European Food Safety Authority

Toxicity testing
(subchronic, chronic, carcinogenicity)

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OBJECTIVE

Identify the potential hazardous properties of a food additive from repeated exposure over a prolonged period of time.

Rationale

Provide information for treatment-related changes and the potential of the FA to cause neurotoxic, immunological, reproductive or endocrine-mediated effects.
General Considerations

• Objectives of subchronic, chronic toxicity & carcinogenicity testing:
  - characterisation of the dose-response relationship
  - identify/establish the NOAEL or the BMDL
  - identify carcinogenic properties of the FA

• End-points of interest:
  - gross observations
  - clinical pathology
  - histopathology
  - reproductive, neurological and immunological endpoints
  - endocrine disruption

• Tiered approach
**Tier 1** (applicable to all additives)

**Subchronic toxicity testing** (Extended)

- **End-points of interest:**
  - General toxicity
  - GI function & tolerance
  - Neurological, immunological, endocrine mediated effects
  - Reproductive effects

- **Testing requirements:**
  - Repeated dose oral toxicity study (90-day) in rats
    (OECD TG 408 with extended parameters to identify neurotoxic, immunotoxic, reprotoxic or endocrine-mediated effects - OECD TG 407)
Toxicity testing - Tiered approach

**Tier 2** (conditional of systemic availability)

Chronic toxicity & Carcinogenicity testing

- **End-points of interest:**
  - Chronic toxicity
  - Carcinogenicity *(in one species)*

- **Testing requirements:**
  - Repeated dose (12-month) oral toxicity study in rats *(OECD TG 452)*
  - Carcinogenicity (24-month) study in rats *(OECD TG 451)*
  - Combined toxicity/carcinogenicity study in rats *(OECD TG 453 and GD 116)*
**Tier 3** (Case-by-case approach)

**Specialised testing** (triggered by the results of Tier 2)

- **End-points of interest:**
  - Specific endpoints (i.e. neurotoxicity, immunotoxicity, etc)
  - Mode of action

- **Testing requirements:**
  - Carcinogenicity bioassay (Transgenic mouse models or 2nd species)
  - Mode of action studies (specialised testing)
Toxicity & Carcinogenicity - Tiered approach

Overview

**Tier 1** *(mandatory)*
- Subchronic extended toxicity testing *(rodent)*
- GI function and tolerance

**Tier 2** *(conditional on triggered)*
- Chronic toxicity testing *(rodent, preferably the rat)*
- Carcinogenicity testing *(rodent, preferably the rat)*
  - (Combined or stand-alone study)

**Tier 3** *(case-by-case approach)*
- Examine further specific endpoints
- Mode of action studies

**Key changes**
- Single species *(rodent)*
- Carcinogenicity *(triggered)*
- Carcinogenicity *(2nd species)*