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

Risk assessment paradigm

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Stakeholders workshop

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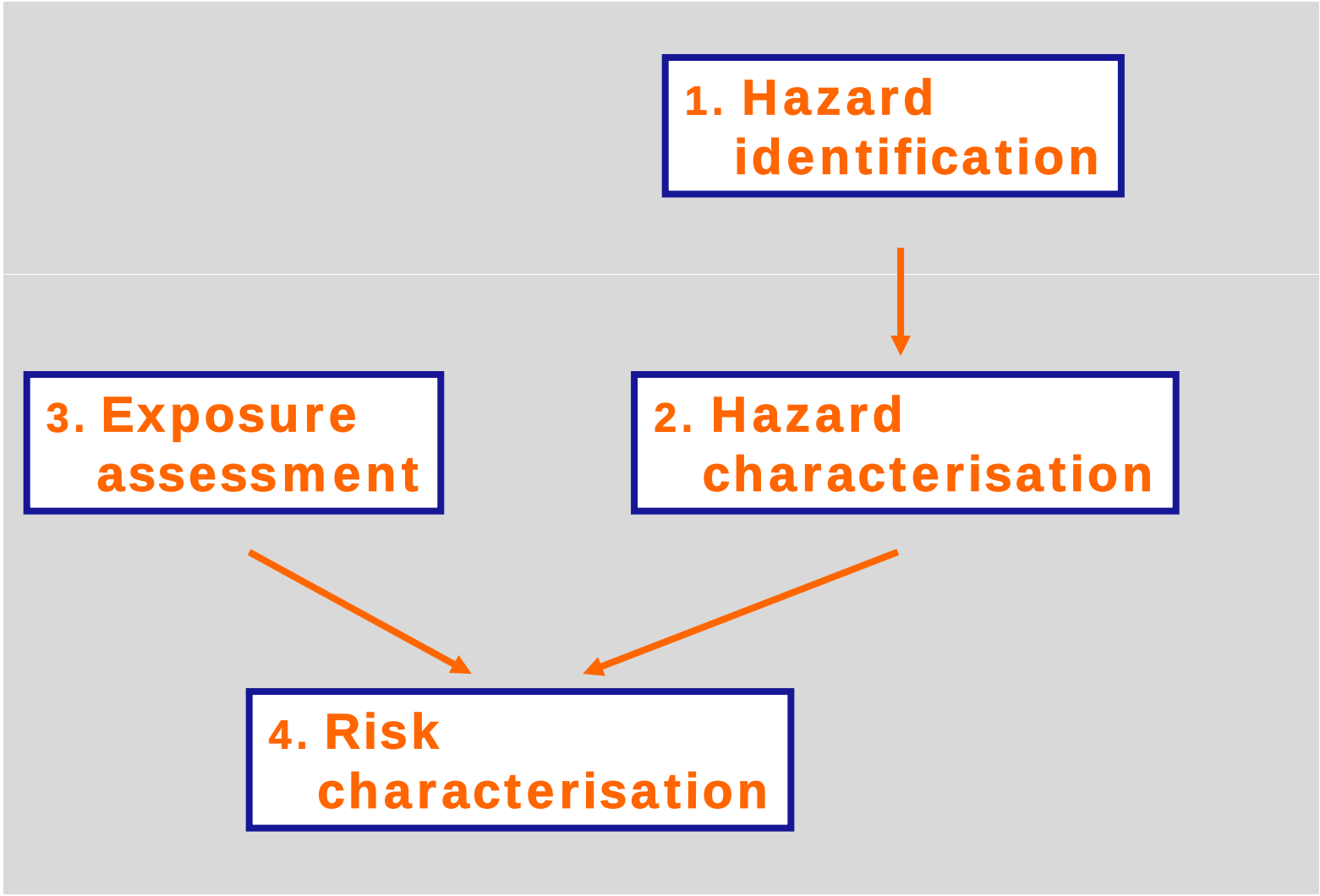
Risk Assessment



Emphasis of guidance is on proportionally generating results driven by science rather than just doing the tests

Risk assessment Paradigm

- **Hazard identification & characterisation**
  - minimal dataset applicable to all compounds
  - principle of the 3 Rs and animal welfare
- **Exposure assessment**

EFSA Guidance

- **Risk characterisation and outcome of the risk assessment**

ANS Panel

- **Unavoidable genotoxic and carcinogenic impurities**
  - **MOE** approach (genotoxic and carcinogenic impurities)
  - **TTC** approach (genotoxic residuals, no carcinogenicity data)

General considerations – Introduction

Rationale

- Regulation 234/2011 requires submission of toxicological data
- provide guidance on data requirements for applicants

- **Design of toxicological studies**
  - minimal dataset applicable to all compounds
  - principle of the 3 Rs and animal welfare
  - detailed testing for specific endpoints
  - case-by-case approach
  - physicochemical & toxicity data of structurally-related compounds
  - structurally active relationships (SARs)

Main sections

Introduction & Risk Assessment paradigm

PART I: **Chemistry and Specifications**

PART II: **Authorisations & evaluations**

PART III: **Proposed uses & Exposure assessment**

PART IV: **Toxicological studies**

Supplementary information

ANNEXES

PART I: Chemistry & Specifications

Objective: *Identify the food additive, potential hazards, and define the material tested*

- **Identity of the substance**
  - single substances
  - simple mixtures
  - complex mixtures
  - polymers
  - **botanicals**
  - **nanomaterials**
  - containing/from microorganisms & **GMOs**
- **Specifications**
- **Manufacturing process**
- **Methods of analysis in food**
- **Stability of the substance, and reaction and fate in food**

Proposed uses & Exposure assessment
PART III:

Objective: *Estimate dietary exposure based on the proposed uses and use levels & the consumption of the proposed foods for various age groups in the EU population*

Two-scenario approach

- **Authorisation** of a new food additive **(Scenario 1)**
- **Modification** of proposed uses or use levels of an authorised food additive **(Scenario 2)**

Assessment using a template

- **Food Additives Intake Model** (FAIM)

PART IV: Toxicological studies
Core areas

Objective: *describe the methods which can be used to identify and characterize hazards*

Core Areas for Evaluation

- **Toxicokinetics**
- **Genotoxicity**
- **Toxicity**
  - subchronic
  - chronic
  - carcinogenicity
- **Reproductive and Developmental toxicity**

PART IV: Toxicological studies
Additional studies

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

Toxicological studies
Tiered approach

European Food Safety Authority

Overview

Tier 1

- **Toxicokinetics** (absorption)
- **Genotoxicity** (in vitro)
- **Subchronic toxicity** (extended 90 day for repro, endocrine, neurotox, etc)

Tier 2

- **ADME** (single dose)
- **Genotoxicity** (in vivo)
- **Chronic toxicity / carcinogenicity**
- **Reproductive** (EOGRTS, developmental-rabbit)

Tier 3

- **ADME** (repeated dose, volunteer studies)
- **Carcinogenicity** (1st and 2nd species)
- **Specialised studies**
- **Reproductive** (F2 generation)

TIER 1 - Applicable to all additives

Requirements

- **Absorption**
- **Genotoxicity**
  - *in vitro* testing
  - genotoxic impurities
- **Extended 90-day toxicity study**
  - repro endpoints
  - endocrine activity
  - other (immune, neuro)

Key issues

- **negligible absorption /Systemic availability**
- **GI toxicity**
- **endocrine activity**

Triggers for Tier 2

- ***Systemic availability***
- ***GI toxicity***
- ***Toxicity in the 90-day study***
- ***Genotoxicity in vitro***

TIER 2 - Triggered testing

Requirements

- **ADME**
  - Single dose
- **Genotoxicity**
  - in vivo testing
- **Chronic / Carcinogenicity**
  - stand-alone or combined
- **Reproductive**
  1. EOGRT study (**rat** - various endpoints)
     - repro & developmental
     - immunotoxicity
     - neurotoxicity
  2. Pre-natal developmental tox (rabbit)

Key issues

- **Chronic / Carcinogenicity** (separate or combined?)
- **Equivocal results**
- **F2 generation** (if triggered)

Triggers for Tier 3

- ***Bioaccumulation***
- ***Positive in vivo genetoxicity***
- ***Chronic toxicity/Carcinogenicity***
- ***Reproductive & Developmental toxicity***

TIER 3 – Specialised studies

Approach to Tier 3 studies

- ***Consideration of all available data***
- ***Case-by-case approach***
- ***Equivocal findings & animal welfare issues***

Indicative testing (if triggered)

- **Toxicokinetics**
  - Repeated dose, volunteer studies
- **Carcinogenicity**
  - Mode of action
- **Repro**
  - F2 generation
- **Specialised studies**
  - immunotoxicity, neurotoxicity, endocrine activity, mode of action

SUPPLEMENTARY INFO & ANNEXES

- **Integrated testing strategies**
- **Reporting & referencing of studies**

Annexes

- Diagram on tiered toxicity testing for food additives
- General data requirements **(Regulation EU 234/2011)**
- Specifications as required by the Commission

Tiered Toxicity Testing Diagram

European Food Safety Authority

TIER 1

- **Absorption**
- **Genotoxicity**
  - In vitro testing
- **Toxicity**
  - Extended 90-day toxicity study

Triggers for considering Tier 2

- ***Systemic availability***
- ***Toxicity in the 90-day study***
- ***Genotoxicity in vitro***

TIER 2

- **ADME**
  - Single dose
- **Genotoxicity**
  - In vivo testing
- **Toxicity**
  (stand-alone or combined)
  - Chronic toxicity
  - Carcinogenicity
- **Reproductive & Developmental toxicity**
  - EOGRTS
  - Prenatal developmental toxicity

Triggers for considering Tier 3

- ***Bioaccumulation***
- ***Positive in vivo genotoxicity***
- ***Chronic toxicity/carcinogenicity***
- ***Reproductive & Developmental toxicity***

TIER 3

- **ADME**
  - Repeated dose, volunteer studies
- **Carcinogenicity**
  - Mode of action
- **Reproductive & Developmental toxicity**
- **Specialised studies**
  e.g. immunotoxicity, neurotoxicity, endocrine activity, mode of action

Although higher tier testing may be required based on results in one of the core areas, such testing would only be required in relevant core areas e.g. where results from absorption or the 90-day study require further tier 2 studies but tier 1 in vitro genotoxicity is negative, there would be no need for tier 2 genotoxicity.