**FSSAI – IITR – CHIFSS Technical Workshop
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OVERVIEW OF FOOD SAFETY ASSESSMENT – NOVEL INGREDIENTS & ADDITIVES

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Safety & Environmental Assurance Centre,
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OUTLINE

- Principles of risk assessment
- Hazard identification & characterisation
- Exposure assessment
- Risk characterisation (ADI)
- Risk assessment of whole foods
- Additional risk assessment tools (HoSU, TTC, PLM)
- Case studies

Risk Assessment Principles

- Ensure foods placed commercially on the market are safe for the consumer and do not present undue risk

$$\text{Risk} = f\,(\text{Hazard x Exposure})$$

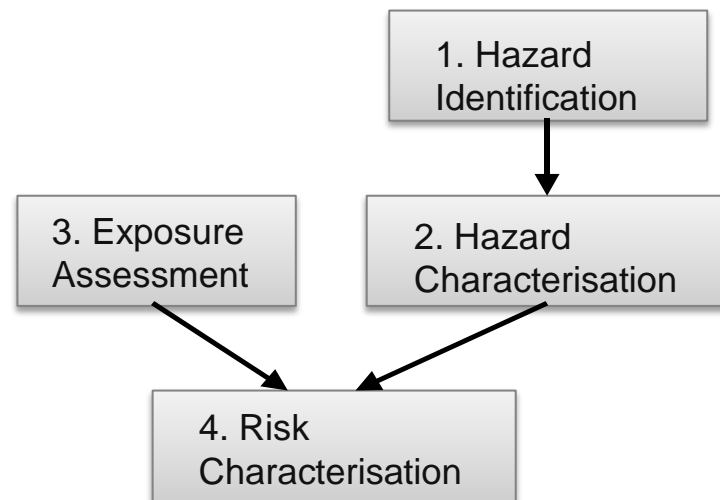- 4 step risk assessment paradigm:
  - Hazard identification
  - Hazard characterisation
  - Exposure assessment
  - Risk characterisation

1. Hazard Identification

3. Exposure Assessment

2. Hazard Characterisation

4. Risk Characterisation
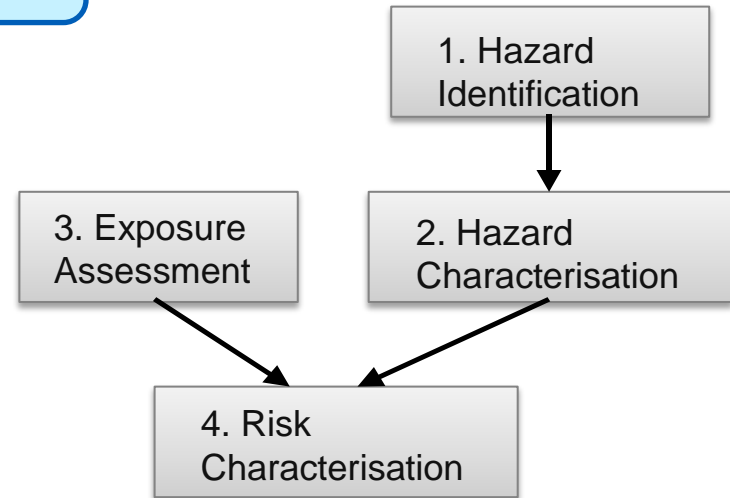
Risk Assessment Principles

Risk = *f* (Hazard x Exposure)

- <u>Risk assessment</u>: A scientifically based process consisting of the following steps: i) hazard identification; ii) hazard characterisation, iii) exposure assessment, and iv) risk characterisation.

- <u>Hazard identification</u>: The identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods

- <u>Hazard characterisation</u>: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents a dose response assessment should be performed.

- <u>Exposure assessment</u>: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical and physical agents via food as well as exposure from other sources if relevant.

- <u>Risk characterisation</u>: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterisation and exposure assessment.

Codex Alimentarius, 2006

1. Hazard Identification

2. Hazard Characterisation

3. Exposure Assessment

4. Risk Characterisation

WORKSHOP: FOOD TOXICOLOGY RISK BASED APPROACHES

$$\text{Risk} = f\,(\text{Hazard} \times \text{Exposure})$$

4 step risk assessment paradigm:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation

1. Hazard Identification

3. Exposure Assessment

2. Hazard Characterisation

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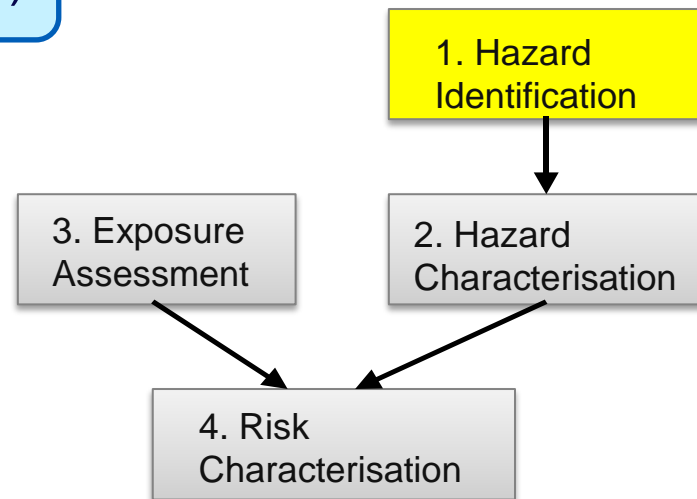
1. Hazard Identification

- **What is known about the chemical(s) already?**

- Information from the supplier

- Regulatory approvals

- Literature search on the chemical
    - Standard toxicology studies
    - Investigative / research publications
    - Media stories

- Uses of the chemical other than food

- Anecdotal information

Build up a picture to determine what the safety issues are and what package of safety support might be needed.

1. Hazard Identification

- For most ingredients - toxicological data already exists

- For some ingredients expert toxicological evaluations will also have been published e.g., EFSA, FDA, CIR, RIFM, FEMA, GRAS

- Wherever possible, existing data for ingredients are used in safety assessments

- All available data (manufacturers, expert bodies, publications) are scrutinised and their robustness established

- QSAR evaluation, including read across to similar chemicals, may be used for an initial evaluation

- Other considerations such as History of Safe Use or human clinical data can be used in a weight of evidence approach

1. Hazard Identification

- If data does not exist, or considered inadequate, toxicological testing may be conducted to identify and characterise the toxicological hazard

- Alternatives to animal testing are employed when possible

- Where no alternative exists, animal testing will be conducted on ingredients e.g. repeat dose toxicity study (28-, 90-day) in rats

- They should be conducted to OECD guidelines and GLP (Good laboratory Practice)

1. Hazard Identification

Sources of Safety Data & Reviews

- Europe – European Food Safety Authority (www.efsa.europa.eu)

- EFSA predecessor – Scientific Committee for Food
  (http://ec.europa.eu/food/fs/sc/scf/index_en.html)

- USA – Food & Drug Administration (www.fda.gov)
  EAFUS List (Everything Added to Food in the US)

  - Global – Joint Expert Committee on Food Additives (JECFA)

  http://apps.who.int/ipsc/database/evaluations/search.aspx

  - Australia & New Zealand – Foodstandards (www.foodstandards.gov.au)

1. Hazard Identification

Systemic Toxicity

Acute toxicity:
- Assessing toxicity after single high dose; conducted in rats/mice
- Not normally relevant to food ingredients;

Sub-chronic studies:
- Designed to assess the toxic effects of a chemical during a short period of time ≤90day
- Studies conducted in rats, mice, dogs - looking for changes in organ function and organ pathology

Chronic studies
- Assessing safety of chemical when given over lifetime to animal - (Rats (2 years) & Mice (18 months)
- Looking for changes in organ function and organ pathology
- Often combined with assessment of carcinogenicity

Carcinogenicity study
- Assesses the ability of chemical to cause cancer when given over life time (studies contacted in rats & mice)

Teratology study
- Assesses ability of chemical to cause damage to developing foetus
- Carried out in pregnant rats or rabbits

Reproductive Toxicology
- Assessing effects in fertility, foetal development and offspring
- Studies conducted in rats & mice over one or more generations

Other

Genoxicity studies
- Designed to assess the ability of chemical to damage DNA & thus cause cancer
- Initial studies conducted in bacteria and in cells. If positive results in the studies then studies in whole animal will be conducted

**Absorption, metabolism, distribution and excretion (ADME)**
- How does the body handle to chemical, where does it go how is it excreted?

WORKSHOP: FOOD TOXICOLOGY RISK BASED APPROACHES

Risk = f (Hazard x Exposure)

4 step risk assessment paradigm:

- Hazard identification
- Hazard characterisation
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- Risk characterisation

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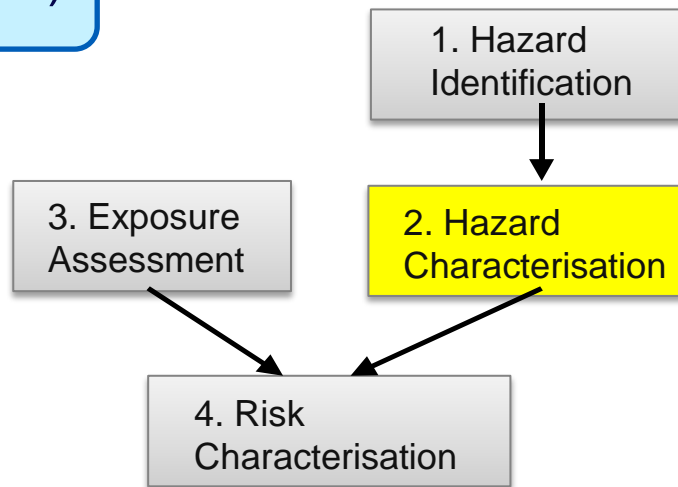
2. Hazard characterisation

What is the safe dose/intake of a chemical?
▪Need to identify the critical effect in the safety data
    -Effect should be <u>relevant</u> for man

▪ No Observed Adverse Effects Level (NOAEL)
    - Dose that produced no adverse effects in the study.
    - Identifying the critical effect in the most sensitive species

Threshold Effects
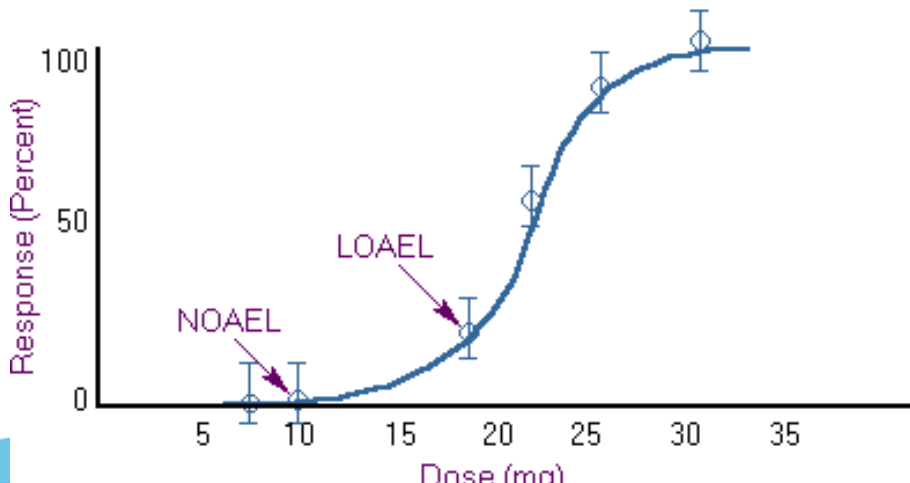
NOAEL: <u>Highest</u> data point at which there was <u>not</u> an observed <u>adverse</u> effect.

LOAEL: <u>Lowest</u> data point at which there <u>was</u> an observed toxic or <u>adverse</u> effect.

WORKSHOP: FOOD TOXICOLOGY RISK BASED APPROACHES
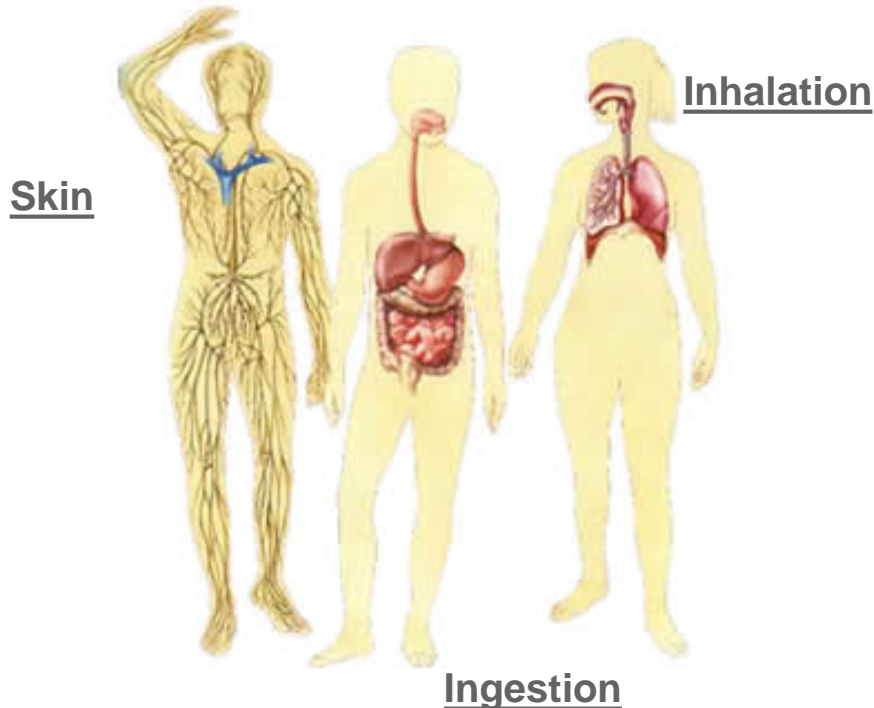
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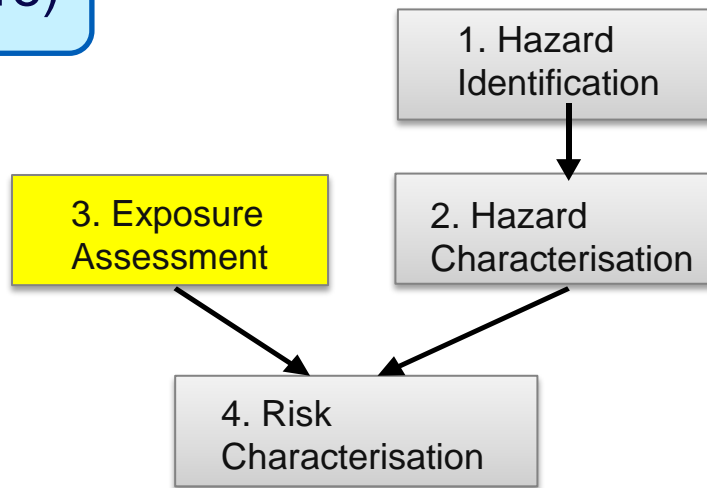
3. Exposure assessment

Routes of Consumer Exposure

Skin

Inhalation

Ingestion

3. Exposure assessment
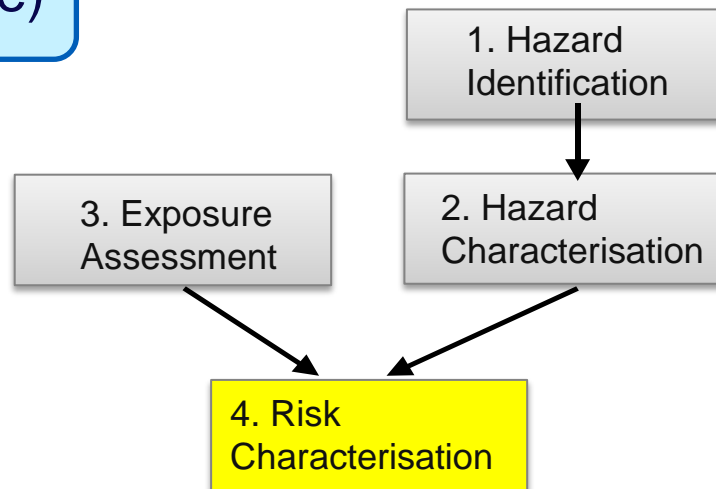
- How much of a chemical are consumers exposed when they eat a food?
    - Need to know
        - Level of chemical in food?
        - Added or measured?
        - How much food is consumed?

- Dietary/nutritional surveys provide data on amounts of food consumed
    - e.g. NDNS in UK, NHANES in US
    - Not all types of food products are covered in surveys

- Assessment approaches
    - <u>Deterministic</u>
        - single point, usually worst case e.g. 95th percentile intake for food consumption & highest level of addition
    - <u>Probabilistic</u>
        - Models intake across the full distribution of intakes. Usually used when considering intake from multiple food sources eg Crème/DaDiet software

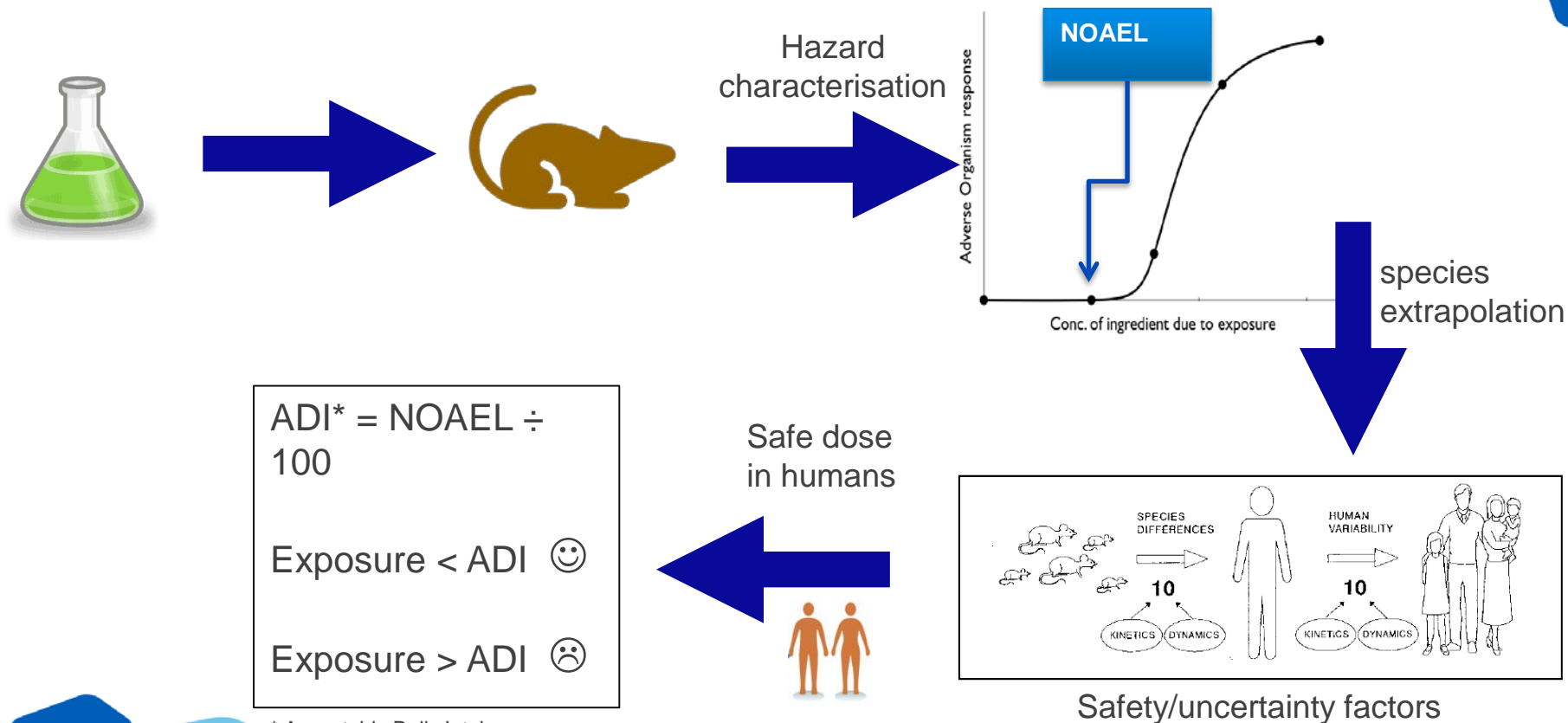# WORKSHOP: FOOD TOXICOLOGY RISK BASED APPROACHES

$$\text{Risk} = f\,(\text{Hazard} \times \text{Exposure})$$

4 step risk assessment paradigm:

- Hazard identification
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- Risk characterisation

```
1. Hazard Identification
        ↓
2. Hazard Characterisation
        ↘
3. Exposure Assessment → 4. Risk Characterisation
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4. Risk characterisation

Hazard characterisation

NOAEL

Adverse Organism response

Conc. of ingredient due to exposure

species extrapolation

ADI* = NOAEL ÷ 100

Exposure < ADI ☺

Exposure > ADI ☹

Safe dose in humans

SPECIES DIFFERENCES

HUMAN VARIABILITY

10

10

KINETICS DYNAMICS

KINETICS DYNAMICS

Safety/uncertainty factors

* Acceptable Daily Intake

4. Risk characterisation

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

$$ADI = \frac{NOEL}{100}$$

- ADIs are established by recognized & independent expert groups or regulatory authorities, e.g.: JECFA, EFSA

- ADIs apply to the whole population except infants <12-weeks of age

- ADI covers all sources of exposure (food, water, inhalation)

- Applicable to any food chemicals: additives, pesticides, contaminants
    - Tolerable Daily Intake (TDI) is used for 'contaminants'

RISK ASSESSMENT WHOLE FOOD/ COMPLEX MIXTURE

Whole Foods

- Macro components of the diet

- Complex mixture of different chemicals

- Toxicological testing is more difficult - 100-fold safety factors often can not be achieved.

Substantial Equivalence

$$= \quad \neq \quad \approx$$

- Does a new food shares health and nutritional characteristics with an existing, familiar food?

- Safety evaluation - focus on differences

- Recognises that existing foods often contain anti-nutrients[1] that can be consumed safely e.g. potatoes (solanine) and tomatoes (α-tomatine alkaloids)

[1] Antinutrients are natural or synthetic compounds found in a variety of foods that interfere with the absorption of vitamins, minerals and other nutrients.

ADDITIONAL RISK ASSESSMENT TOOLS

i. HISTORY OF SAFE USE

Definition

"significant human consumption of food (over several generations and in a large diverse population) for which there exists adequate toxicological and allergenicity data to provide reasonable certainty that no harm will result from the consumption of the food"

- Health Canada, 2003

Safety assessment

- Characterisation
- Details of use
- Previous human exposure
- Health effects
- Potential hazards

Constable et al (2007). History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms. *Fd. Chem. Toxicol.* 45 2513-2525.

ADDITIONAL RISK ASSESSMENT TOOLS

i. HISTORY OF SAFE USE

Applied to the Safety Assessment of Novel Foods?

Characterisation

- Biology (origin, genetic diversity)
- Geographic distribution
- Composition
  - Proximate analysis
  - Nutritional profile
  - Chemical hazards (toxicants, allergens, contaminants)
  - Bioactives

Details of use

- Preparation & processing (fermentation, soaking, peeling, cooking)
- Purpose (food, supplement, pharmaceutical)
- Pattern of consumption
- Intake (ranges, populations)
- Known limitations of use (cultural practice, specific uses)

Previous human exposure

- Which populations – diversity?
- Genetic background, age groups

Health effects

- Evidence from human exposure
  - Known adverse effects
  - Case reports
  - Known precautions
  - Over-consumption
  - Mis-use
  - Specific sub-populations

Potential hazards

- Toxicology data
- Nutritional data
- Allergens
- Known contaminants
- Bioactives eg phytoestrogens

ADDITIONAL RISK ASSESSMENT TOOLS
ii. THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

Definition

Threshold of exposure for chemicals of known structure below which there is no appreciable risk to human health.

CATEGORY		DESCRIPTION	TTC (mg/person/day)
Cramer Class I	Low toxicity	Substances with simple structures for which efficient modes of detoxification exist in our body.	1.8
Cramer Class II	Moderate toxicity	Substances that are less innocuous than in Class I, but do not contain structural features suggestive of toxicity like those in Class III.	0.54
Cramer Class III	High toxicity	Substances suggesting significant toxicity or containing reactive functional groups.	0.09

A useful approach for risk assessing Food Chemicals, when:
- Present in foods at low concentrations
- Little or no toxicity data eg contaminants from processing or packaging, or flavour components
- A reliable assessment of intake of the chemical must be possible

Exclusions
- High potency carcinogens
- Neurotoxicants
- Allergens
- Endocrine disruptors

ILSI EUROPE CONCISE MONOGRAPH SERIES

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

A TOOL FOR ASSESSING SUBSTANCES OF UNKNOWN TOXICITY PRESENT AT LOW LEVELS IN THE DIET

Munro et al (1996, 1999), Kroes et al (2000, 2004)).
ILSI Europe Concise Monograph Series (2005). Threshold of toxicological concern
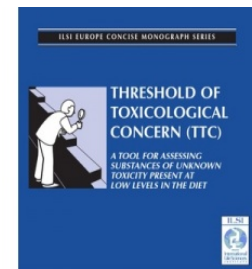
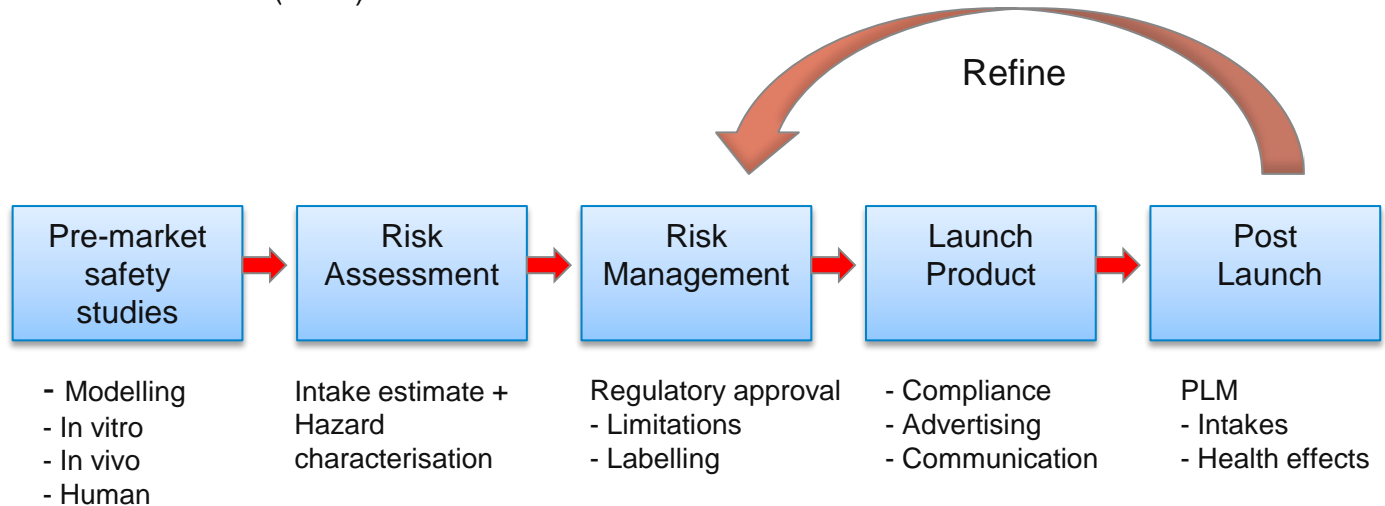# ADDITIONAL RISK ASSESSMENT TOOLS

iii. POST LAUNCH MONITORING (PLM)

Definition

A hypothesis driven scientific methodology for obtaining information through investigations relevant to the safety of a (novel) food after market launch - ILSI (2008)

Use of market data to refine the risk assessment

A complement to risk assessment

Refine

| Pre-market safety studies | → | Risk Assessment | → | Risk Management | → | Launch Product | → | Post Launch |

- Modelling
- In vitro
- In vivo
- Human

Intake estimate + Hazard characterisation

Regulatory approval
- Limitations
- Labelling

- Compliance
- Advertising
- Communication

PLM
- Intakes
- Health effects

Hepburn *et al* (2008). Review: The application of post-market monitoring to novel foods. *Fd. Chem. Tox.* 46 9-33.

WHOLE FOOD/ COMPLEX MIXTURE

- What is the source of the material?

    - Natural, synthetic, biotechnology

    - Methods of extraction/ synthesis including solvents used

- Is it a novel process?

    - Focus on the product of the process ie food

    - Identification of the changes vs traditional counterpart

- Analytical/compositional/nutritional characteristics of the novel food

    - source of material/changes due to new processing

    - Impurities/contaminants

- Can <u>substantial equivalence</u> be established?

    - Biological/chemical comparison to a traditional counterpart

Reference: Howlett et al (2003). The Safety Assessment of Novel Foods and Concepts to Determine their Safety in Use. Int. J. Fd. Sc. Nutr. 54 1-32

WHOLE FOOD/ COMPLEX MIXTURE

- Previous history of human exposure

  - Comparison to traditional counterpart (if available)

- Expected applications and the predicted exposure

  - Purpose

  - Food categories and use levels (usually worst case; over-estimates)

- Necessity, appropriateness and outcome of safety studies

  - Fate in biological systems

  - Standard toxicology, feeding studies

  - Focussed toxicity studies

  - Allergenicity

  - Human studies: focussed effects, target populations, efficacy….

Reference: Howlett et al (2003). The Safety Assessment of Novel Foods and Concepts to Determine their Safety in Use. Int. J. Fd. Sc. Nutr. 54 1-32

WHOLE FOOD/ COMPLEX MIXTURE

Risk Assessment

$$Risk = f \text{ (hazard x exposure)}$$

- **Hazard**
- Acute toxicity
- Allergy
- Systemic toxicity
- Reproduction toxicity/teratology
- Mutagenicity/carcinogenicity
- Functional activity/ pharmacology

Exposure
- Type of product(s)
- Target consumer
- Consider vulnerable groups
- Claim
- Misuse

- Consider impact on nutrition

  - micro- versus macro-ingredients

  - need to carry out human studies

Reference: Howlett et al (2003). The Safety Assessment of Novel Foods and Concepts to Determine their Safety in Use. Int. J. Fd. Sc. Nutr. 54 1-32

RISK BASED APPROACHES: SUMMARY

- Basic principle is to understand the toxicological hazard and how the consumer is exposed (Risk = f(Hazard x Exposure)

- Characterise the risk e.g.
     Acceptable Daily Intake (ADI) = NOAEL ÷ 100

- Substantial equivalence is a useful concept for whole foods

- Additional risk assessment tools include
  - History of Safe Use
  - Threshold of toxicological concern
  - Post Launch Monitoring

WORKSHOP: FOOD TOXICOLOGY RISK BASED APPROACHES

Case Studies

Safety & Environmental Assurance Centre, Unilever
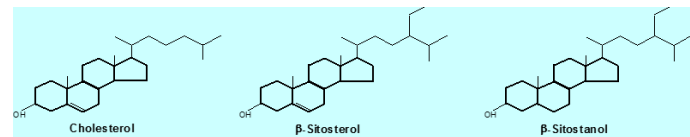
CASE STUDIES – NOVEL FOODS

- Plant sterols

- Brahmi in tea

- Chia seeds

- Noni juice

CASE STUDIES: PLANT STEROLS (OVERVIEW)

Plant Sterols – blood cholesterol lowering

- Natural components of diet;
- Lowers blood cholesterol by blocking absorption

Risk assessment

- Extensive safety package – all studies published
  - ADME, genotoxicity, sub-chronic rat feeding study, reproduction studies
  - Extensive clinical studies

- Standard risk assessment
  - NOAEL = 3900mg/kg BW/day;
  - ADI* = 130mg/kg BW/day
- Risk assessment supported by
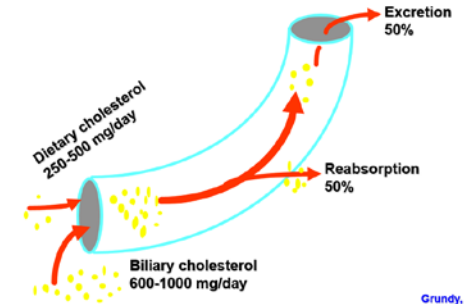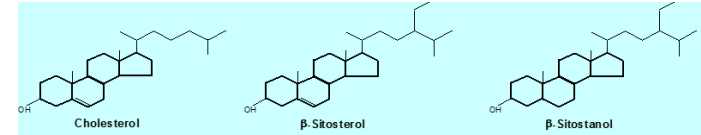 - History of safe Use
  - Post Launch Monitoring
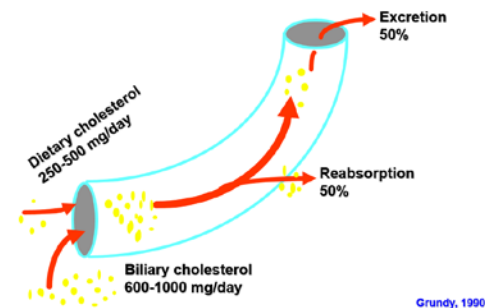
$$ADI = NOAEL \div SF$$

* An appropriate safety factor of 30 (rather than default of 100) was established (based on lack of toxicity, human data, Renwick (1991) approach)
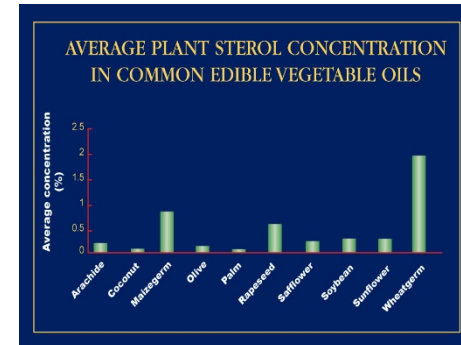
PLANT STEROLS - HISTORY OF SAFE USE

- Plant sterols are naturally occurring molecules structurally comparable to cholesterol

- Present in the diet as minor components of vegetable oils, fruits & vegetables

  - average daily intake 200 - 400 mg/day

  - present in standard Flora 0.3g/100g

- 20g of pro.activ contains the same level of Plant Sterols as:-
  - 4 Loaves of wholemeal bread
  - 0.6 kg of Sunflower seeds
  - 8 bags of peanuts
  - 12 Avocados

- Cholesterol lowering effect known since early 1950s (e.g. Pollak et al (1953)

Cholesterol   β-Sitosterol   β-Sitostanol

Grundy, 1990

AVERAGE PLANT STEROL CONCENTRATION IN COMMON EDIBLE VEGETABLE OILS

WHY WAS SAFETY TESTING REQUIRED?

- 5-10 fold increase in consumption of Plant Sterols

- Any other biological activity other than cholesterol lowering?

- Insufficient safety data available in the literature to support the increased consumption
  - possible accumulation in tissues/toxicological consequences?
  - Interference with the absorption of nutrients/drugs?
  - Gut morphology/ physiology/ biochemistry/ microflora?
  - Possible effects on the reproductive system

TOXICOLOGY PROGRAMME

- Mutagenicity   Wolfreys & Hepburn (2002)
  - Bacterial mutation assay (Ames test)   Lea et al (2004)
  - In vitro cytogenetics

- Absorption, distribution, Metabolism   Sanders et al (2000)
  & Excretion (ADME)

- Sub-chronic toxicity   Hepburn et al (1999)
  - 13 week feeding study in rats

- Reproduction Toxicity
  - in vitro oestrogenic potential   Baker et al (1998)
  - in vivo oestrogenicity
  - Two generation reproduction study in rats   Waalkens et al (1999)

- Physiological effects in humans   Ayesh et al (1999)
  Weststrate et al (1999)

- Post Launch Monitoring   Lea & Hepburn (2006)

EFFECTIVENESS LITERATURE REVIEW

STUDY	LENGTH OF STUDY	n	INTAKE OF FREE STEROL (g/day)	REDUCTION TC%	REDUCTION LDLC%
Pollak (1953)	12.3+3.2d	4	5	22.4	
	15.2+2.6d	10	7	27	
	12.4+1.3d	12	10	31.7	
Pollak & Kritchevsky (1981)					
reviewed 52 studies	27+4 wk	17+3	13+1.1	20+1.5	
7 studies	38.6+24 wk		16.1+2.7	16	
1 study	180 wk	16	15-18	18.2+2.4	
18 studies	27.3 wk	22	15	12.8+1.4	
Best et al (1956)	6 wk	9	5-6	6.7-20	
Joyner & Kuo (1955)	4 wk	8	6-15	18.2+4.5	
Best & Duncan (1954)	12.2 mo	24	18-25	15	
Farquhar et al (1956)	10.1 wk	15	12-18	19.5	
Farquhar & Sokolow (1958)	8 wk	15	18	15.5	20.2
Les & Lees (1976)	280 d	7	15	14.4	-
Beveridge et al (1964)	16 d	171	0.9-2.3	8	-
Lees et al (1977)	56-441 d	9.31	3.0	7-12	-
Mattson et al (1982)	1 mo	9	1g (single)	-	-
Vanhanen & Miettinen (1992)	9 wk	9	0.7	6 (NS)	
Miettinen & Vanhanen (1994)	9 wk	7-8	0.7	5 (NS)	6 (NS)
Pelletier et al (1995)	4 wk	12	0.74	10	16

SAFETY STUDIES PLANT STEROLS: CONCLUSIONS

- No evidence of genotoxicity

- Absorption is very low

- No toxicity seen in 13 week rat feeding study
  - NOAEL of 6.6g plant sterol ester/kg body weight/day

- No effect on reproductive system including oestrogenicity

- No indication of adverse effects in a large number of human studies

- Standard risk assessment
  - NOAEL = 3900mg/kg BW/day;
  - ADI* = 130mg/kg BW/day

$$ADI = NOAEL \div SF$$

* An appropriate safety factor of 30 (rather than default of 100) was established (based on lack of toxicity, human data, Renwick (1991) approach)

CASE STUDIES: BRAHMI IN TEA

Brahmi (*Bacopa monnieri*)

- Traditionally used in Ayurveda as a tea
- Key components are saponin glycosides linked to enhanced cognitive performance

Risk assessment – defining History of safe Use

History of Use - Exposure

- **Origin of ingredient**
- **Specification**
  - **Finger print analysis**
- **Preparation/ processing**
- **Population exposed**
- **No of people exposed**
- **Duration of exposure**
- **Pattern of use**
- **Bioavailability**

**Evidence of Concern - Hazard**

- **Toxicology data**
  - **High Concern: Reproductive or developmental toxicity, mutagenicity, organ toxicity, carcinogenicity**
- **Biological effects/mechanism of action**
- **Evidence of adverse effects in man (literature review or existing clinical data)**

→ Unilever has developed a HoSU scoring tool

Neely *et al* (2011). A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use. Tox. Int. 18 S20-9

Fingerprint analysis
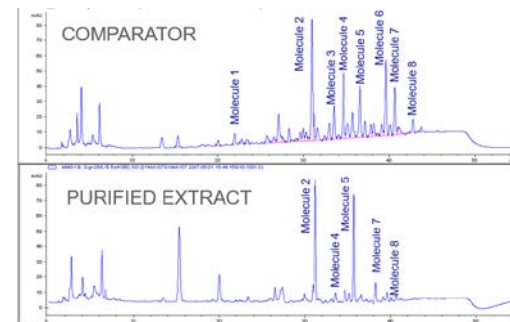
CASE STUDIES: CHIA SEEDS

Chia seeds: ingredient in bread (5%), source of ω-3 FA's

- *Salvia hispanica* L
- Pre-Columbian civilisations
- Roast, ground – porridge/drink
- Insufficient 'history of safe use' in modern society
- Incomplete information on:
  - Composition/ bioavailability
  - Storage/processing
  - Possible allergen cross-reactivity?
  - Anti-nutritional/toxicity?

- Additional clarification required
- EFSA concluded that there is no reason to consider this novel food ingredient nutritionally disadvantageous to the consumer
- Now widely used in Europe

END

CASE STUDIES: NONI JUICE

EU Novel Food assessment (EU SCF, 2002)

- Origin – Polynesia, SE Asia
- Marketed in US and elsewhere

Safety assessment

- History of safe use
  - A few case studies of hepatitis
- Additional information provided:
  - Absence of anthroquinones
  - Sub-chronic rat toxicity studies
  - Genotoxicity
  - Allergenicity
- Acceptable at observed intake (30ml)
  - No convincing evidence for a causal relationship between acute hepatitis observed in the case studies and the consumption of noni juice

SPARES

2. Hazard characterisation

Threshold Effects
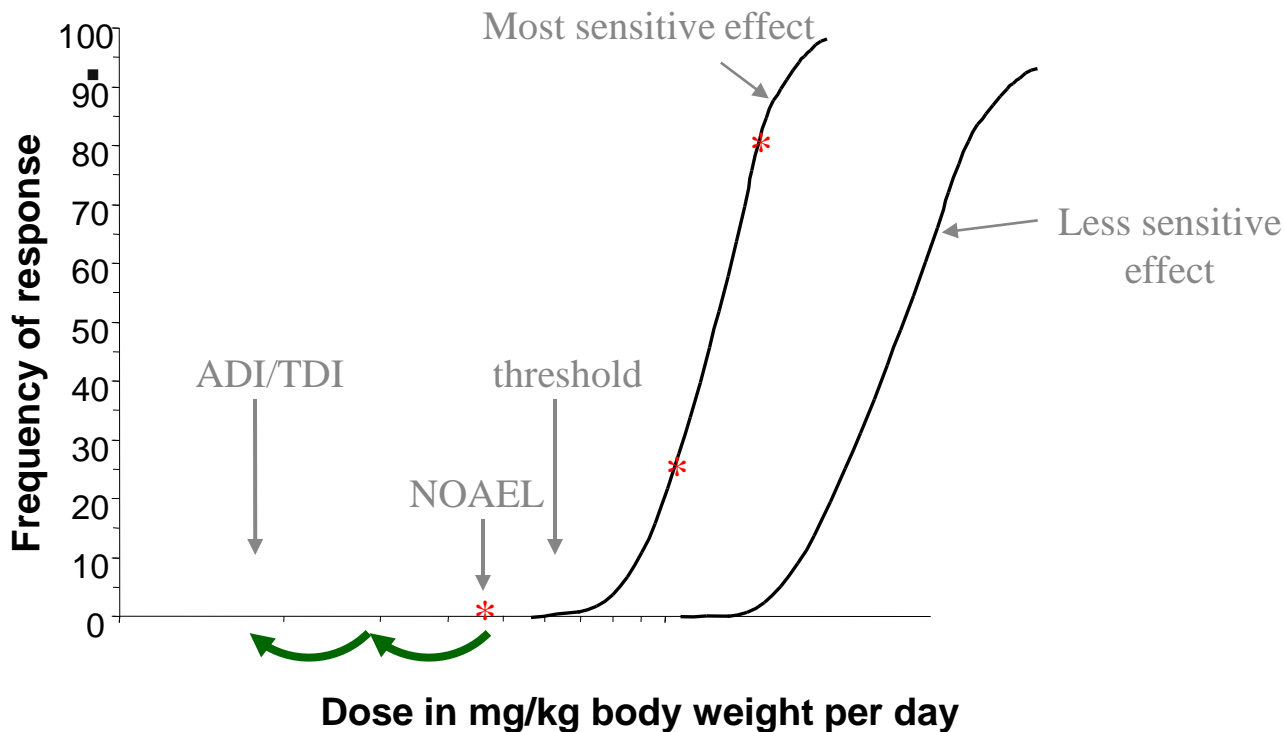
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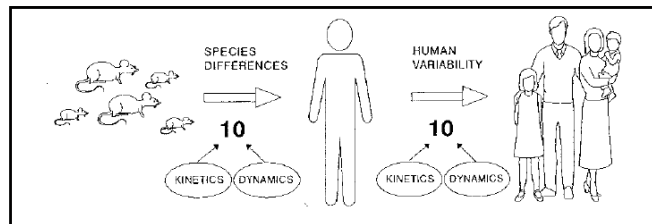
Non-threshold Effects

- Classic example is the <u>potential to cause cancer through the direct binding to DNA</u>

- **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

4. Risk characterisation

Margin of Safety (MoS) for Food Safety

- MOS =   NOAEL/Exposure

- MOS for ingredient or contaminant in food where the effect is
  <u>thresholded</u> should be > 100;

  Made up of 2 factors of 10 x 10

  - Additional data (eg history of safe use) can reduce the factors

- Margin of Exposure (MOE) for ingredient or contaminant in food
  where the effect is <u>not thresholded</u> should be > 10,000

EFSA
Margin of Exposure Approach

Susan Barlow
EFSA Scientific Committee