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European Food Safety Authority

Toxicity testing

(subchronic, chronic, carcinogenicity)

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Stakeholders workshop
21 September 2012, Brussels

Toxicity
(subchronic, chronic, carcinogenicity)

efsa
European Food Safety Authority

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**

Toxicity testing - 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)

or

  - Combined toxicity/carcinogenicity study in rats (OECD TG 453 and GD 116)

Toxicity testing - Tiered approach

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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)