EFSA FCM Network, November 2022

Discussion on the assessment of natural compounds and complex mixtures

Safety assessment of natural compounds/mixtures from renewable biological resources

Laurence Castle, EFSA FAF Panel, CEP FCM WG

Assessment of natural compounds & complex mixtures

Activity started in Spring 2022

Reporting is expected in Summer 2023

Aim for this meeting:-

- to describe the general direction of our considerations
- to allow for comments and input

Disclaimer: This is work in progress so nothing should be taken as 'fixed' at this time, nor taken to represent the views of the WG-FCM.

Background to the activity

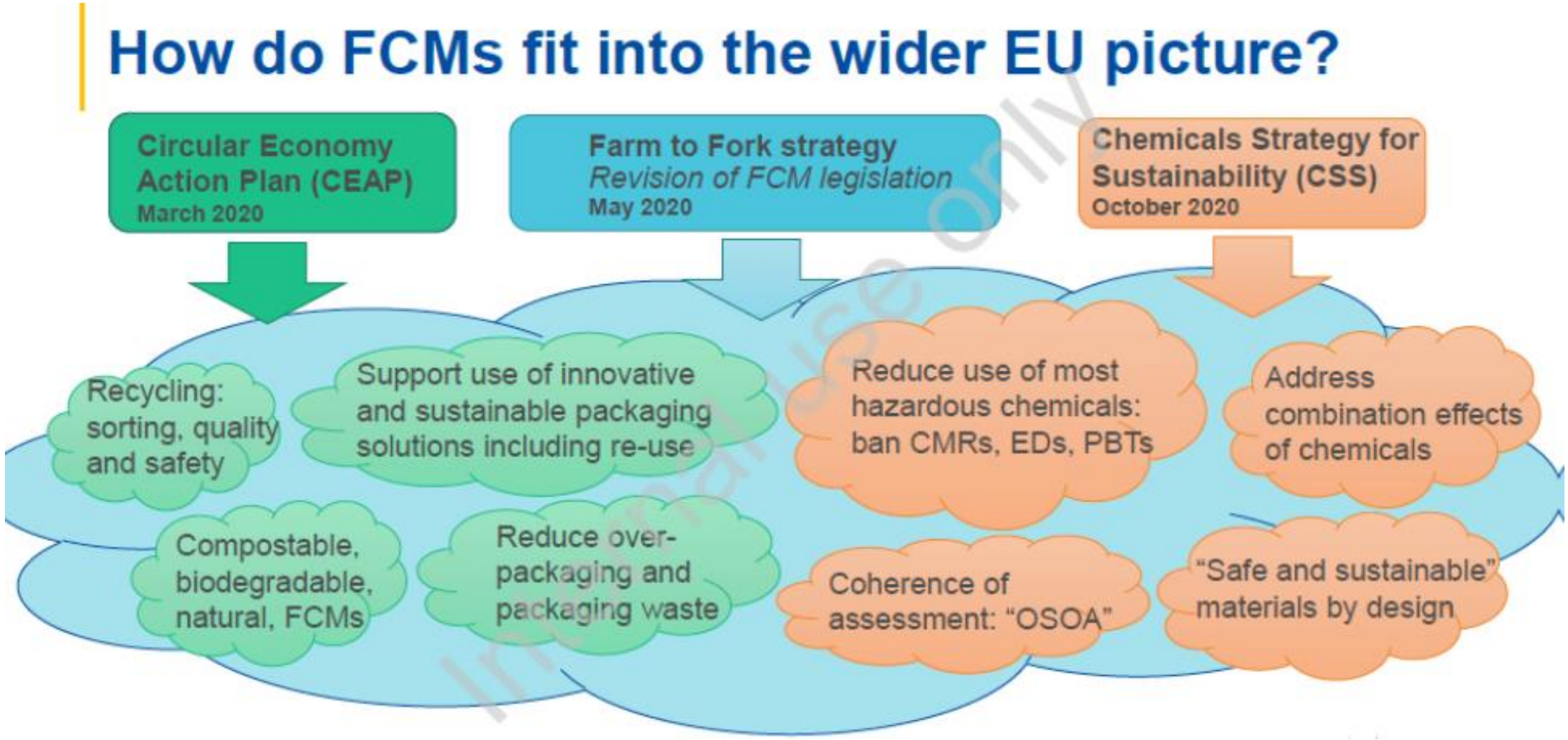
EC discussions on the revision of the FCM framework legislation*

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

*See presentation #26 “Discussion on the revision of the FCM framework legislation” by the EC on Day-3.

Wider background to the activity*



*See presentation #26 "Discussion on the revision of the FCM framework legislation" by the EC on Day-3.

FCM examples that have informed the discussions

1. Ground sunflower seed hulls
2. Bleached cellulose pulp from soft wood
3. Coffee husk cups
4. Citrus seeds/endocarp/skin cups
5. Waste coffee grain cups
6. Chitin and chitosan
7. Starches
8. Polyhydroxyalkanoates

Other EFSA areas that have informed the discussions

To learn and understand how other EFSA areas deal with the assessment of substances from natural sources:-

1. Novel foods
2. Botanicals
3. Enzymes
4. FEEDAP additives
5. Smoke Flavours

(Qualified Presumption of Safety QPS)

Observations made along the way

- (Mixtures from) natural compounds are not safe *per se*. For example, many foods are known to contain toxic components.
- Uses and assessment of natural compounds/complex mixtures triggers additional uncertainties especially regarding the safety of the uncharacterised fraction.
- Harmonisation (or, at least, coherence) with other EFSA approaches seems possible and is needed.

Observations made along the way

- All components <1,000 Da potentially must be assessed individually or as a mixture according to EFSA Guidance documents (EFSA CEF Panel, 2008;EFSA Scientific Committee, 2019a,b).
- Waiving part of the data requirements for substances derived from edible food sources (e.g. food, food ingredient, QPS botanical) seems acceptable.
- Data requirement should be the same for all food contact substances (FCS), including mixtures from natural compounds (i.e. waiver could apply to all FCS falling under the same criteria).

DRAFT assessment scheme to date

Citrus seeds/endocarp/skin cups
Waste coffee grain cups
Chitin and chitosan

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

No →

Yes ↓

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

No ↓

I.A. Tox testing waived = ENZ (edible parts of plants or animals) = SCF, 2001 + comparison of exposures (acceptable level, see doc) and 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 (migrating) LMWF peaks acc. to CAT IV

Ground sunflower seed hulls
Coffee husk cups

CAT II: Is the substance a **non-consumed part of a food plant or animal**?

No →

Yes ↓

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

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

If not equivalent -> **either** assessment of the new (migrating) LMWF substances ⇔ I.B. **or** QPS →

Bleached cellulose pulp from soft wood

CAT III: Is the substance a derived from a **not food plant or animal**?

No →

Yes ↓

Botanical approach = **QPS** assessment: tox testing waived if an **adequate body of knowledge exists** (presumption of safety)

a. taxonomy,
b. body of knowledge on the group of botanical to reach a decision on their safety
c. toxicity of naturally occurring substances of concern and if so knowledge on dose under which there is no concern,
d. end use, i.e. presence of a substance of concern in the given botanical does not mean it will be also present in the preparation and if present at a dose causing a health concern.

If no QPS -> CAT IV

Polyhydroxyalkanoates

CAT IV: Assessment **following FCM tiers of the LMWF of the mixture/substance itself and of migrating LMWF not present in the substance itself (*for CAT I.B. the new (migrating) 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) -> consideration to be provided
d. Possible comparison with other (comparable, equivalent) dietary source of exposure

Citrus seeds/endocarp/skin cups
Waste coffee grain cups
Chitin and chitosan

Ground sunflower seed hulls
Coffee husk cups

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

No

CAT II: Is the substance a **non-consumed part of a food plant or animal**?

No

Yes

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

Yes

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

If equivalent ⇨ I.A. (comparison of exposures (acceptable level, see doc) and reported safety/adverse effect/history of safe use)

No

I.A. Tox testing waived = ENZ (edible parts of plants or animals) = SCF, 2001 + comparison of exposures (acceptable level, see doc) and reported safety/adverse effect/history of safe use

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

If not equivalent -> **either** assessment of the new (migrating) LMWF substances ⇨ I.B. **or** QPS

Bleached cellulose pulp from soft wood

Polyhydroxyalkanoates

No

CAT III: Is the substance a derived from a **not food plant or animal**?

No

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

Yes

Botanical approach – **QPS** assessment: tox testing waived if an **adequate body of knowledge exists** (presumption of safety)

a. taxonomy,
b. body of knowledge on the group of botanical to reach a decision on their safety
c. toxicity of naturally occurring substances of concern and if so knowledge on dose under which there is no concern,
d. end use, i.e. presence of a substance of concern in the given botanical does not mean it will be also present in the preparation and if present at a dose causing a health concern.

If no QPS -> CAT IV

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) -> consideration to be provided
d. Possible comparison with other (comparable, equivalent) dietary source of exposure

DRAFT assessment scheme to date

Citrus seeds/endocarp/skin cups
Waste coffee grain cups
Chitin and chitosan

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

No →

Yes ↓

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

No ↓

I.A. Tox testing waived = ENZ (edible parts of plants or animals) = SCF, 2001 + comparison of exposures (acceptable level, see doc) and 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 (migrating) LMWF peaks acc. to CAT IV

Ground sunflower seed hulls
Coffee husk cups

CAT II: Is the substance a **non-consumed part of a food plant or animal**?

No →

Yes ↓

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

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

If not equivalent -> **either** assessment of the new (migrating) LMWF substances ⇔ I.B. **or** QPS →

Bleached cellulose pulp from soft wood

CAT III: Is the substance a derived from a **not food plant or animal**?

No →

Yes ↓

Botanical approach = **QPS** assessment: tox testing waived if an **adequate body of knowledge exists** (presumption of safety)

a. taxonomy,
b. body of knowledge on the group of botanical to reach a decision on their safety
c. toxicity of naturally occurring substances of concern and if so knowledge on dose under which there is no concern,
d. end use, i.e. presence of a substance of concern in the given botanical does not mean it will be also present in the preparation and if present at a dose causing a health concern.

If no QPS -> CAT IV

Polyhydroxyalkanoates

CAT IV: Assessment **following FCM tiers of the LMWF of the mixture/substance itself and of migrating LMWF not present in the substance itself (*for CAT I.B. the new (migrating) 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) -> consideration to be provided
d. Possible comparison with other (comparable, equivalent) dietary source of exposure

Discussion on the assessment of natural compounds and complex mixtures

Safety assessment of natural compounds/mixtures from renewable biological resources

- Questions ?
- Comments ?
- Inputs / suggestions ?