Committed *since 2002*
to ensuring that Europe's food is safe

European Food Safety Authority

Additional Information
Guidance on Food Additive

Anastasia Kesisoglou

Scientific Officer, FIP unit, EFSA

Stakeholders workshop
21 September 2012, Brussels

Additional toxicological studies
PART IV

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

Additional toxicological studies
General considerations

efsa
European Food Safety Authority

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

efsa
European Food Safety Authority

❖ 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)

Immunotoxicity – Tiered approach

European Food Safety Authority

❖ 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