Additional Information

Guidance on Food Additive

Anastasia Kesisoglou

Scientific Officer, FIP unit, EFSA

Stakeholders workshop
21 September 2012, Brussels
**OBJECTIVE**

To examine specific biological processes, not fully considered under the core areas, to allow for an adequate risk assessment.

**RATIONALE**

Allow an adequate risk assessment when additional information is necessary.
End-points of interest:

- **ADME** (Human studies - volunteers)
- **Immunotoxicity**
- **Hypersensitivity/ Allergy & Food intolerance**
- **Neurotoxicity**
- **Endocrine activity**
- **Mechanisms and mode of action**

*Consider all available data from core studies*
**Human studies**

**General considerations**

**Rationale:** Extremely valuable for risk assessment for human beings and diminishing the uncertainty in extrapolating from animal studies.

**General considerations**

- We encourage such studies, but **not** mandatory.
- Not possible to rely on animal data for some endpoints (i.e. gastrointestinal discomfort).

**Pre-requisites**

- Adequate animal and other data.
- Consider experience from human therapeutic agents.
- Compliance with ethical & legal standards (i.e. ethical body, consent by volunteers, etc.)
Human studies
Types

- **Human Volunteer studies:**
  - **ADME**
    - enhance the predictive value of testing in animals
    - validate the experimental database acquired
    - aid interpretation of adverse findings
    - diminish uncertainties when extrapolating from animals
  
  - **Tolerance**
    - investigations of symptoms not studied in animals
      (e.g. headaches, etc)
  
  - **Other special studies**
    - allergy, behaviour or cognitive function
Immunotoxicity
General considerations

➢ **Immunotoxicity**
  - induction of changes in immune response
    (i.e. immunosuppression or immunostimulation)
  - preliminary indications of potential immunotoxicity

❖ **Tier 1** (Applicable to all additives)

**Indications of immunotoxic or immunomodulatory effects**
  - Repeated dose oral toxicity study (90-day) in rats (OECD TG 408)
**Tier 2**

**Indications (or confirmation) of immunotoxic or immunomodulatory effects**

- EOGRTS: cohort on developmental immunotoxicity in rats (OECD TG 443)
- chronic toxicity/carcinogenicity (OECD TGs 452, 451 or 453)

**Tier 3** (case-by-case approach)

**Specialised functional, mechanistic & disease model studies**

- Further studies

(Guidance for Immunotoxicity risk assessment for chemicals – WHO/IPCS, 2012)
Allergy/ Hypersensitivity, Food Intolerance Considerations

**Allergy** *(immunological origin)*
- No validated studies
- Dermal or inhalation sensitisation studies to be considered (if relevant)
- Human data (from existing studies) available on oral food challenges & prick testing to be used
- Evaluation of allergenic components *(Guidance on Allergenicity of GMOs – EFSA, 2010)*
- **Weight of evidence approach**

**Intolerance reactions** *(no immunological origin)*
- Difficult to predict
- No validated experimental methods
- No clinical studies allowed prior to marketing
- Data from post-marketing surveillance
- Reporting of adverse effects *(human studies)*
Neurotoxicity testing - Tiered approach

**TIER 1** (applicable to all additives)

**Indication of neurotoxic effects**

- **End-points of interest:**
  - Changes in clinical signs
  - Functional observatory battery
  - Motor activity
  - Brain weight; histopathological changes

- **Testing requirements:**
  - Repeated dose oral toxicity study (90-day) in **rats**
    *(OECD TG 408)*
Neurotoxicity testing - Tiered approach

Tier 2 (triggered by results at Tier 1)

Confirm or further characterise the neurotoxic response

- **End-points of interest:**
  - Clinical observations
  - Auditory startle; motor activity
  - Neuropathology of F1 pups and adult animals

- **Testing requirements:**
  - EOGRTS: cohort on developmental neurotoxicity in rats
    (OECD TG 443)

Consider information from other studies
**Neurotoxicity testing - Tiered approach**

**Tier 3** (case-by-case approach)

**Extensive behavioural and morphological tests**

- **End-points of interest:**
  - Clinical observations
  - Auditory startle; motor activity
  - Neuropathology of F1 pups and adult animals

- **Testing requirements:**
  - Developmental neurotoxicity in rats *(OECD TG 426)*
Other information

Information on existing authorisations and evaluations:
(PART II)

- date of and body which carried out the evaluation
- details of evaluation including critical studies and NOAELs/LOAELs and BMDL values
- any uncertainties, uncertainty factors used & safety values derived (e.g. ADIs)

COMPREHENSIVE LITERATURE REVIEW