New Approaches to Chemical Risk Assessment

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IAFP's European Symposium
on Food Safety 2016, Athens, Greece

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International Life Sciences Institute

Current Tools and Approaches in Chemical Risk Assessment

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Risk assessment

the basis

All substances are poisons.
The dose makes the poison.
Paracelsus, 1493-1541

- **Hazard:** A chemical agent in food with the potential to cause harm (relates to the inherent properties of the substance that make it capable of causing adverse effects).

- **Risk:** Probability of occurrence of an adverse health effect, weighted for its severity, that may result from the exposure under defined conditions to a chemical hazard in food.

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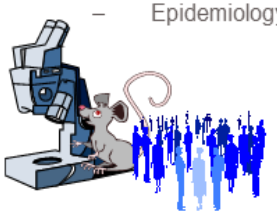
Risk assessment

Basic principles

1) Hazard id:

- Toxicology
- Epidemiology



2) Hazard characterization:

- Dose response
- Safe level

3) Exposure assessment:

- Analytical data
- Levels of addition

Occurrence in food

- Food consumption

Other sources

Exposure

COMPARE

4) Risk characterization: ▶ Risk management:

- Probability
- Severity

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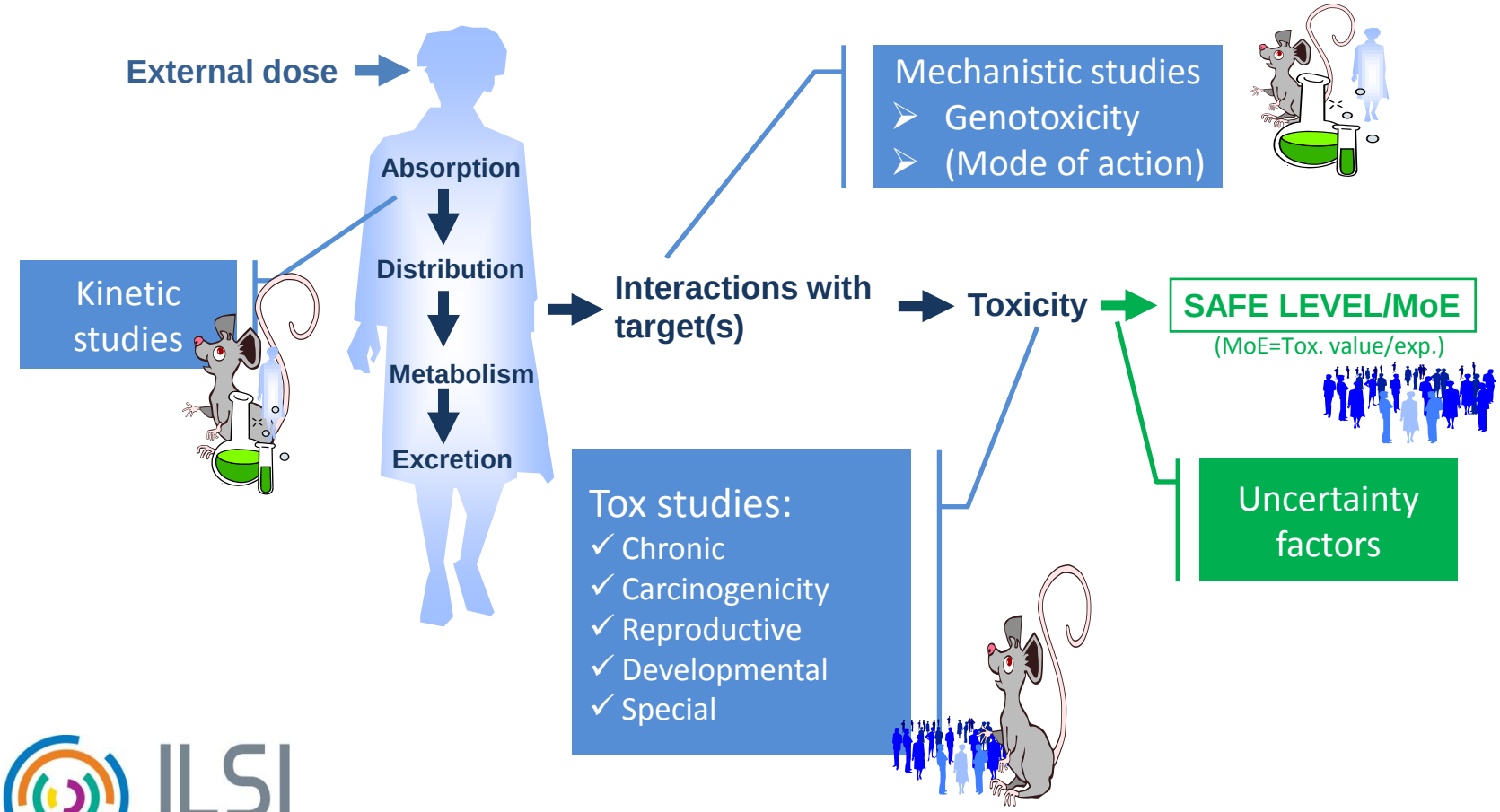
Risk assessment:

hazard identification



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Hazard identification:

defining extent of testing

- Human/Animal information (clinical, epidemiological, tox, …)
- Production volume
- Usage (agricultural, food technological purposes, …)
- Anticipated exposure (extent, pattern, …)
- Populations exposed (whole population, infants, …)
- Chemical structure (structural alerts, …)
- …

Level of concern

(determine extent of testing & study design)

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Hazard identification/toxicity testing

Regulatory requirements

For highest level of concern (e.g. life-time exposure of whole population such as with pesticides), a complete toxicological database on 1-3 species is required:

- **Kinetics**
  - Metabolism/Toxicokinetics
- **Mechanism**
  - Mutagenicity (DNA-damage)
- **Toxicity tests**
  - (Acute toxicity)
  - Sub-acute toxicity (28 days)
  - Sub-chronic toxicity (90 days)
  - Chronic toxicity (2 years)
  - Carcinogenicity (2 years)
  - Reproductive toxicity
  - Teratogenicity (malformations)
- **Other studies (where indicated)**
  - *Ad hoc* studies on special endpoints (e.g. behavioral studies)
  - Mechanistic studies

Dose-response

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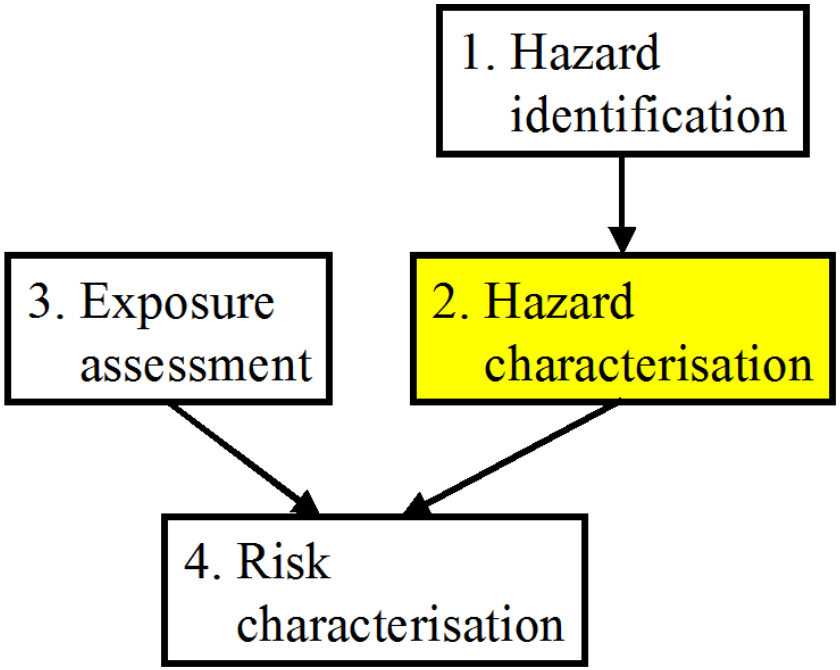
Hazard characterization:
Translate tox data into human relevant values



Hazard characterization:
Identification of the most important adverse effect(s) and analysis of the dose-response relationship to define **a safe exposure in human** or a level associated with a determined level of risk.

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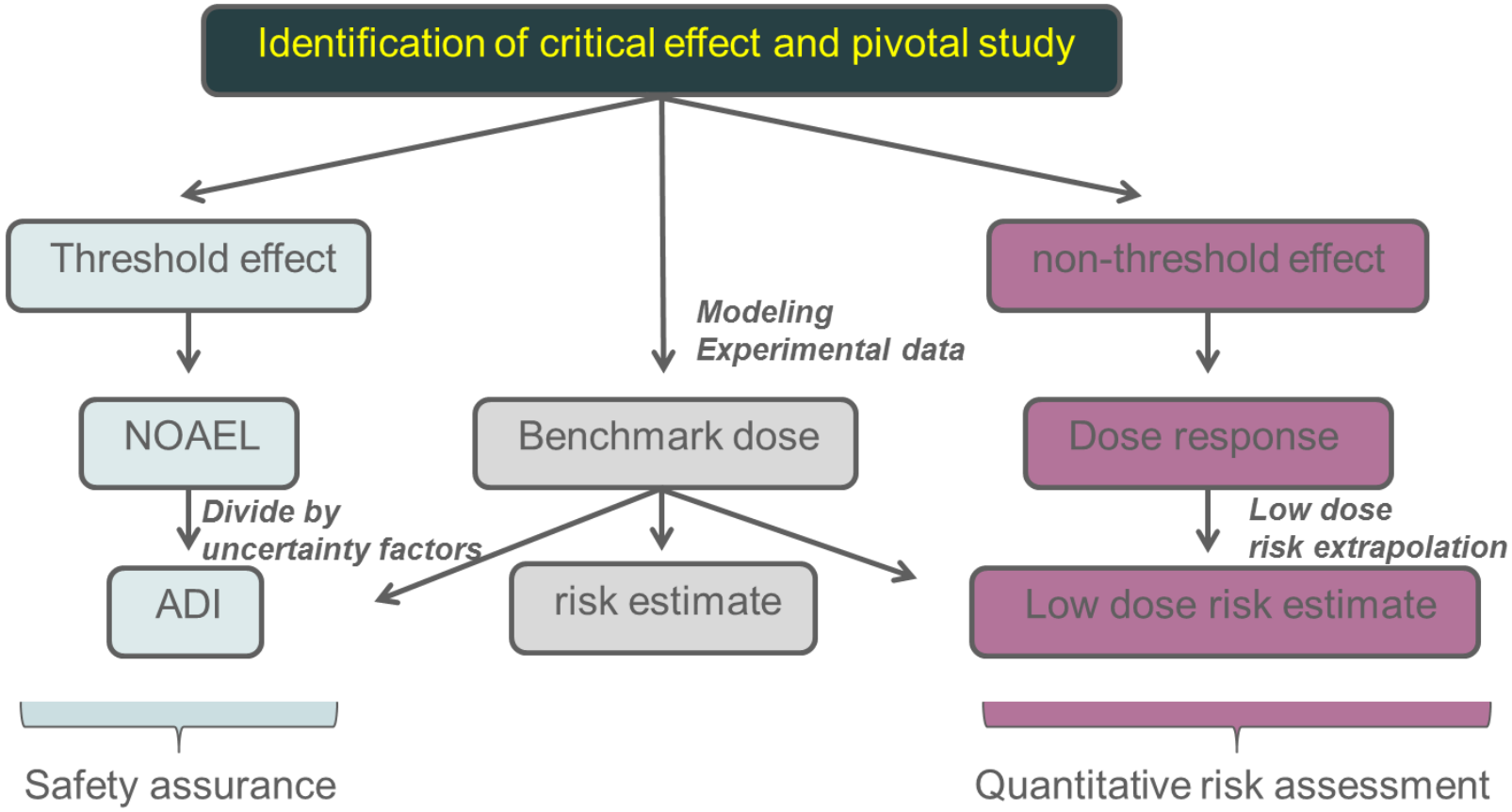
Hazard characterization:

basic principles



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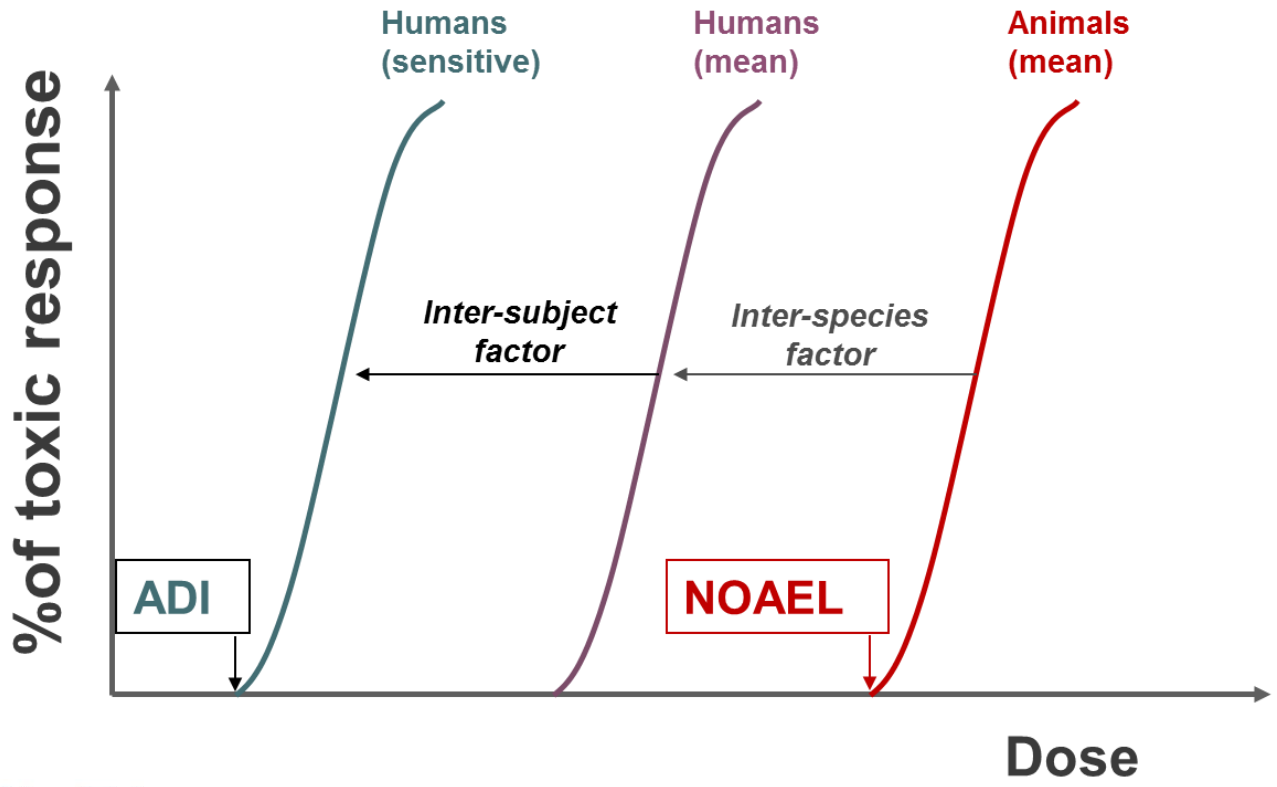
NOAEL: No Observed Adverse Effect Level
ADI: Acceptable Daily Intake

Hazard characterization:

threshold effects

Translate toxicological data into safe level in human



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ADI : *Acceptable Daily Intake*
Threshold : *Dose of a agent/substance below which no effect is expected*
NOAEL : *No Observed Adverse Effect Level (safe level in animals)*

Safe level of exposure in human

threshold effects

Acceptable Daily Intake (ADI)

Estimated amount of a substance, expressed on a body mass basis (usually mg/kg bw/day), to which a human subject may be exposed daily over lifetime without appreciable health risk

- ADIs apply to the whole population except infants under 12-weeks of age
- Applicable to any food chemicals: additives, pesticides, vet drugs, contaminants, mycotoxins, ….
- ADI covers all sources of exposure
- TDI (tolerable daily intake), for contaminants
- If chemical accumulating: pTWI (provisional tolerable weekly intake), pTMI (provisional tolerable monthly intake)
- Group ADI (compounds with additive effects)
- ADI is not a threshold for harmful effects in human
- Significance of excursion above ADI depends on duration and magnitude of the excess, and specific toxicological properties.

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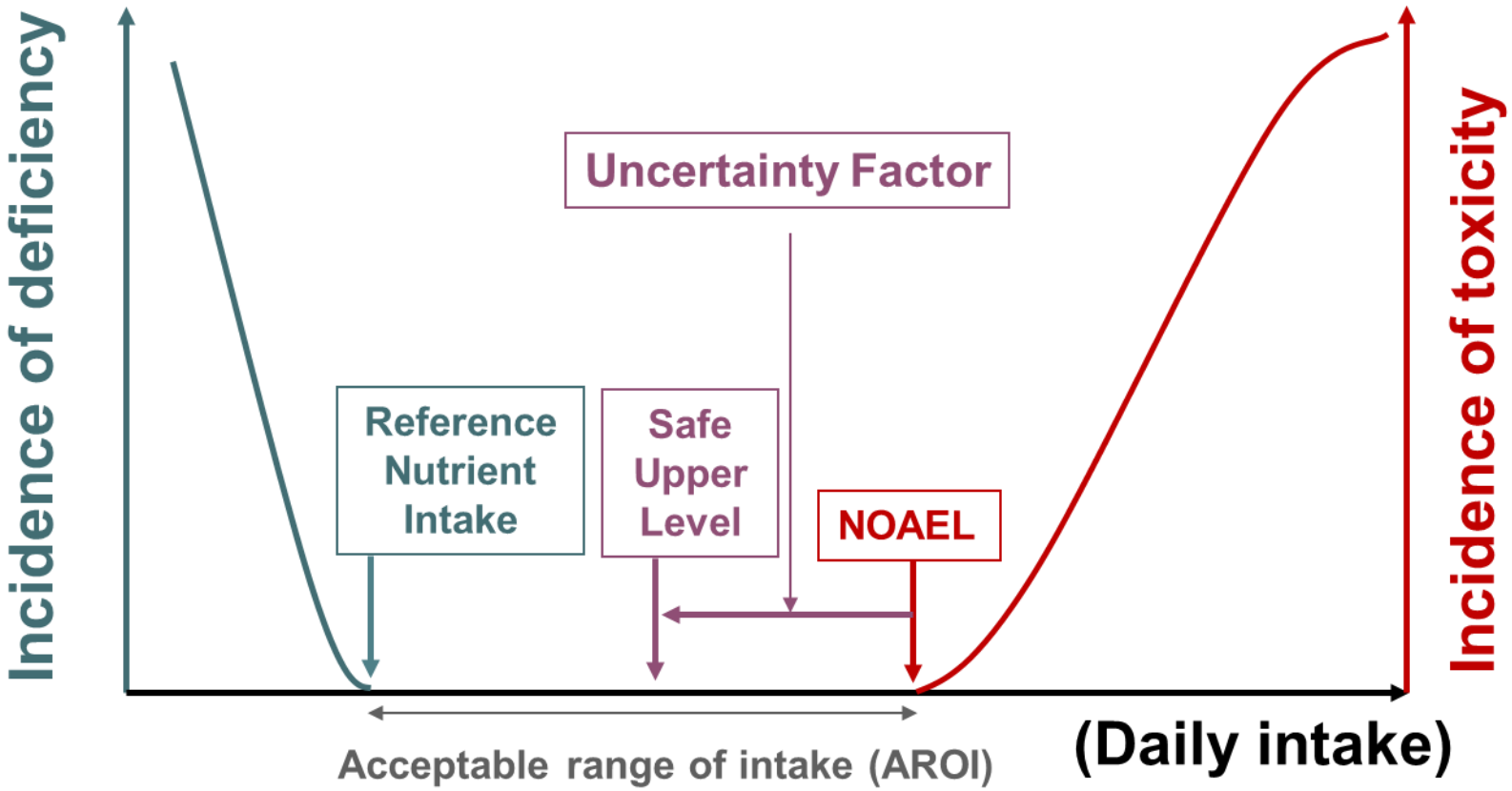
Trace elements and vitamins:

preventing toxicity and deficiency



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Hazard chacterization:

non-threshod effects

- The potential to cause cancer through the direct binding to DNA is the main example of non-threshold effect
- **No safe level assumed** (*'1 molecule increases the risk'*)
- **Quantitative Risk Assessment (QRA)** models the animal data at high doses to estimate risk for human-relevant exposures (low doses)
- A **'Virtual Safe Dose'** (**VSD**) can be estimated.
  It corresponds to a life-time excess risk deemed tolerable for the society (management/government decision)
- 1 cancer case per million (10^{-6}) of exposed people over life-time is often used as a tolerable lifetime excess risk

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Hazard chacterization:

non-threshod effects

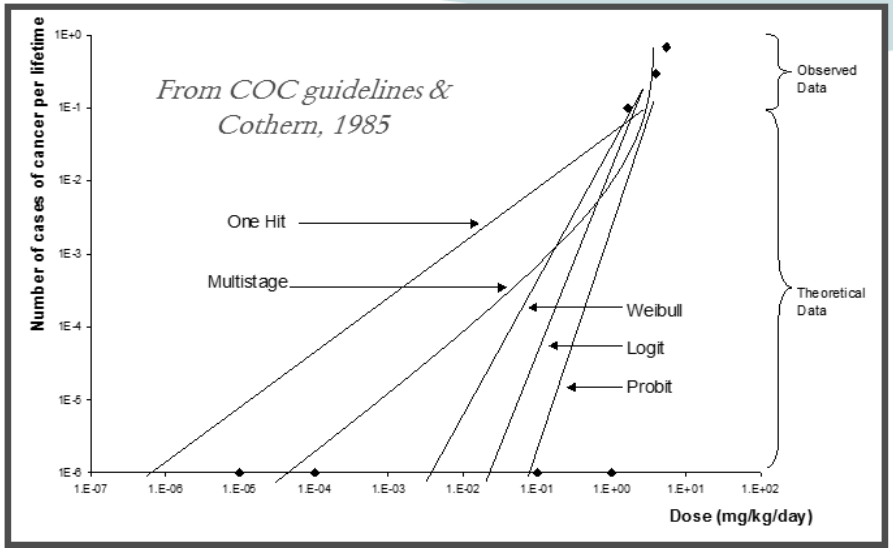
QUANTITATIVE RISK ASSESSMENT

Low Dose Extrapolation

Requires extrapolation over a very large range of doses (out of the observation range)

No adequate simulation of the carcinogenic processes by any model (especially for extrapolating from high doses in animals to low human exposure)

Numerical risk estimate more influenced by selected mathematical models than by actual data

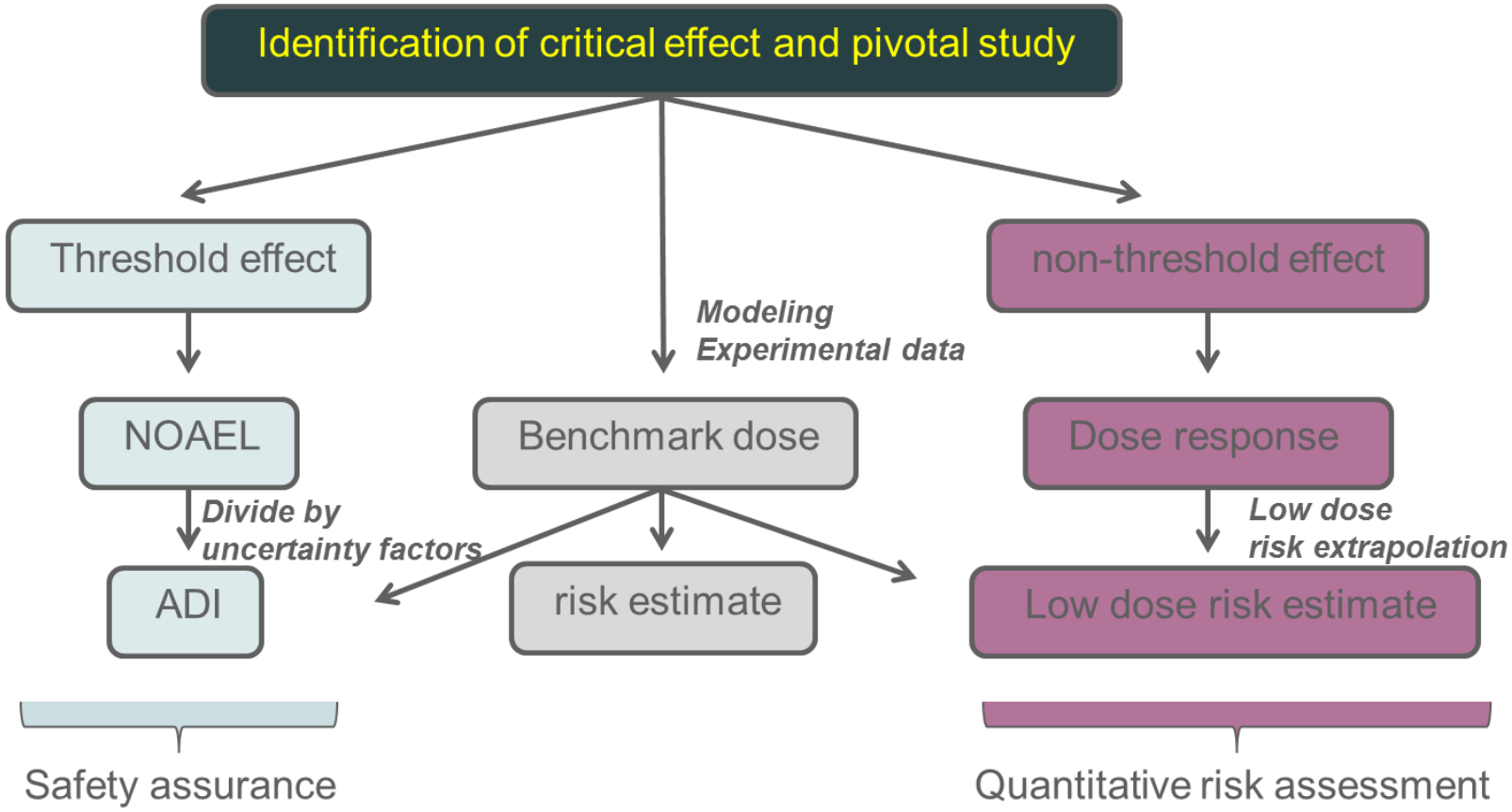


Applications (controversial):

- *Linear dose-response*
- *Over-conservative*
- *Simple risk ranking?*
- *Priority setting for management?*
- *Assess impact of mitigation measures*

Hazard characterization:

basic principles



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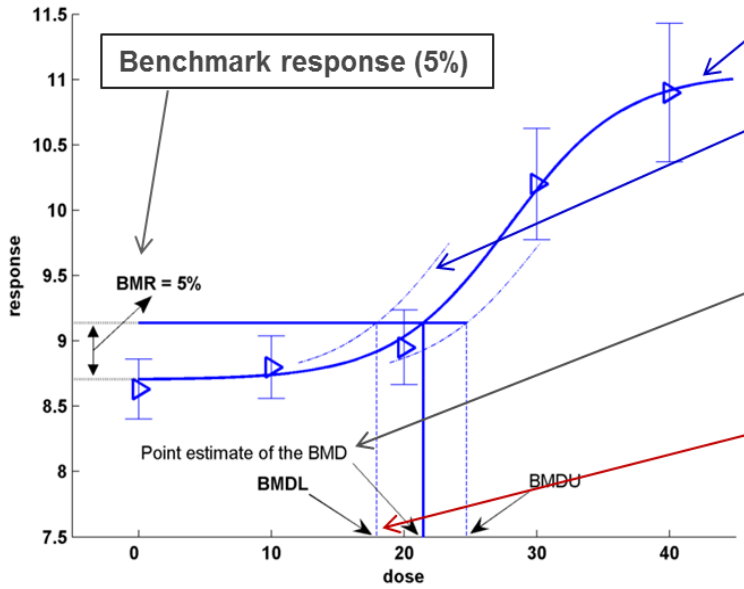
NOAEL: No Observed Adverse Effect Level
ADI: Acceptable Daily Intake

Hazard characterization alternative

Benchmark dose modelling



Fitted dose-response model

Lower 95%-confidence bound: 95% confidence that the effect at BMDL does not exceed the BMR

Benchmark dose (BMD) point estimate: corresponds to a low but measurable effect, denoted as BMR

BMD lower confidence lower bound ($BMDL_{05}$) : 95% confidence that the effect at BMDL does not exceed the BMR

- Alternative approach of dose-response assessment
- Account for shape of dose-response, less dependant on dose spacing
- Can provide quantification and variability in the dose-response data
- Can be applied to various types of compounds and endpoints (threshold or not)

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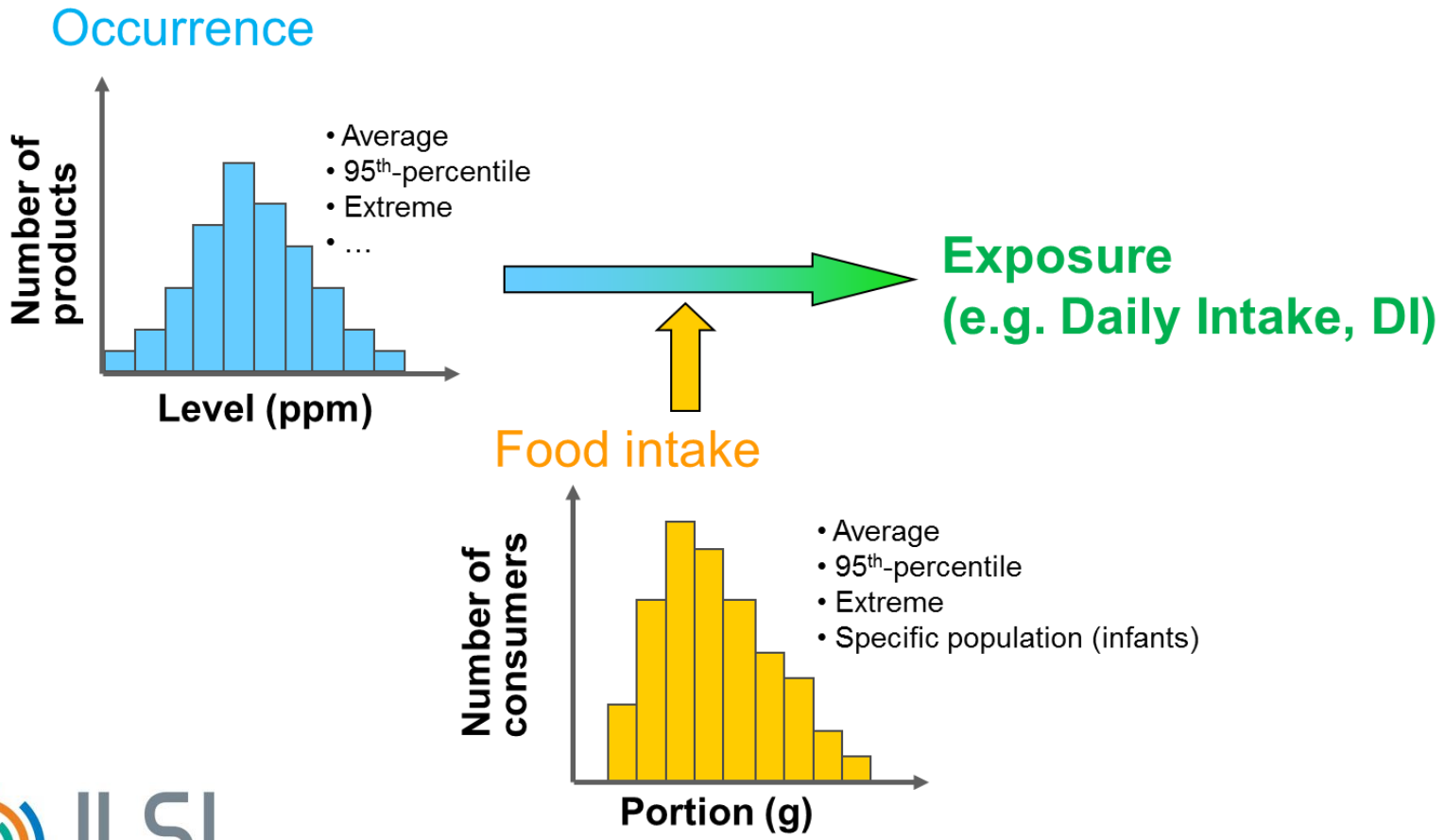
Exposure assessment:

combining occurrence and food intake data



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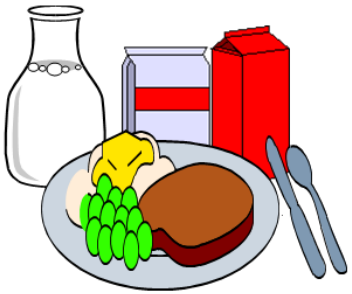
Exposure to contaminants:

Data required/available: occurrence

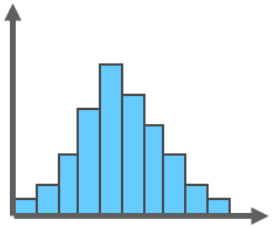
Recipes



Raw materials

Food products

- **Analytical data**
- **Internal/external (published)**
  - *Limit of detection/determination*
  - *Validity of the methods*
  - *Sampling*
  - *Matrix effects*
  - *…*



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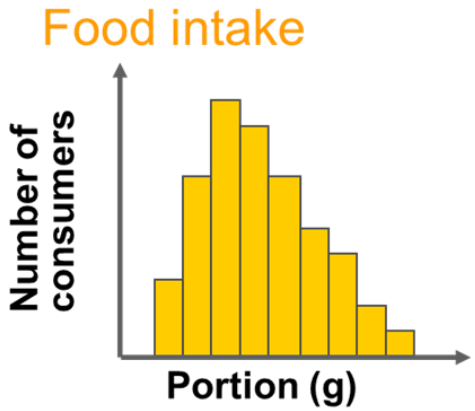
Exposure to contaminants:

Data required/available: food intake

- Recommended consumption
- Anticipated intake (new products)
- WHO/FAO diets
- Data from surveys (published, e.g. EFSA)
  - **Scientific publications**
  - **Raw data (EFFA database)**
  - **Contract organisations**



scenarios

- **Point estimates** (occurrence, food intake):
  - Worst-case
  - 95th-percentile
  - Average
  - Population specific
  - Diet models, country/region specific.
  - …
- **Probabilistic:**
  - Contract organisations, FACET

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Risk characterization

- **Margin of Safety (MoS):**
  - When a health-based guidance value is available (ADI, TDI, TTC)

$$MoS = \frac{ADI}{Exposure}$$

- ✓ MoS >>1 (safe)
- ✓ MoS < 1 (manage)
- ➢ **Size of MoS?**

- **Margin of Exposure (MoE):**
  - When only a toxicological value is available (experimental, predicted)
  - When a defined level of risk is available (e.g. BMDL)

$$MoE = \frac{Tox\ value/BMDL}{Exposure}$$

- ✓ **Must cover uncertainties:**
  - Inter-species differences
  - Inter-individual differences
  - Extrapolation LOAEL/NOAEL
  - Exposure duration
  - ….
- ➢ **Size of MoE?**

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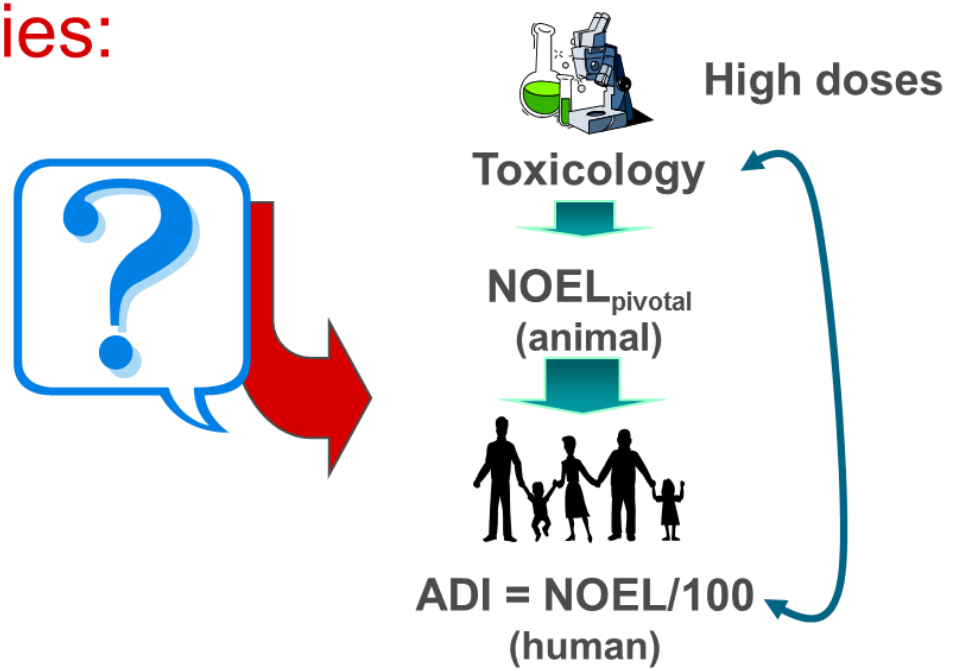
Novel ingredients / New products:
Standard approach may not be feasible

Macrocomponents:
- *Magnitude of over-exposure is limited*

Viable microorganisms:
- *Pathogenicity, gut microflora, colonization*

Functional properties:
- *Mechanisms*



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Novel ingredients / New products :

A case-by-case stepwise approach

Novel Food / Ingredient, New product
- Characterization
- Anticipated use / Exposure
- Nutritional / Toxicological information

Comparator
- Specifications
- Condition of use / Exposure
- Nutritional / Toxicological info.

History of (safe) use?

Compare

- No difference:
  - ✓ *'As safe as'*
- Differences:
  - ➢ *Additional information required*

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Novel ingredients / New products : *Product comparison*

- No significant difference with a traditional food:
  - No further data required
- No significant difference with a traditional food, except a few specific characteristics:
  - Additional data required focusing on these characteristics
- Product is similar to a health / medicinal product:
  - Need to assess relevance of available data for a food application
- No traditional food or health product counterparts:
  - Thorough safety assessment (data required)

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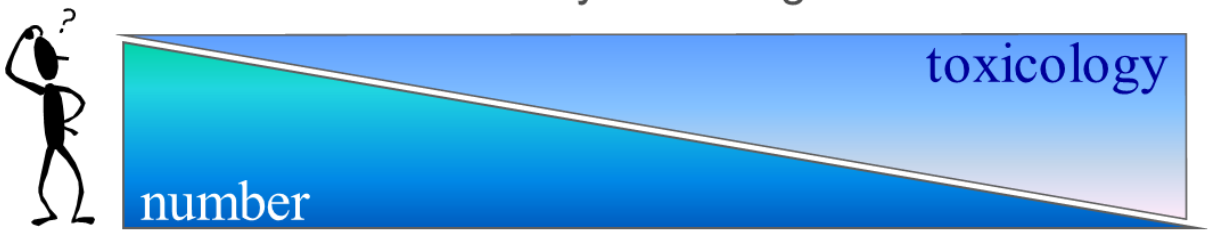
Looking at the future

- Chemicals may compromise food safety
- Trigger public, scientific and industrial concern
- Risk assessment has been a successfull tools to address food safety issues
- But …..
  - 5 000 000 man made chemicals known
  - 80 000 chemicals in commercial use today
  - 100 000 naturally occurring substances



- There is a big need for toxicological risk assessment
- Regulatory toxicology is not the solution

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Regulatory toxicology is being challenged

Ethical reasons:

- Reduce/Refine/Replace (3Rs)

Scientific reasons:

- Human relevance of animal data/Interspecies differencies
- High experimental doses to low human exposure extrapolation
- Little mechanistic understanding
- …

Economic reasons:

- Testing capacity (ressources/timing)
- Cost contraints

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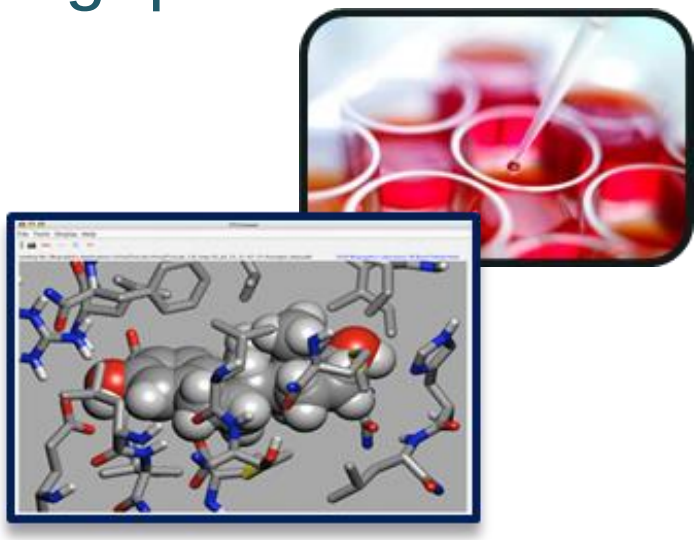
The way forward:

- **Alternative methods are being developped (*In vitro, in silico*) to replace the use of animals:**
  - More mechanistic
  - More human relevant (test systems, level of exposure)
  - Cost effective, high throughput
  - ….
  - **Good progress**



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