



Guidance on Novel Foods

Key issues regarding kinetic data

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OUTLINE

- **The EFSA Guidance document**
- **Aspects raised in the public consultation**
- **Requests for additional information**

Examples from the past and considerations of the NDA Panel.

THE GUIDANCE 2.8. – GENERAL CONSIDERATIONS

- Critical for the development of appropriate toxicity testing strategy.
- Important information for the interpretation of study results.
- Without information on absorption in the animal model, no conclusions can be drawn on the (toxicity) study.
- Relevant for the toxicological and nutritional aspects.
- Similarities and differences between experimental animals and humans should be considered.
- Evidence of differences in kinetics due to age, physiological state, disease state, etc. may require additional specific kinetic studies.

2.8. ADME - APPROACH

Approach depends on the type of test material:

- Single substance, simple (well defined) mixture.
- Complex mixture (e.g. ethanolic extracts).
- Whole foods.



2.8. ADME - SINGLE SUBSTANCE/SIMPLE MIXTURE

NF Guidance aligns with the tiered approach suggested in the ANS Guidance for additives.

- Tier 1: Intestinal absorption yes/no.
- Tier 2: Studies to define distribution, metabolism and excretion and other basic toxicokinetic parameters following a single dose.
- Tier 3: to investigate possible bio-accumulation.



2.8. ADME - TIER 1

Whether the compound or breakdown products are absorbed from the gastrointestinal tract

- **in vitro, in vivo and/or ex vivo tests**
- **No or negligible absorption based on theoretical considerations or experimental studies** may provide a scientific justification for not undertaking higher tiered toxicological studies.
 - sufficient sensitivity needed.
 - to show that neither its breakdown or metabolites are absorbed.
 - adequate considerations of physico-chemical parameters
 - further details → ANS Guidance.

2.8. ADME - TIER 2

Studies to define distribution, metabolism and excretion and other basic toxicokinetic parameters following a single dose

- In vivo data on absorption, distribution, metabolism and excretion needed.
- OECD 417 protocol to provide information on systemic exposure after a single dose (C_{max} , T_{max} , AUC, $T_{1/2}$, bioavailability).

2.8. ADME - TIER 3

Triggered by limited or slow excretion or any other mechanism leading to possible bio-accumulation

- Repeated dose toxicokinetic studies involving steady-state.
- Additional data to predict ADME in humans.
- On a case-by-case basis: human studies.

2.8. ADME - COMPLEX MIXTURES, WHOLE FOOD

- ANS Guidance: «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.



2.8. ADME

- For Novel Foods, ADME assessment should also address **nutritionally significant constituents** where kinetic data on these constituents are important considerations for the evaluation of the nutritional impact of the NF.
- With respect to NF 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 Scientific Committee, 2011a).

PUBLIC CONSULTATION - ADME

❖ For novel foods from microorganisms, fungi, algae, plants, animals, cell and tissue cultures, clarification was sought on whether one marker would be sufficient to evaluate ADME or whether several markers are required. Challenges related to the assessment of ADME for plants and other complex organisms were highlighted.

The Panel considers that the type (single substance or complex mixture) rather than source of the NF is relevant for the approach to investigate ADME. For complex mixtures, the guidance refers to the EFSA guidance for food additive evaluations (EFSA ANS Panel, 2012) which recommends focusing on toxicologically relevant constituents. (Novel Foods: also nutritionally relevant constituents).

REQUESTS FOR ADDITIONAL INFORMATION (1)

- Absence of ADME data.
- Information on absorption, but not on metabolism, distribution or excretion.
- Impact of the production process that may affect the bioavailability of the NF (or its components) not considered.
- Contradictory considerations and information regarding absorption („not absorbed” to avoid further studies; „absorbed” to keep the door open for health claim application).
- Poorly designed studies or studies provided from the literature not pertinent to the NF.



REQUESTS FOR ADDITIONAL INFORMATION (2)

- Bio-accumulation not investigated despite aspects which may suggest accumulation.
- No information on ADME provided on critical components of an extract (complex mixture).



EXAMPLE FROM THE PAST – SYNTHETIC HYDROXYTYROSOL

- ADME data for rats and humans were provided (from literature and the NF) and shown to be similar in both species.
- No indication for bio-accumulation (neither from literature nor from toxicokinetic and toxicological studies, including a 90 d rat study).

The Panel accepted a MoE of 100 (90 d study NOAEL – anticipated intake for children).

“Taking into account that the anticipated daily intake of the NF would be in the range of or even less than the exposure to hydroxytyrosol from the consumption of olive oils and olives, which has not been associated with adverse effects, and considering the **similar kinetics of hydroxytyrosol in rats and humans**, the Panel considers that the MoE for the NF at the intended uses and use levels is sufficient for the target population.”



Thank you
for your
attention !