

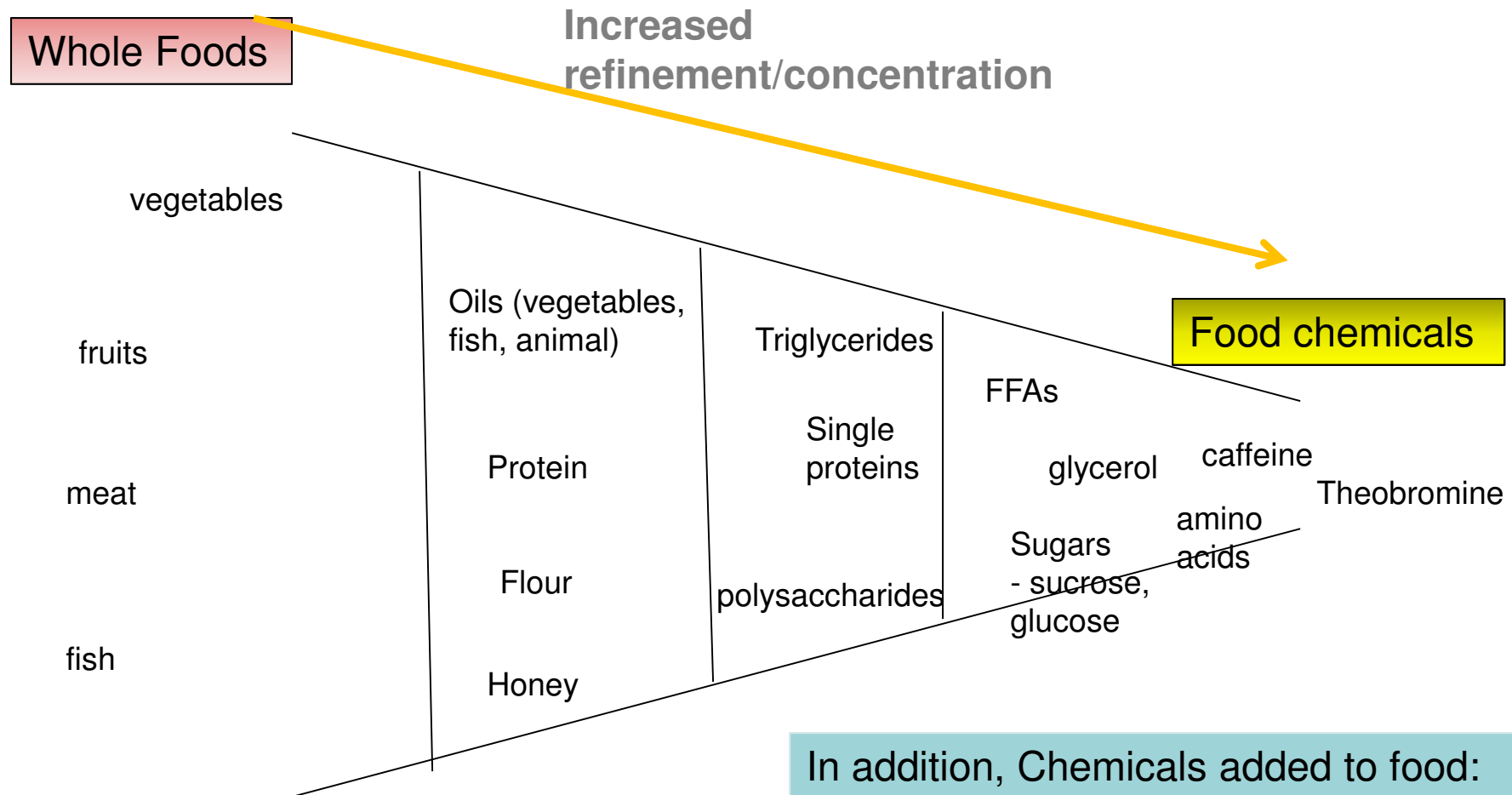


Risk Assessment Approaches for Food Safety

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Sept 2012



What is Food – from a toxicologists perspective?



In addition, Chemicals added to food:

- Intentionally
- Unintentionally (contaminants)

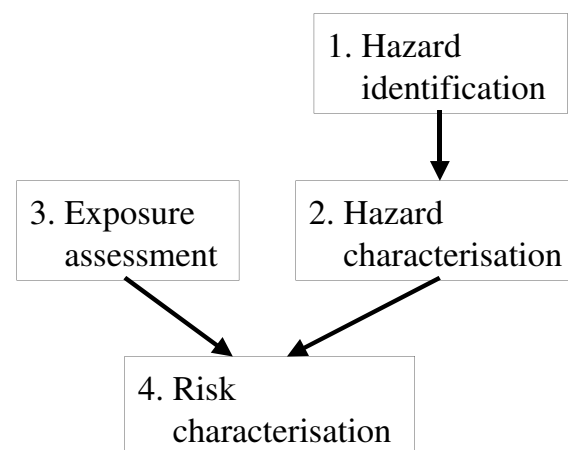
Food Safety Assessment Principles

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

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

- 4 step risk assessment paradigm

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



- Food safety testing is 'case by case' and where practical uses a traditional comparator

Approach to Food Safety Assessment



Safety assessment approach should be to assess either:

- 1) Individual chemicals/simple mixtures, or**
- 2) Whole food/ complex mixture**

Approach needs to be considered on a case by case basis.

Understand what is the safety question to address?

eg

- New type/strain of vegetable
 - Do we understand what the chemical differences are?
- New food additive/ functional ingredient

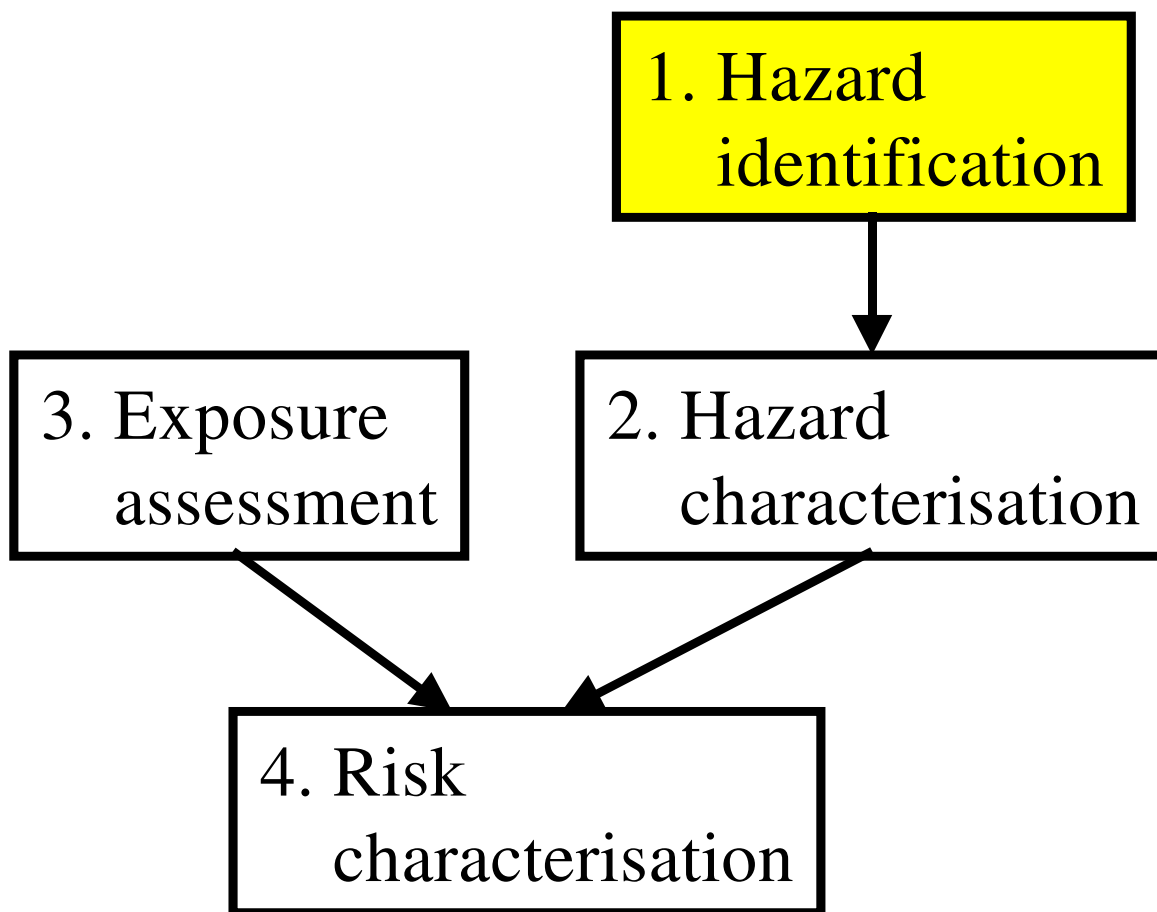
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How do you Demonstrate the Safety of a Single Chemical or Ingredient?



Hazard Identification:

- what is known about the chemical?

- Information from the supplier
- 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.

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

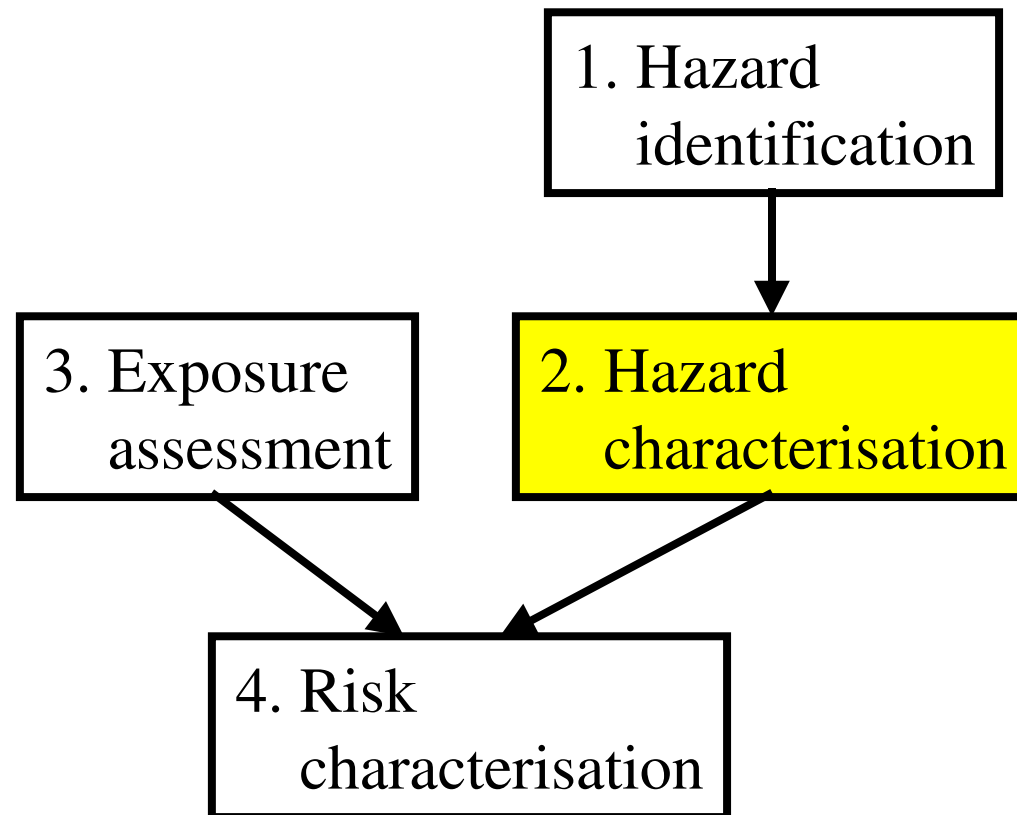
Hazard Identification:

- types of toxicology studies



- Acute
- Sub-chronic
- Chronic
- Carcinogenicity
- Genotoxicity
- Teratogenicity
- Reproductive toxicology
- Absorption, distribution, metabolism & excretion

Hazard Characterisation

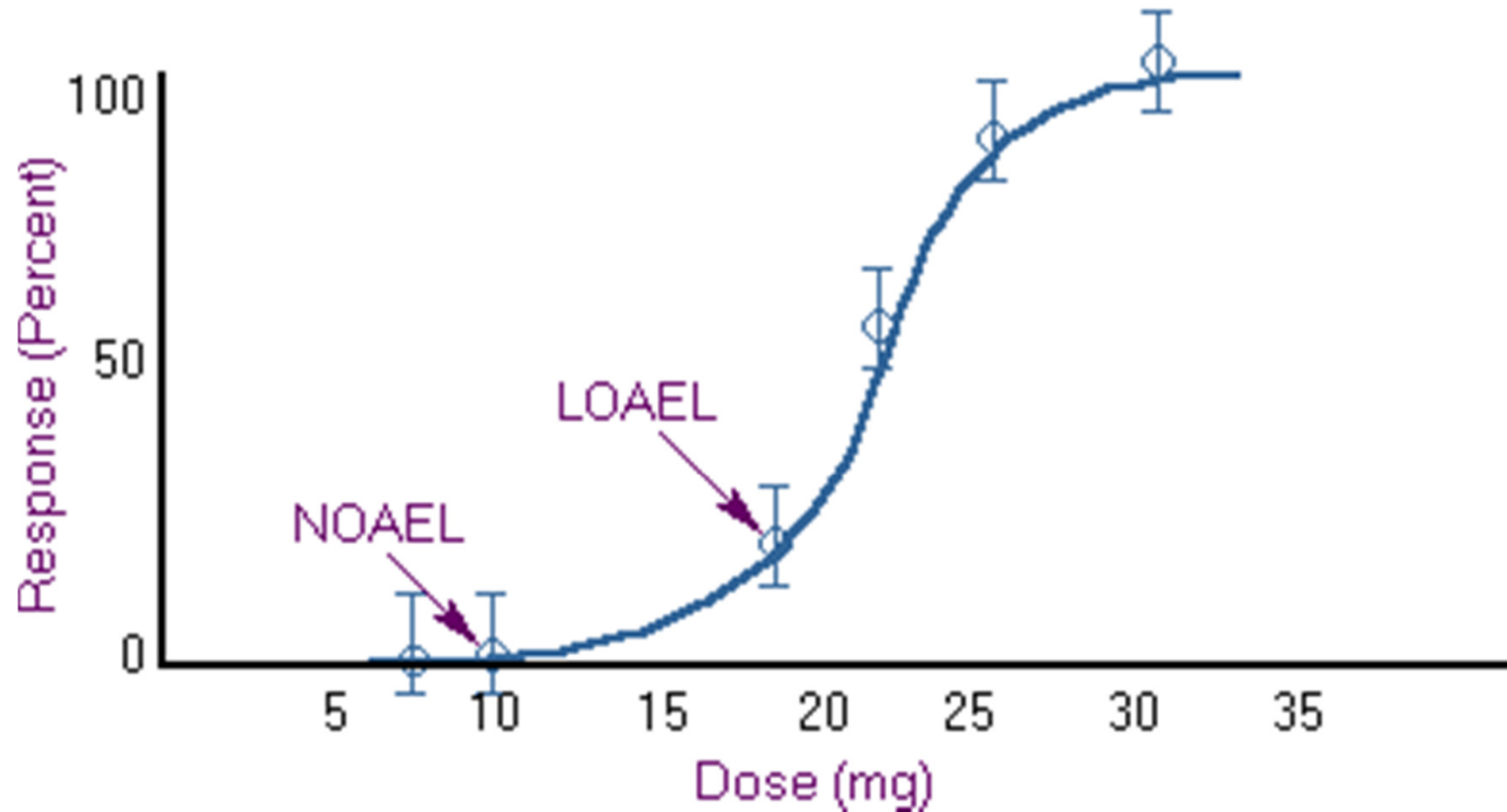


Hazard Characterisation:

What is the safe dose/intake of chemical?

- Need to identify the critical effect or endpoint in the safety data package
 - Effect should be relevant for man
 - Observed at the lowest dose level in the data-set
- No observed adverse effects level (NOAEL)
 - Dose that produced no adverse effects in the study.
 - Identifying the critical effect in the most sensitive species

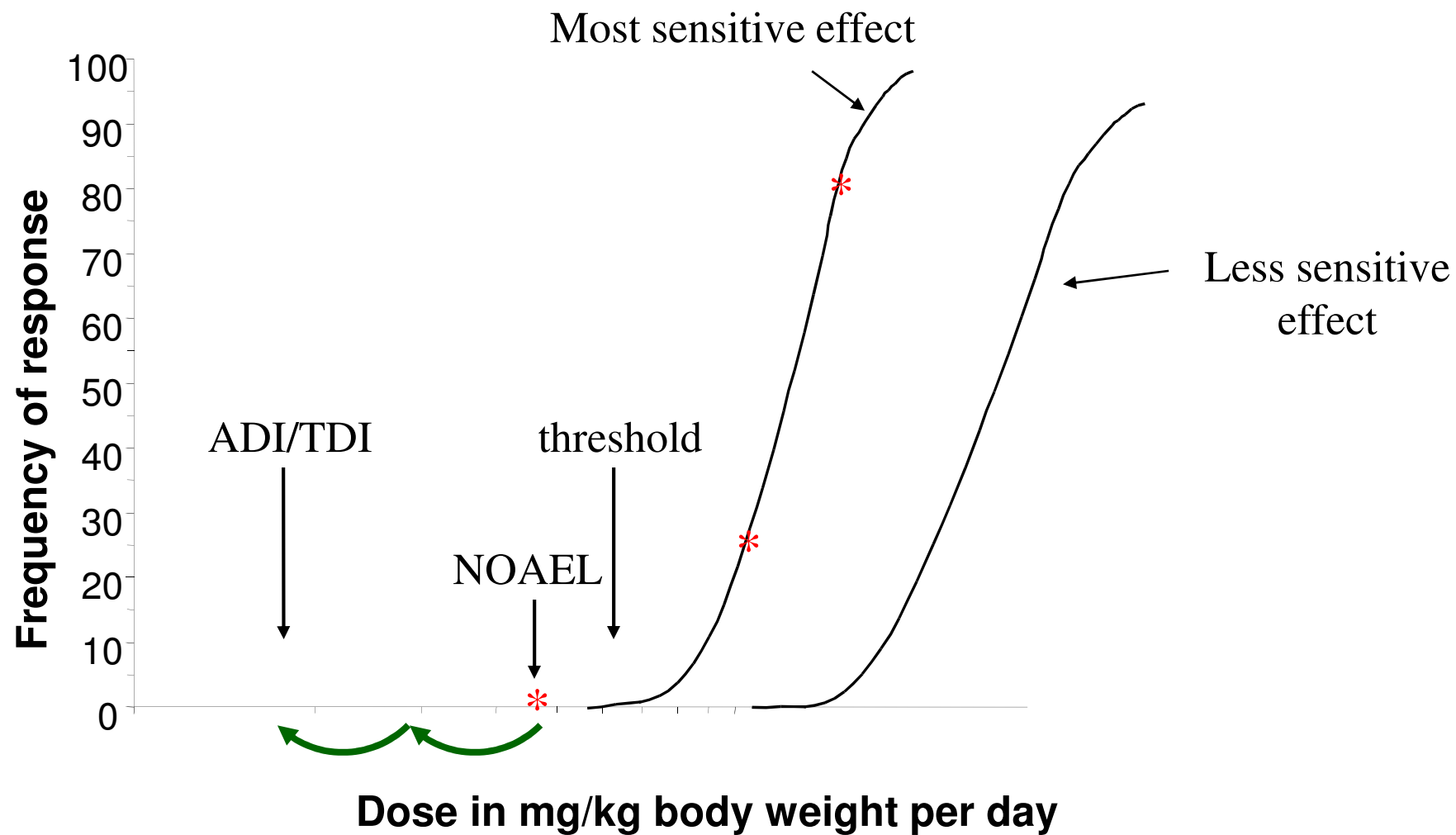
Hazard Characterisation: NOAEL/LOAEL



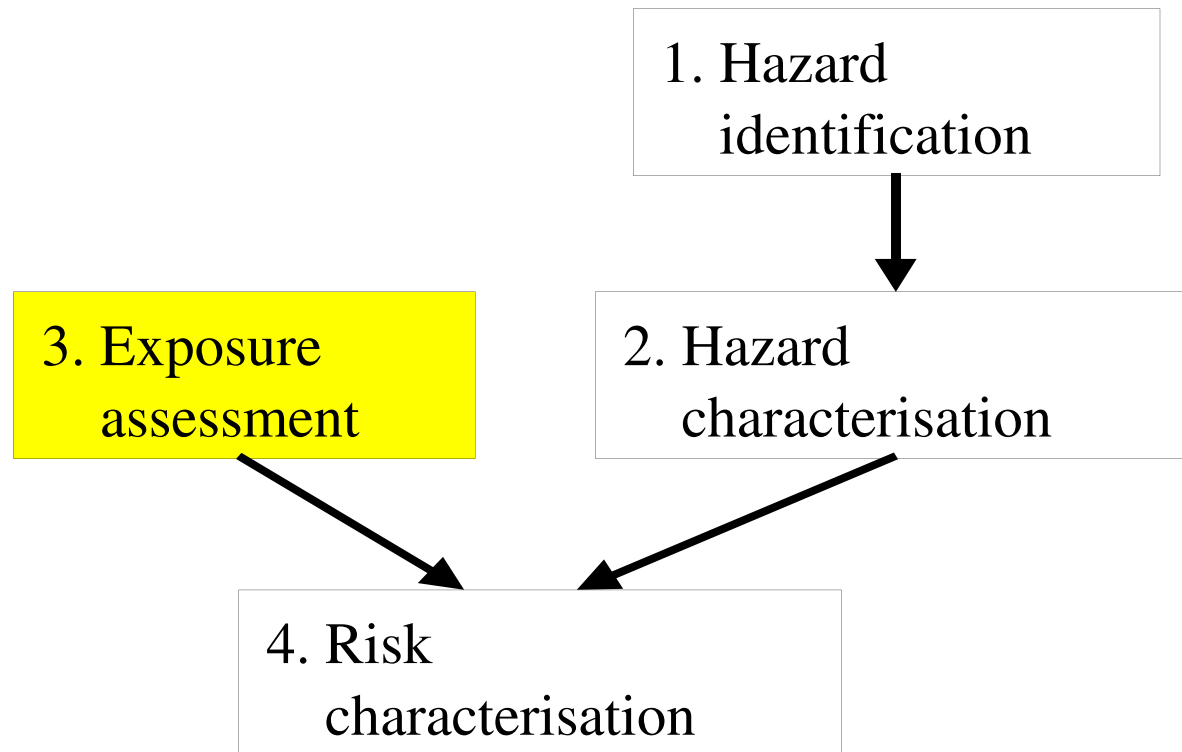
NOAEL: Highest data point at which there was not an observed adverse effect.

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

Hazard Characterisation: Threshold effects



Exposure Assessment

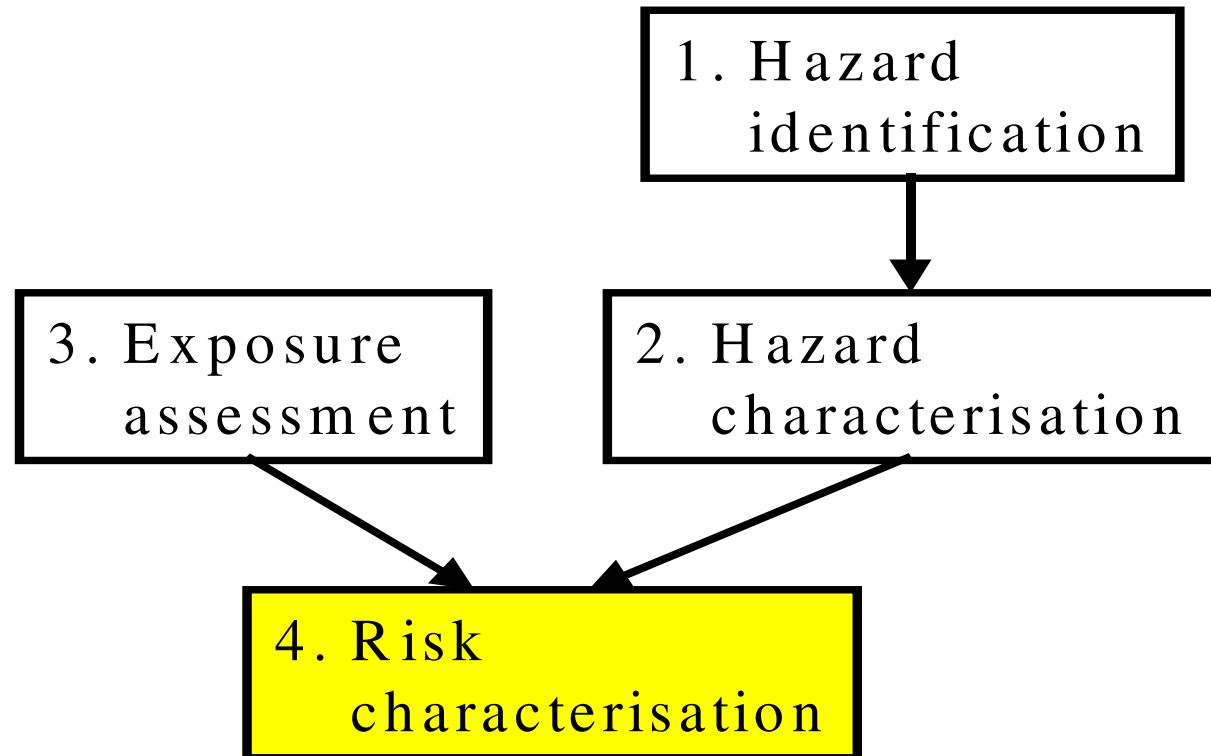


Exposure Assessment



- How much of a chemical are consumers exposed to when they consume a particular food product e.g. Tea?
 - 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 covered in survey e.g. shot drinks
 - Product types may be "rolled up" to broad categories e.g. ice tea within tea category
- Assessment approaches
 - Deterministic – single point, usually worst case e.g. 95th percentile intake for food consumption & highest level of addition
 - Probabilistic - Models intake across the full distribution of intakes. Usually used when considering intake from multiple food sources eg Creme software

Risk Characterisation



Is the chemical safe for consumers at level present in food?

- What is the ADI (mg/kg bw/day) or TDI (for contaminants)?
- What is the intake of chemical?
 - Will typically look at high consumer of food product (95th/97.5th percentile on the intake curve)
- Is intake < ADI/TDI ?
 - If yes no safety concerns
- What if intake > ADI/TDI?
 - Occasional excursions above ADI/TDI unlikely to pose safety concern since it is based on lifetime exposure
 - Exception – chemicals that are acutely toxic e.g. pesticides. Acute Reference Dose used in risk assessment
 - Prolonged intake above ADI/TDI is undesirable

Risk Assessment Approaches for Non-Threshold Effects



- **For some chemicals in food no safe dose can be identified**
 - Typically contaminants
 - Chemicals that are genotoxic carcinogens i.e. cause cancer by damaging DNA
- **ALARA principle**
 - Levels should be As Low As Reasonably Achievable
 - Risk management measures employed to consider what can realistically be done to reduce exposure
- **Margin of Exposure**
 - New approach entering into risk assessment area
 - Utilises data from toxicology studies in different way
 - It is the difference (margin) between the dose humans are exposed to and the dose causing low level effects in tox study
 - For genotoxic carcinogen MOE should be $\geq 10,000$ (EFSA)

MOE/MOS for Food Safety

- margin of exposure/ margin of safety

- MOE or MOS = NOAEL/Exposure
- MOE/MOS for ingredient or contaminant in food where the effect is thresholded should be > 100 (can be lower with history of exposure)
 - Made up of 2 factors of 10 x 10
 - Interspecies (animal to man) variation in toxicokinetics (4) and toxicodynamics (2.5), $4 \times 2.5 = 10$
 - Intraspecies (human) variation in toxicokinetics (3.2) and toxicodynamics (3.2), $3.2 \times 3.2 = 10$
- MOE for ingredient or contaminant in food where the effect is not thresholded should be > 10,000
(BMDL₁₀ used for genotoxic carcinogens)

Approach to Food Safety Assessment



Safety assessment approach should be to assess either:

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- 2) Whole food/ complex mixture**

Whole foods:

- Macro components of the diet
- Often complex mixtures
- Toxicological testing is more difficult (to conduct as well as to interpret!)

Substantial Equivalence



- Concept is used to determine whether a new food shares similar health and nutritional characteristics with an existing, familiar food with an established history of safe use.
- Is the starting point in the safety evaluation rather than an end-point
- Allows the safety evaluation to focus on where there are differences
 - Eg glyphosate tolerant maize, only difference is 5-EPSP gene/protein
 - Toxicity/ allergenicity focus on EPSP protein
- Recognises that existing foods often contain anti-nutrients that can be consumed safely eg potatoes (solanine) and tomatoes (α -tomatine alkaloids)

What is a Novel Food?



- Recognised in legislation in EU, Australia/New Zealand, Canada

European Union (EU Novel Food Regulation 258/97)

- Approval required if not used for human consumption in the EU community before 15 May 1997 **and** fall into the following categories:
 - new or intentionally modified primary molecular structure;
 - consisting of, or isolated from, micro-organisms, fungi or algae;
 - consisting of, or isolated from plants, or food ingredients isolated from animals **except** for those obtained by traditional propagating or breeding practices, and having a **history of safe food use**; or
 - has been applied a production process not currently used, resulting in significant changes in the composition/structure which affect their nutritional value, metabolism or level of undesirable substances
- If substantially equivalent to existing foods with a **history of safe use**, then a simplified notification procedure can be used

Safety Assessment of (Novel)Foods:

Case by case considerations (1 of 3)

- 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 substantial equivalence 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

Safety Assessment of (Novel)Foods:

Case by case considerations (2 of 3)

- 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....

Safety Assessment of (Novel)Foods:

Case by case considerations (3 of 3)

- Risk Assessment – more case by case

Risk = function (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
 - greater need to carry out human studies

Additional Risk Assessment Tools



- History of Safe Use (HoSU)
- Threshold of Toxicological Concern (TTC)
- Post Launch Monitoring (PLM) or Post Market Monitoring (PMM)

History of Safe Use

- traditional foods



- Not subjected to standard toxicological tests to establish Acceptable Daily Intakes
- Foods are complex and may contain hazardous materials, e.g. toxicants, anti-nutritionals, pharmacologically actives, contaminants
- Foods prepared and used in traditional ways considered to be safe for the consuming population on basis of long-term human experience
 - Level of safety regarded as “acceptable” by the consumer

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

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

Note: May require intensive research and/or the generation of data

History of Safe Use

- Noni juice

- Species: *Morinda citrifolia* L
- Origin: Polynesia, S.E. Asia
- Marketed in US and elsewhere
- No untoward reactions noted
- Additional info provided:
 - Absence of anthroquinones
 - Toxicity studies (sub-acute, sub-chronic)
 - Genotoxicity
 - Allergenicity
- Acceptable at observed intake (30 ml)



EU Scientific Committee for Food (2002)



History of Safe Use

- 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 info on:
 - Composition/ bioavailability
 - Storage/processing
 - Possible allergen cross-reactivity?
 - Anti-nutritional/toxicity?
- Additional clarification required



European Food safety Authority (2005)

Threshold of Toxicological Concern (TTC)

- Threshold of exposure for chemicals of known structure, below which there is no appreciable risk to human health
- Rulis (1986) Threshold of Regulation - based on carcinogenic risk
 - Following earlier work of Frawley (1967) and Cramer et al (1978)
 - Probabilistic assessment of potency of known carcinogens
- FDA (1995) ToR adopted for indirect food additives
 - Set at 0.5ppb in the diet (\equiv to 1.5ug/person/day assuming consumption of 1.5kg food & 1.5kg drink/day)
- Adapted by Munro et al (1996, 1999), Kroes et al (2000, 2004)
- Foods
 - JECFA (1997) – adopt approach to establish safety of flavouring substances
 - ILSI Europe* endorse use of TTC for low level food contaminants/ingredients
- Pharma
 - EMEA (2004), Muller (2006) – genotoxic impurities;
- Cosmetics
 - Colipa (2006) - expert group looking at TTC for cosmetic ingredients

* ILSI Europe Concise Monograph Series (2005). Threshold of Toxicological Concern (TTC).

Threshold of Toxicological Concern (TTC)

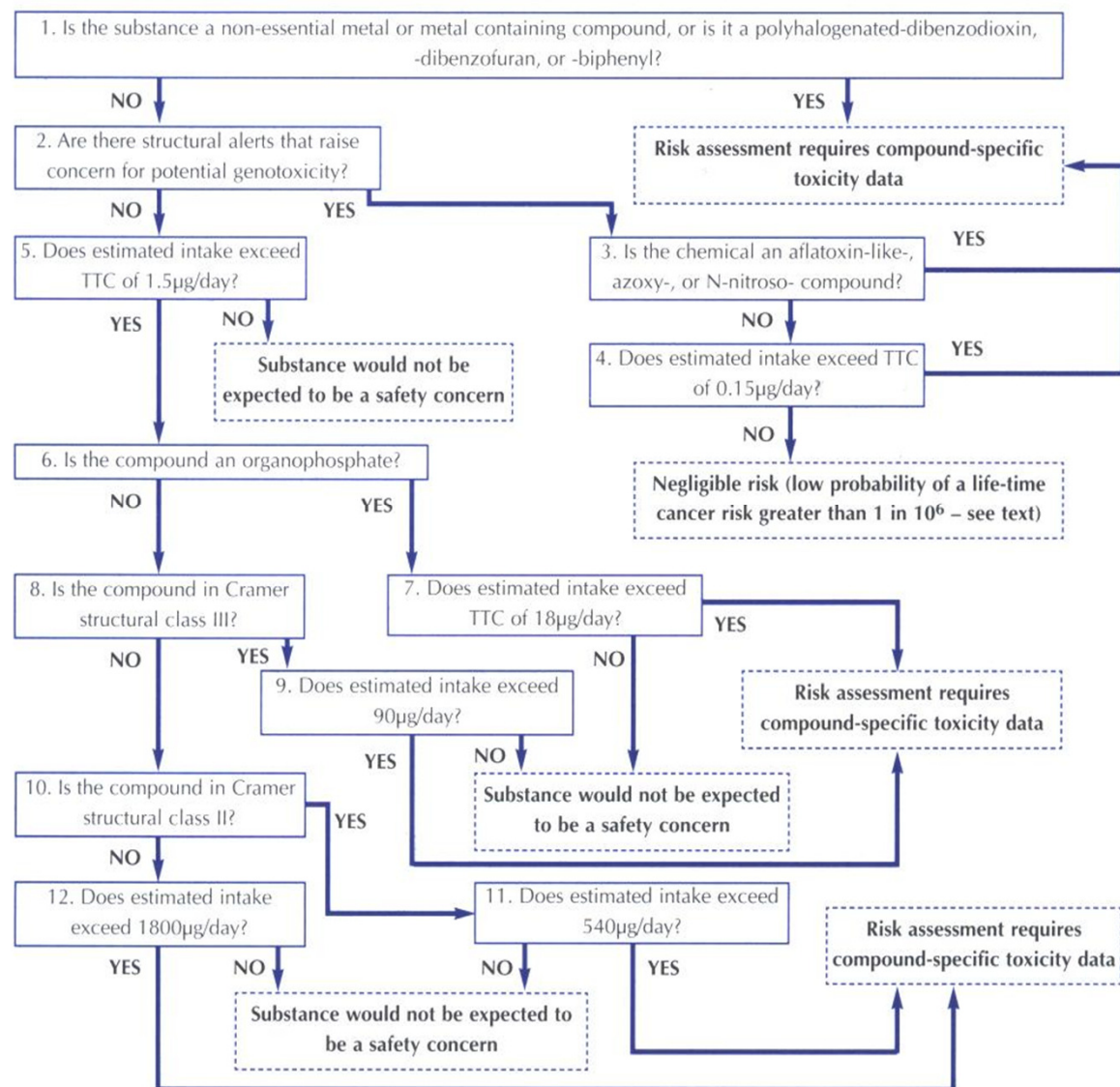
- Chemicals ranked on the basis of their toxicity

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 i.e genotoxic (aflatoxin-like, azoxy- and nitroso- compounds) and non genotoxic (TCDD and steroids)
 - Neurotoxicants
 - Allergenicity
 - Accumulation eg dioxins, heavy metals
 - Endocrine disruption

Kroes et al. (2004) TTC Decision Tree

Decision tree proposed by ILSI Europe to decide whether substances can be assessed by the TTC approach
(From Kroes *et al.*, *Food and Chemical Toxicology* 42, p76, 2004)



Post Launch Monitoring



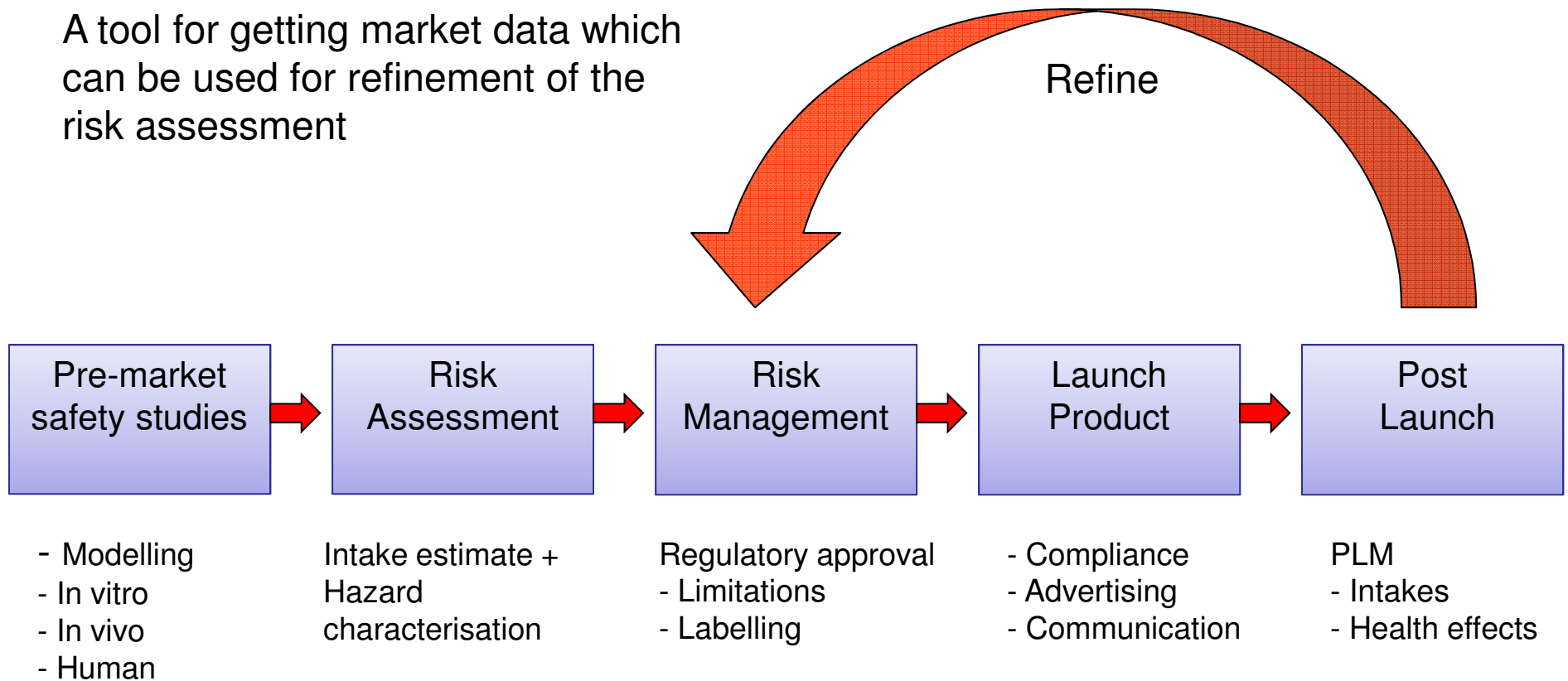
Definition: A hypothesis driven, scientific methodology for obtaining information through investigations relevant to the safety of a (novel) food after market launch (ILSI, 2008).

A tool for:

- Confirming that the **product use** is as **predicted** on the pre-market assessment
- Provide reassurance that **effects observed** in the pre-market assessment occur with **no greater** frequency or intensity in the post market phase than anticipated
- Investigate the **significance** of any **adverse effects** reported by **consumers** after market launch

Post Launch Monitoring: a complement to risk assessment

A tool for getting market data which can be used for refinement of the risk assessment



Post Launch Monitoring

- possible criteria to trigger PLM



Intake

- If EDI is close to ADI – monitor real consumption patterns
- Original application for one product; further applications leading to different exposure patterns
- Product intended for use in foods for certain populations

Health

- Possible (side-) effects identified in pre-market
- Reassurance of no adverse effects – but need a reasoned hypothesis, system to collect signals
- If significant number of complaints received?
- If new issues highlighted – further research?

EDI – estimated daily intake

Concept of Post Launch Monitoring (PLM)



- No mandatory regulatory requirement; but has been recognised by some regulatory agencies.....
- ‘PLM should, where appropriate, be performed for foods derived from genetically modified sources, specifically where there is no traditional comparator available’. (EFSA, 2004, 2006)
- PLM data ‘will provide additional reassurance regarding long term safety of products, as well as their impact on the food supply’. (FSANZ, 2005)
- Condition for approval of phytosterol esters in fat spreads in EU
‘Establish a surveillance programme accompanying the marketing of the product..... In order to estimate the extent to which the product is reaching its target group, And to estimate exposures to phytosterols from this source in other population groups....’.
(Committee Decision 2000/500/EC)

Summary – Risk Assessment Approaches

- Risk based assessment
 - Risk = f (Hazard x Exposure)
- Hazard identification
 - Published studies
 - Identification of critical effect & NOAEL
- Exposure
 - Dietary surveys
 - Assessment approaches – deterministic (worst case), probabilistic
- Risk characterisation – is chemical safe
 - Acceptable daily intake (ADI)
 - Margin of safety (MoS)
 - Non-thresholded effects
 - As Low as Reasonably Achievable (ALARA)
 - Margin of Exposure (MoE) (genotoxic carcinogen $\geq 10\,000$)
- Whole Foods
 - Substantial equivalence
 - Case by case considerations
- Additional risk assessment tools
 - History of Safe Use (HoSU)
 - Post Launch Monitoring (PLM)
 - Threshold of Toxicological Concern (TTC)