Draft Guidance Novel Foods

Absorption, Distribution, Metabolism, Excretion and Toxicology

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Section 7

Absorption, Distribution, Metabolism, and Excretion (ADME)

7. ADME (1)

- Critical for the development of appropriate toxicity testing strategy including the selection of appropriate animal models.
- Important information for the interpretation of study results.
- Differences between experimental animals and humans.

Consider **tiered approach** to toxicokinetic testing which are described in section 4.1 on « Toxicokinetics (ADME) » of the EFSA Guidance for food additive evaluations (EFSA ANS Panel, 2012).

Negligible absorption may provide a scientific justification for not undertaking higher tiered toxicological studies.

Single substances and simple mixtures should normally be tested according to the same principles as those applied to food additives. As a default, absorption of the Novel Food or its breakdown products should be assessed.

7. ADME (2)

- For food additives in the form of **complex mixtures**, the ANS Guidance states that *«conventional metabolism and toxicokinetic studies may not be feasible for all components in the mixture, but should be provided for **toxicologically relevant constituents**. Toxicologically relevant constituents are 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 and the rationale for their selection provided »*.
- **Whole foods** should be tested like complex mixtures as stated in the ANS Guidance.

7. ADME (3)

- For Novel Foods, ADME assessment should also address **nutritionally significant constituents** where toxicokinetic data on these constituents are important considerations for the evaluation of the nutritional impact of the Novel Food.
- With respect to Novel Foods consisting of "**engineered nanomaterials**", applicants should consider the specific requirements and follow the approach as set out in the EFSA Scientific Committee Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (in particular, sections on in vitro digestion studies and ADME studies) (EFSA, 2011).

Section 9

Toxicological Information

9.1 GENERAL CONSIDERATIONS (1)

Toxicological studies should be carried out with test material:

- **representative** of the Novel Food as intended to be marketed, i.e. the test material should be manufactured according to the production process described in section 2,
- meet the **compositional characteristics** provided in section 3 and meet the **specifications** proposed in section 4.
- If this is not the case, a rationale should be provided to substantiate why the material used for the toxicological studies is representative of the novel food and **appropriate** for safety assessment.
- Tests should be conducted in accordance with international guidelines (e.g. **OECD**) and according to the principles of Good Laboratory Practices (**GLP**).

9.1 GENERAL CONSIDERATIONS (2)

All relevant knowledge on the Novel Food should be considered for the toxicological testing including:

- the identity, chemical structure, composition, and physico-chemical properties of the Novel Food;
- previous human consumption of the Novel Food and its source;
- anticipated uses, maximum use levels and the resulting intakes;
- available toxicokinetic data;
- available toxicological data on the Novel Food or its constituents;
- available human studies.

In case of insufficient data also (quantitative) structure activity relationship **((Q)SAR)** data, toxicological data on structurally related substances **('read-across')** or the Threshold of Toxicological Concern **(TTC) approach** should be considered.

9.1 GENERAL CONSIDERATIONS (3)

Consider **tiered toxicity testing approach** proposed for food additives as the default approach:

- It integrates the core areas of **toxicokinetics, genotoxicity, repeated dose toxicity testing and reproductive and developmental toxicity** (EFSA ANS PANEL, 2012).
- **Additional studies** may be needed to examine specific biological processes. Other studies that may be relevant include immunotoxicity, hypersensitivity and food intolerance, studies on neurotoxicity, endocrine activity and mechanisms and modes of action.
- Deviations from this approach and/or its non-applicability should be reasoned with sound scientific arguments based on the elements listed in the bullet points above.

9.2 GENOTOXICITY

Basic component of chemical risk assessment to

- identify substances which could cause **heritable damage** in humans;
- predict potential **genotoxic carcinogens** in cases where carcinogenicity data are not available.

The Scientific Committee recommended a step-wise approach for the generation and evaluation of data on genotoxic potential (EFSA 2011):

- Basic battery of *in vitro* tests as a first step and follow-up approaches in the event of positive results.
- Recommendations on test types, interpretation of results and other issues in testing the genotoxicity of substances present in food are described in detail in the Scientific Committee Opinion.

For some **complex mixtures** and whole foods it may be necessary to focus on specific constituents of the Novel Food. Deviations should be argued on a case-by-case basis.

9.3 SUBCHRONIC TOXICITY (1)

In line with the Guidance for food additives, a **subchronic toxicity study** should normally be submitted.

- To identify adverse effects following repeated exposure via an appropriate oral route.
- Should allow to identify a BMDL or a NOAEL.
- May provide indications for the need for additional studies.

The study should normally be conducted for at least **90 days** (OECD TG 408), modified to include some **additional parameters** (as described in OECD TG 407 - 28-day oral toxicity studies in rodents) to allow for identifying substances with a potential to cause neurotoxic, immunological, reproductive organ effects or endocrine-mediated effects.

9.3 SUBCHRONIC TOXICITY (2)

- When toxicokinetic data indicate a **lack of systemic availability**, studies should at least investigate both pathological and physiological effects in the gastrointestinal tract.
- The effects of unabsorbed materials on gastrointestinal function and tolerance should be investigated.
- Additional markers of potentially **adverse nutritional and/or metabolic effects** should be considered on a case-by-case basis.

For '**whole foods**', the testing requirements should be determined using **a case-by-case approach.** Special considerations are required with regard to dose selection and the **avoidance of possible nutritional imbalances** (Guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed; EFSA SC, 2011).

9.4 CHRONIC TOXICITY AND CARCINOGENICITY

Potential trigger for chronic toxicity or carcinogenicity studies include, among others, critical findings in the subchronic study as well as results of *in vitro* or *in vivo* toxicity tests, including genotoxicity tests.

Further guidance on the triggers for these studies and their implementation are outlined in the Guidance on food additives (EFSA ANS Panel, 2012) and respective OECD Guidelines (OECD TG 451, 452 or 453).

9.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

To be considered in the light of toxicokinetics and toxicity data, including read-across data.

Any indications of **effects on reproductive organs** or parameters, for example in the modified 90-day oral toxicity, will trigger testing for reproductive and developmental toxicity. Reproductive and developmental toxicity testing may not be required, if argued on a case-by-case basis.

9.6 SPECIFIC CASES (1)

9.6.1 Insects

- Present draft guidance applicable also for insects (if NF)
- Consider Opinion of the EFSA Scientific Committee on potential hazards related to the use of farmed insects as food (EFSA SC, 2015).

Important factors to consider are, among others:

- Methods for **farming** and processing or **collecting from the wild**,
- **Species and substrate** (“feed”) to be used,
- Additional biological and chemical hazards when collecting from the wild.

9.6 SPECIFIC CASES (2)

9.6.3 Engenieered Nanomaterials

Where the Novel Food containing or consisting of “engineered nanomaterials”, the applicant should consider the **Guidance on the risk assessment of the application of nanoscience and nanotechnologie**s in the food and feed chain from EFSA’s Scientific Committee (EFSA SC, 2011).

9.6 SPECIFIC CASES (3)

9.6.2 Microorganisms (1)

A wide variety of microorganisms (MO) are used in food production, often present in high concentrations as viable bacteria in the final product.

Qualified presumption of safety (QPS)

Some of these MO have a history of safe use and have been assigned the QPS status by EFSA which constitutes a preliminary safety assessment (EFSA BIOHAZ Panel, 2015).

This QPS list includes **taxonomic groups** that have not raised safety concerns so far, and others for which some safety concerns exist but could be defined and addressed with "qualification" as expressed in the QPS list. Therefore, any strain of MO, the identity of which could be unambiguously established and assigned to a QPS group, would be exempted from the need for an exhaustive safety assessment other than satisfying the **criteria specified** previously (EFSA SC, 2008) and assessing the risk of **antimicrobial resistance** (EFSA FEEDAP Panel 2012).

9.6 SPECIFIC CASES (4)

For those microorganisms for which safety properties are less well understood, a safety assessment should be provided.

- **Complete strain characterisation** by fully assembled and validated whole-genome sequence analysis to enable the detection of virulence-related genes, antibiotic resistances and their potential horizontal transfer, and other potentially adverse metabolic features (e.g. toxins, D-lactate, etc.).
- **Phenotypic characterisation of potential antimicrobial resistances** following EFSA recommendations (EFSA FEEDAP Panel, 2012)
- **Characterisation of other potentially adverse phenotypic features** e.g. potential toxin production, haemolytic activity, infectivity, adverse immune effects, etc..
- Numbers of **viable microorganisms in the final product** and stability.

Thank you for your attention !