



# SAFETY EVALUATION OF FOODS: NEW APPROACHES & NGRA\*

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Unilever  
UK

\*Next Generation Risk Assessment

# SAFETY & ENVIRONMENTAL ASSURANCE CENTRE (SEAC)



PROTECTING CONSUMERS, WORKERS & OUR ENVIRONMENT BY ENSURING UNILEVER'S PRODUCTS & PROCESSES ARE SAFE & SUSTAINABLE BY DESIGN

CENTRE OF EXCELLENCE – SAFETY &  
ENVIRONMENTAL SUSTAINABILITY SCIENCES

## APPLYING SCIENCE



### GOVERNANCE

We provide scientific evidence to manage safety risks & environmental impacts for new technologies

## ADVANCING SCIENCE



### NEW CAPABILITY

We harness the latest science to create new tools to assess innovations of the future

## SHARING SCIENCE



### COLLABORATION

We partner with leading scientists from around the globe

# UNILEVER'S SAFETY GOVERNANCE



We use scientific evidence-based risk and impact assessment methodologies to ensure that the risks / impacts of adverse human health and/or environmental effects from exposure to chemicals used in our products, processes & packaging are **acceptably low**.



## THE CODE OF BUSINESS PRINCIPLES



**Innovation**  
In our scientific innovation to meet consumer needs we will respect the concerns of our consumers and of society.  
We will work on the basis of sound science, applying rigorous standards of product safety.

**Competition**  
Unilever believes in vigorous yet fair competition and supports the development of appropriate competition laws. Unilever companies and employees will conduct their operations in accordance with the principles of fair competition and all applicable regulations.

**The Environment**  
Unilever is committed to making continuous improvements in the management of our environmental impact and to the longer-term goal of developing a sustainable business.

**Bribery & Corruption**  
Unilever does not give or receive

Unilever accounting records and supporting documents must accurately describe and reflect the nature of underlying transactions. No und or unrecorded account, fund or will be established or maintain

**Conflicts of Interests**  
All employees and others working for Unilever are expected to avoid personal activities and financial interests could conflict with their responsibilities to the company.  
Employees must not seek gain for themselves or others through or of their positions.

**Compliance - Monitoring - Reporting**  
Compliance with these principles is an essential element in our business

Code of Business Principles and Code Policies  
ENGAGING EXTERNALLY

## RESPONSIBLE INNOVATION



Unilever has global standards that apply to all research and innovation, including on: the safe and sustainable design of new products, processes and packaging; product and brand development; open innovation collaborations; and publication of our scientific research.

### Musts

All employees involved in scientific research and innovation activity **must** comply with all standards relevant to their area of work, notably in order to:

- Ensure that risks for consumer safety, occupational safety and the environment are suitably assessed and managed;
- Ensure appropriate specifications of raw materials, products and packaging;
- Ensure effective management of consumer safety risks from

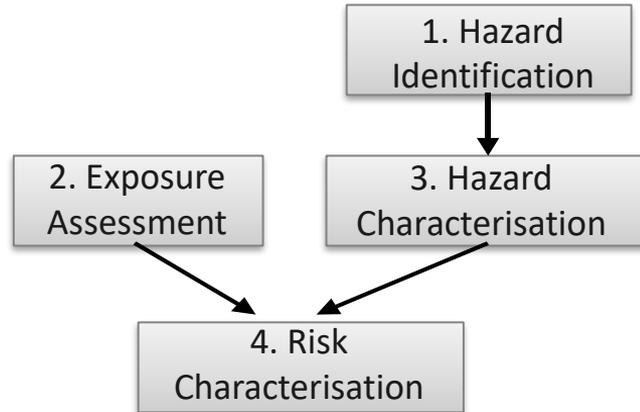
Innovation is fundamental to Unilever's business success and a core part of our global strategy. The integrity and objectivity of our Science are a key foundation for our approach to responsible innovation. Safety is non-negotiable.

# RISK ASSESSMENT PRINCIPLES

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

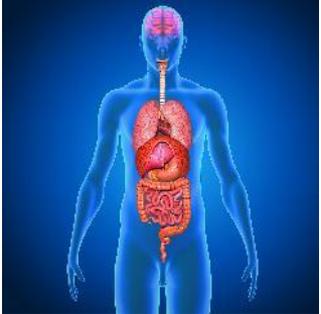
Toxicological Hazard

- Acute toxicity
- Allergy (type I)
- Systemic toxicity
  - sub-chronic
  - chronic
- Reproductive toxicology
- Teratogenicity
- Genotoxicity
- Carcinogenicity

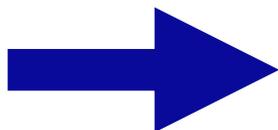


Exposure

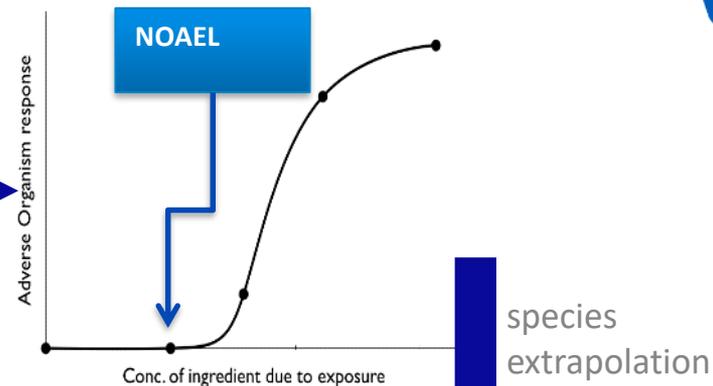
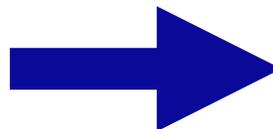
**Ingestion:**  
-Food & drink



# CONVENTIONAL RISK ASSESSMENT APPROACH



Hazard  
characterisation



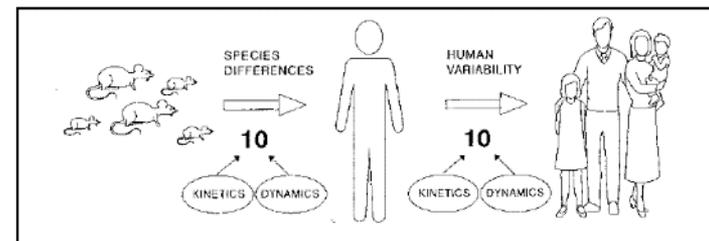
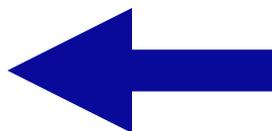
$$ADI^* = NOAEL \div 100$$

Exposure < ADI ☺

Exposure > ADI ☹

\* Acceptable Daily Intake

Safe dose  
in humans



Safety/uncertainty factors

# 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

= ≠ ≈

- Does the new food share health and nutritional characteristics with an existing, familiar food?
- Safety evaluation - focus on differences
- Recognises that existing foods often contain anti-nutrients<sup>1</sup> that can be consumed safely e.g. potatoes (solanine) and tomatoes (α-tomatine alkaloids)

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

# OTHER TOOLS IN FOOD SAFETY

## History of Safe Use



“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”

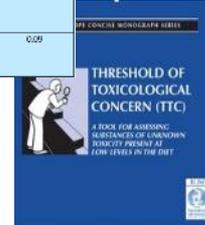
Health Canada

Safety assessment (Constable et al, 2007)

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

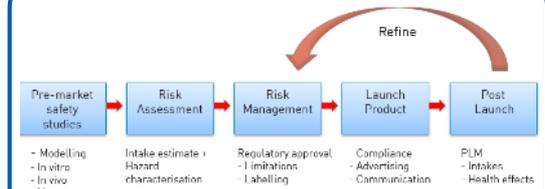
## Threshold of Toxicological Concern (TTC)

CATEGORY	DESCRIPTION	TTC (mg/bodyweight/day)
Chemical Class I	Substances with simple structures for which sufficient number of data/exposure exist to use toxicity	1.5
Chemical Class II	Substances that are less innocuous than in Class I but do not contain structural features suggestive of toxicity like those in Class III	0.04
Chemical Class III	Substances suggesting significant toxicity or containing reactive functional groups	0.01



- Threshold of exposure for chemicals of known structure below which there is no appreciable risk to health
- Based on structure chemicals are classed as low, mod, high toxicity
- Useful for chemicals present in food at low concn. e.g. contaminants
- Little or no toxicity data required
- Reliable estimate of intake possible

## Post Launch Monitoring (PLM)



- A hypothesis driven scientific approach for obtaining information through investigations relevant to the safety of a (novel) food after market launch
- Uses market data (e.g. food intakes, consumer complaints) to refine safety assessment
- A complement to safety assessment (not replacement)

# CASE STUDIES: NONI JUICE



## EU Novel Food assessment (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

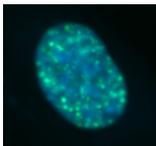
# THE WORLD IS CHANGING



Rapid advances in scientific knowledge e.g. genomics, exposure science



Huge Technological advances e.g. HTS, informatics, computational toxicology



Speed of innovation creating novel materials e.g. nano, biotechnology



Scientific value of animal studies being challenged

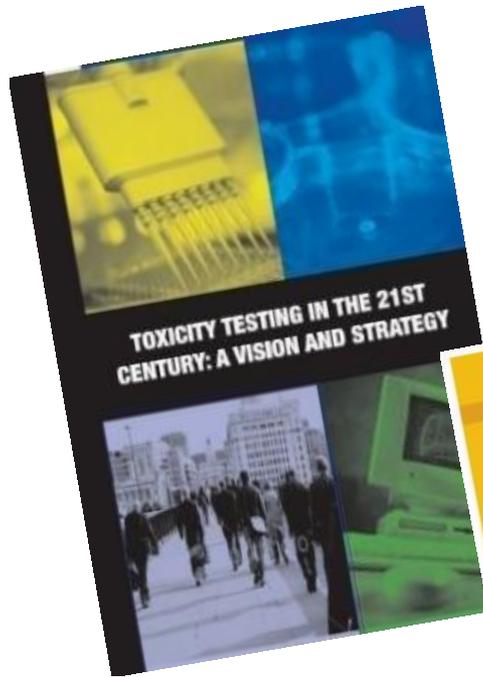


Consumer demands to stop animal testing

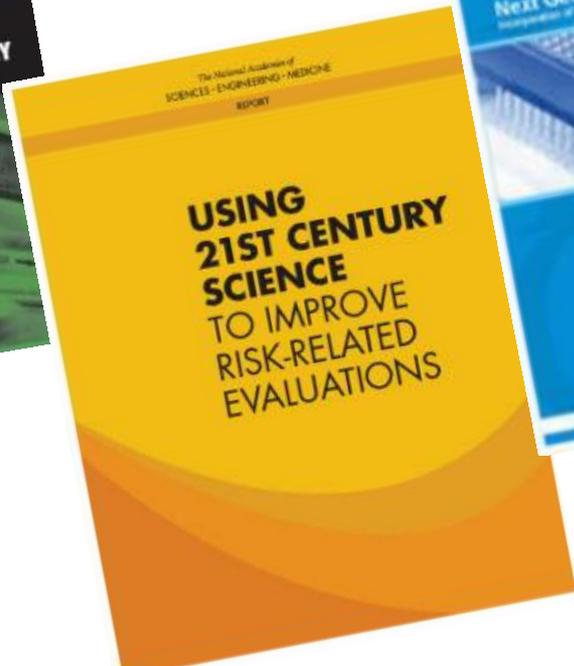


Too many chemicals – not enough animals/money/time !

# TOXICOLOGY: 21<sup>ST</sup> CENTURY SCIENCE



2007



2017



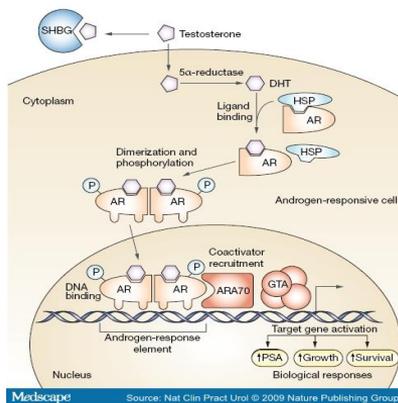
# WHAT IS NGRA? - NEXT GENERATION RISK ASSESSMENT



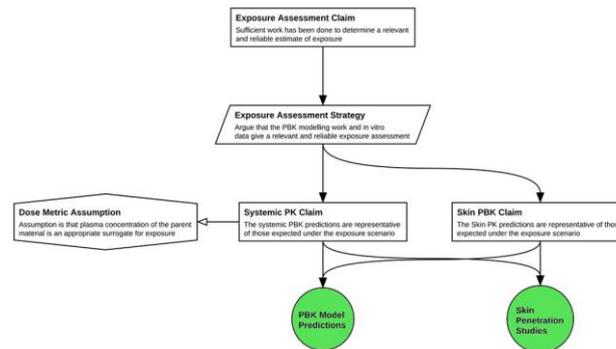
- Using new tools and approaches to build a risk assessment to enable decisions to be made (without animal tests)
- An exposure-led risk assessment solution to biological pathway-indicated hazard concerns (rather than endpoints in animals)



Exposure led

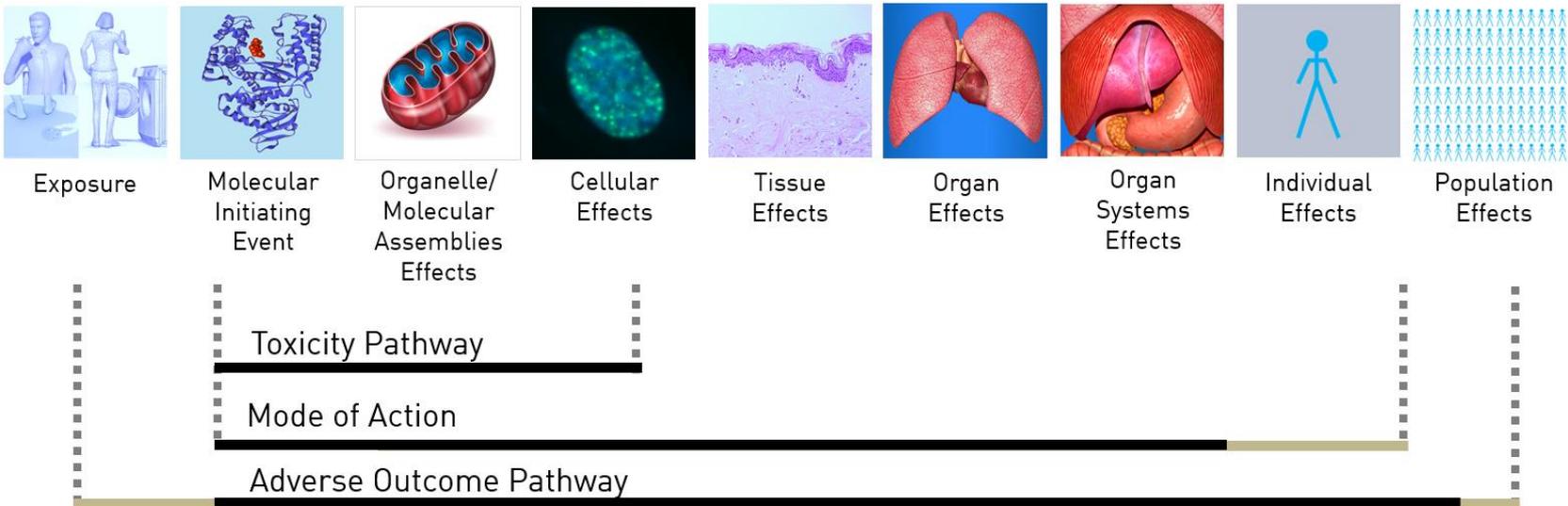


Mechanistic

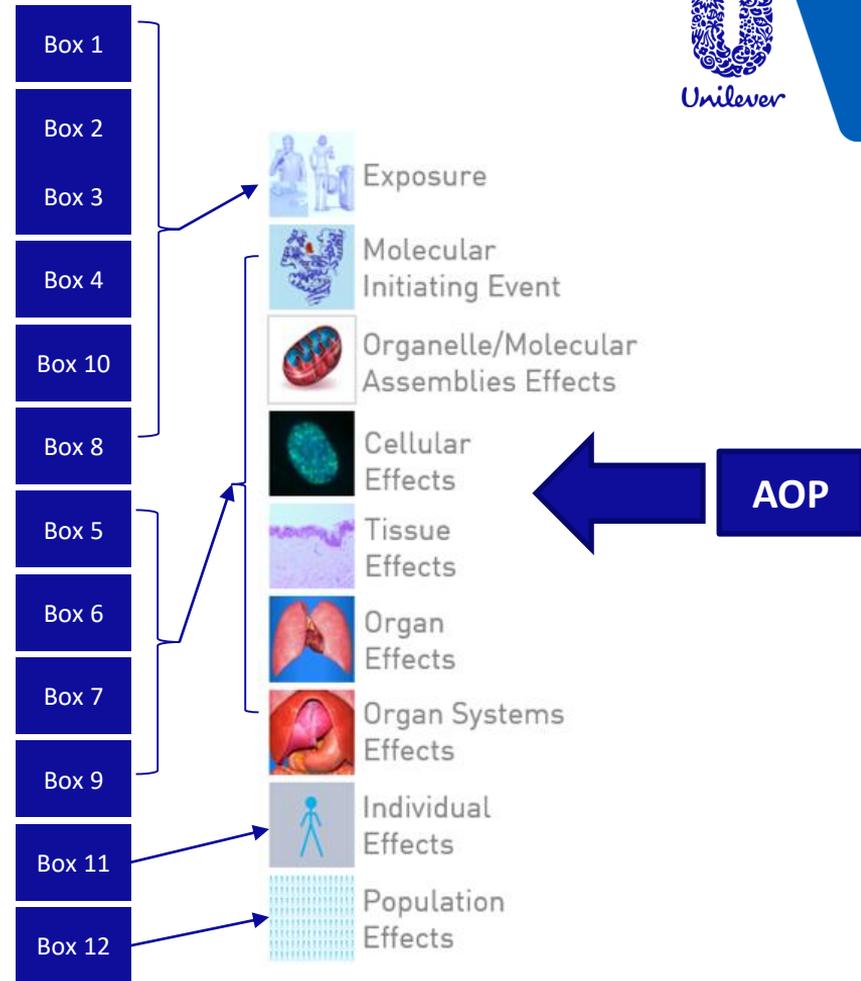
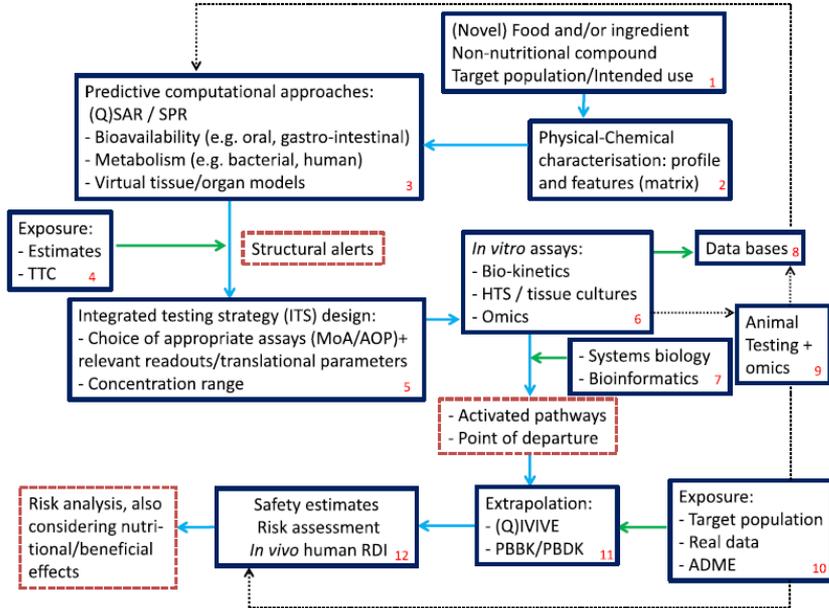


Hypothesis driven

# PATHWAYS BASED TOXICOLOGY

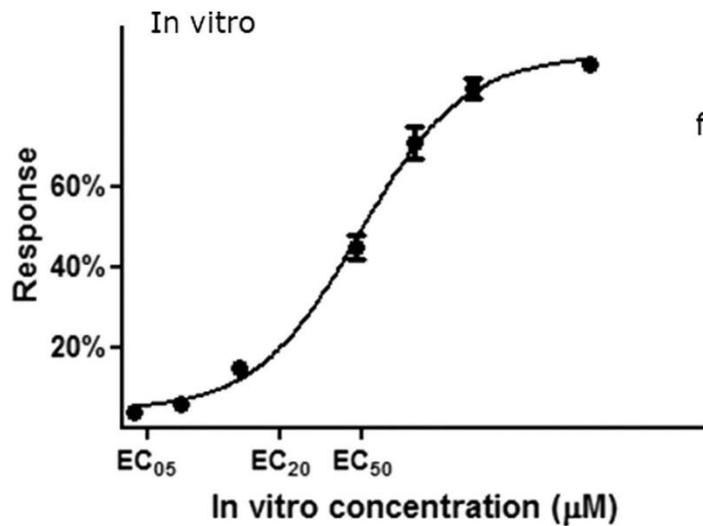


# ROADMAP FOR SAFETY ASSESSMENT OF FOOD AND INGREDIENTS

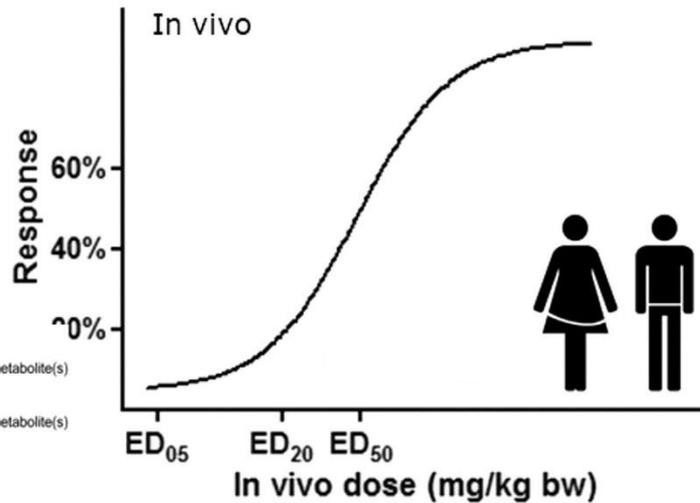
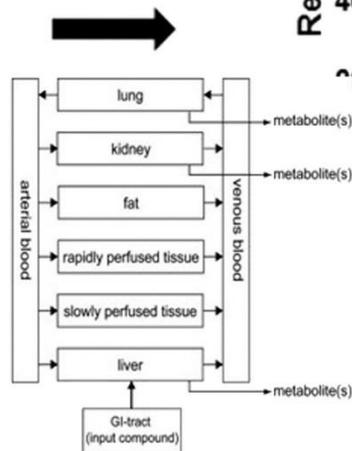


Blauboer, et al., 2016

# IN VITRO TO IN VIVO EXTRAPOLATION



PBK model  
facilitated reverse  
dosimetry



POD for risk assessment

# NON-ANIMAL APPROACHES IN NOVEL FOODS

MATERIAL	NON-ANIMAL TOOLS	ANIMAL DATA SUBMITTED	DECISION
Mung bean protein isolate	<ul style="list-style-type: none"><li>• In vitro digestibility</li><li>• Allergenicity assessments</li><li>• History of Safe Use</li></ul>	<ul style="list-style-type: none"><li>• Rat faecal digestibility</li></ul>	<ul style="list-style-type: none"><li>• US GRAS with FDA notification (2017)</li><li>• In vivo data was unnecessary for safety assessment</li></ul>
Orthosilicic acid – vanillin complex	<ul style="list-style-type: none"><li>• History of Safe Use</li><li>• In vitro genotoxicity</li></ul>	<ul style="list-style-type: none"><li>• Acute rat oral</li><li>• 90day rat oral</li></ul>	<ul style="list-style-type: none"><li>• EFSA authorised use (2017)</li><li>• Solubility issues severely limited value of in vivo studies</li></ul>
Egg membrane hydrolysate	<ul style="list-style-type: none"><li>• History of Safe Use</li><li>• In vitro genotoxicity</li><li>• In vitro allergenicity</li><li>• Human clinical</li></ul>	<ul style="list-style-type: none"><li>• Acute rat oral</li><li>• G.pig sensitisation</li></ul>	<ul style="list-style-type: none"><li>• EFSA authorised use essentially based on HoSU and nature of material (2018)</li><li>• Questionable value of in vivo studies</li></ul>

Non-animal approaches delivered greater insights for safety evaluation compared to conventional animal approaches

# 9 PRINCIPLES OF NGRA

## 4 Main overriding principles:

- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

## 3 Principles describe how a NGRA should be conducted:

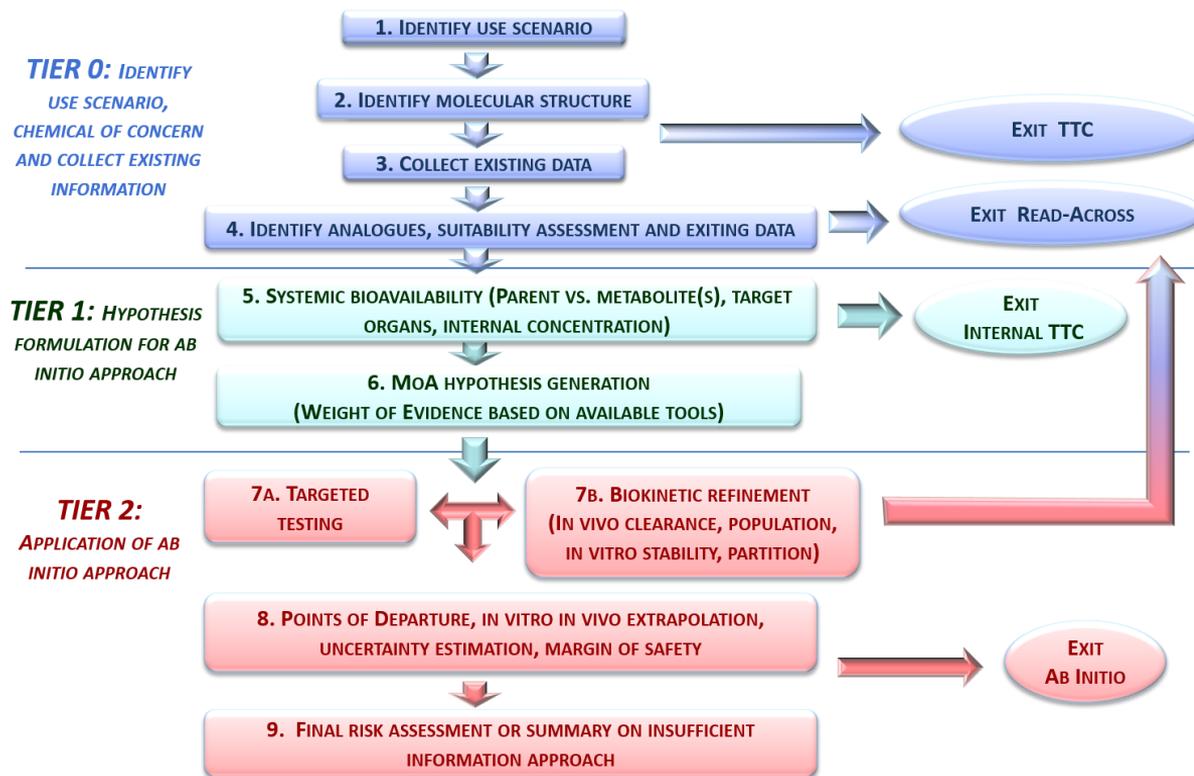
- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

## 2 Principles for documenting NGRA:

- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented

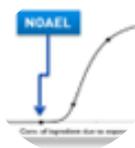


# NGRA: TIERED FRAMEWORK FOR COSMETICS



- Read across
- Exposure-based waiving
- In silico* tools
- Metabolism and metabolite identification
- Physiologically-based kinetic modelling
- In chemico* assays
- 'Omics
- Reporter gene assays
- In vitro* pharmacological profiling
- 3D culture systems
- Organ-on-chip
- Zebrafish larva assays
- Pathways modelling
- Human studies

# CHALLENGES/OPPORTUNITIES



**Research programmes** – fill the gaps in the risk assessment



**Build capability and capacity** – new scientific skills e.g. informatics and computational toxicology



**Regulatory acceptance** – new regulatory frameworks



**India**, major food producer, opportunity to build & contribute to this science

# IMPORTANT TO COLLABORATE & FORM STAKEHOLDER PARTNERSHIPS

