Toxicological studies
PART IV

CORE AREAS FOR EVALUATION

- **Toxicokinetics** (ADME)
- **Genotoxicity**
- **Toxicity** (subchronic, chronic, carcinogenicity)
- **Reproductive** & **Developmental toxicity**
- **Additional studies** (immunotoxicity, neurotoxicity, human, etc)

OBJECTIVES

- **Implementation of characterisation of hazard**
- **Dose response data for risk characterisation**

Design Considerations – Toxicity studies

Rationale

- Tiered approach (balancing data requirements against other considerations)
- Experimental studies and human data

❖ Design of toxicological studies – Issues to consider

- compliance with EU standards & regulations (i.e. welfare standards)
- principle of the 3 Rs and animal welfare
- toxicity studies should comply to international agreed test guidelines (e.g. OECD) and performance standards (e.g. GLP)
- Administration route: oral

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to ensuring that Europe's food is safe

European Food Safety Authority

Toxicokinetics (ADME)

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Stakeholders workshop
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Toxicokinetics

OBJECTIVE

Describe the systemic exposure of the food additive and its relationship to dose levels.

RATIONALE

Selection for appropriate species & doses for toxicity testing

General Considerations

European Food Safety Authority

❖ Aims of toxicokinetics testing:

- determine systemic absorption to the chemical and its metabolites
- understanding of processes involved in ADME
- define possible species differences

❖ End-points of interest:

- systemic exposure/systemic availability
- absorption, distribution, metabolism
- mechanisms of toxicity

Other considerations:

- toxicologically relevant constituents
- matrix effect
- **negligible absorption**

Negligible absorption

Demonstration of negligible absorption either through experimental studies or from theoretical considerations

CONSIDERATIONS

- **Physicochemical parameters:**

  chemical structure, molecular weight, octanol water partition coefficient, aqueous solubility, molecular shape, charge & dissociation constants

- **Study design parameters:**

  % of absorption, robustness of study design and performance, sensitivity & specificity of methods of detection, detection limits, amount in faeces, dose accountancy

- **Other parameters:**

  likelihood of persistence in tissues, predicted metabolic stability, results of tier 1 testing

Toxicokinetics - Tiered approach

TIER 1 (applicable to all additives)

Absorption studies & *in vitro* gastrointestinal metabolism

❖ **End-points of interest:**

- Absorption from GI tract
- Stability in GI tract

❖ **Testing requirements:**

- absorption (*in vitro, in vivo* & *ex vivo* models)
- stability of the compound (*in vitro* GI metabolism & other models)

Toxicokinetics - Tiered approach

TIER 2 (applicable to additives with systemic availability)

Define distribution, metabolism & excretion, and other toxicokinetic parameters (single dose)

- **End-points of interest:**
  - 'where it goes'
  - 'what happens to it'
  - 'how quickly it is removed'

- **Testing requirements:**
  - *in vivo* assessment of ADME
  - Toxicokinetics (OECD TG 417)

Toxicokinetics - Tiered approach

TIER 3 (triggered by limited excretion or bioaccumulation)

Define toxicokinetic parameters (repeated dose)

- **End-points of interest:**
  - ADME (repeated dose-animals)
  - Other studies (predict ADME in humans)
  - Volunteer studies (humans)

- **Testing requirements:**
  - repeated dose studies in animals
  - human kinetic studies (volunteer studies)