Reproductive & Developmental Toxicity Guidance on Food Additive

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**Objective**

Identify the potential of a food additive, which is systemically absorbed (or crosses the placenta), to impair reproduction and prenatal and postnatal development and function.

**Rationale**

- Systemic availability of FAs
- Substance crossing the placenta
General Considerations

- **Objectives of reproductive & developmental toxicity testing:**
  - Identify substances which cause reproductive effects
  - Identify substances which cause lethal, teratogenic or other toxic effects on the embryo and foetus
    - prenatal (via the mother) and to FAs
    - postnatal (via maternal milk) exposure to FAs

- **End-points of interest:**
  - fertility and reproductive function
  - developmental (pre- and postnatal)
  - specific (immunotoxicity, neurotoxicity, endocrine disruption)

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

Identify reproductive and endocrine effects

- End-points of interest:
  - Reproductive effects
  - Endocrine effects

- Testing requirements:
  - Extended repeated dose oral toxicity study (90-day) in rats (OECD TG 408)
Reproduction - Tiered approach

There is no Tier 2 if absorption is negligible

**Tier 2** (triggered)

**Reproductive (functional) and developmental effects**

- **End-points of interest:**
  - Fertility and Reproductive function
  - Developmental toxicity (pre- and postnatal)
  - Developmental neurotoxicity and immunotoxicity, endocrine effects

- **Testing requirements:**
  - Prenatal developmental toxicity in *rabbit* (*OECD TG 414*)
  - Extended One Generation Reproductive Toxicity Study in *rats* (*OECD TG 443*)
Reproduction - Tiered approach

**TIER 3** (triggered by results in Tier 2)

**Case-by-case approach (additional studies)**

- **End-points of interest:**
  - Endocrine effects
  - Developmental neurotoxicity
  - Developmental immunotoxicity
  - Mode of action

- **Testing requirements:**
  - Developmental neurotoxicity (*OECD TG 426*)
  - Mode of action studies
  - *Multi-generation study (conditional) for existing FAs* (*OECD TG 416*)
Reproduction - Tiered approach

Overview

**Tier 1** (mandatory)
- 90-Day Extended Toxicity Testing (reproductive, endocrine effects)

**Tier 2** (triggered)
- Prenatal Developmental Toxicity Study (rabbit)
- Extended One-Generation Reproductive Toxicity Study (rodent, rat)
  - reproductive, developmental and specific endpoints

**Tier 3** (triggered)
- Examine further specific endpoints (case-by-case approach)

**Key changes**
- single species (rodent)
- EOGRTS replacing multi-generation study
- ‘triggers’ (F2 generation)
- endocrine activity