMENTS OF CONSENSUS 4/4

- Identity & composition are key. Variability is critical.
- EFSA SC guidance on mixture (SC, 2019a,b) is a combined approach
  - Still requires some identification, quantification and substances assessment
  - Whole Mixture Approach (WMA) is useful and has limitations (genotoxicity, TK).
- **Substance** in the sense of FCM (Regulation, SCF Guidelines, Note for Guidance): single substance; synthetic, defined or non-defined mixture. Here, more a non-defined (complex) mixture - could also be defined or single - used as starting substances or additives used to manufacture any FCMs article types (e.g. rubber, silicones). Could be particulates, extract, modified.

POSSIBLE CONCEPTUAL FRAMEWORK

POSSIBLE CONCEPTUAL FRAMEWORK

As a pre-requisite: non-tox 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 (as much/relevant as possible based on expert judgement (e.g. NF/FLAV) incl. contaminants, pesticides and identified substances of concern (targeted analysis). Possible variability related to age, growth conditions, geographical origin, and batch to batch needs to be addressed (NF:≥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; see S15 NFppt22.9.22 & Guidance on Botanicals).

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 MIGRATION AND 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

Note: animals should not be farmed for that aim (we do not see why it would not be covered).

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 (acceptable level tbd) 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

- A **part of a plant derived from food production (Case 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 ESFA SC guidance on mixtures, LMWF, FCM tiers
- Proposing a way forward (draft) to assess ADME when needed (migration > 5 mg/kg food, see next slide)
- Examples: cellulose bleached pulp

Case III: Assessment - **following FCM tiers - of the LMWF of the mixture/substance itself and of migrating LMWF not present in the substance itself (*for Case I.B. only the new LMWF peaks/substances)***

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 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 preferred.

   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 FCM when > 5ppm; S10 SMK). A draft way forward is proposed next slide.

c. Possible comparison with other (comparable, equivalent) 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) as WMA**

If no adverse effects observed at high doses (e.g. Limit Test in OECD TG 408) and/or (?) rationale (based on available additional information e.g. ADME, dissociation in natural constituents with no accumulation potential) -> no further assessment is needed

If indications of an accumulation, e.g., of pigments (due to the mixture itself or as derivatives)

CBA

Possible restrictions -> no further assessment

CBA

If adverse effects (not necessarily being an indication of accumulation)

In vitro and *in silico* tools to evaluate relevant intrinsic (log K_{OW}) and/or TK parameters (possible metabolism; more lipophilic metabolites; comparative *in vitro* metabolism (*pesticides, FEEDAP*) ;

Evaluation of the relevance (toxicological profile/amount) of compounds in the mixture ("possible" cut-off criteria/uncertainties?)

High priority compounds are main/major components of the mixture: TK data on main components (EFSA Panels, Mixtox EFSA GDs)

"Low priority" compounds based on exposure/migration (and low tox profile?): *cut-off level for undefined compounds* (EFSA Panels: NF; smoke flavourings; feed additives (*as low as possible*))

❑ **FCM tier 3: migration ≥ 5 mg/kg food: based on full data set** -> an ADME is required for the main/major components of the mixture (CBA)

Thank you for your attention

Questions?