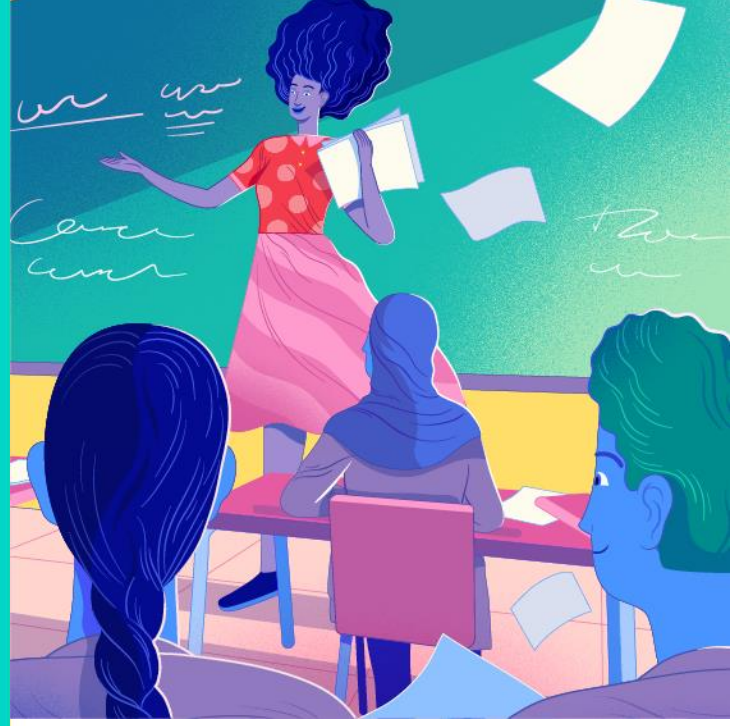
Strategy for Application of New Approach Methodologies (NAMs) in Food Safety Assessment



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Outline

- Introduction
- NGRA framework
- Methods in NGRA
- Sulforaphane case study
- Summary and discussion

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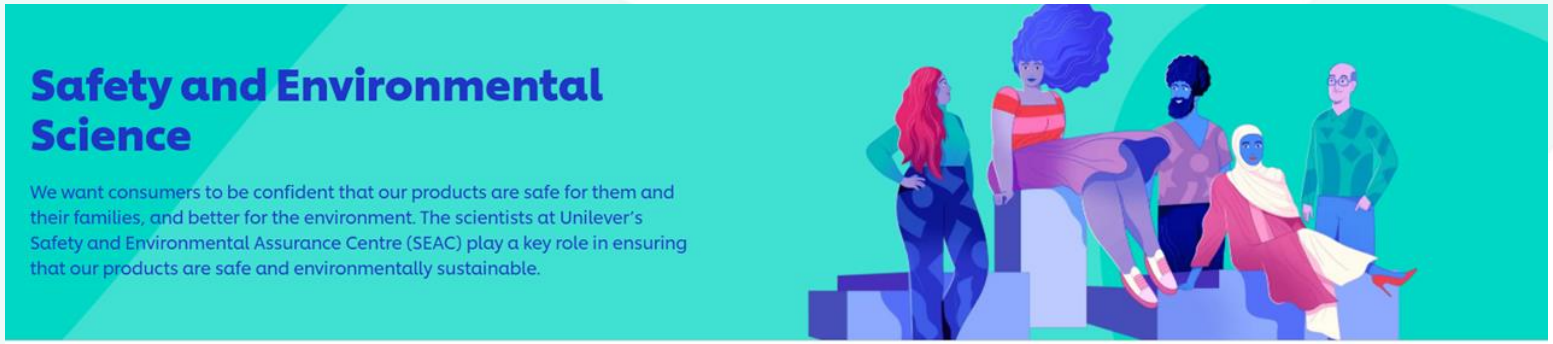
One of the world's largest consumer goods companies, with over 400 brands

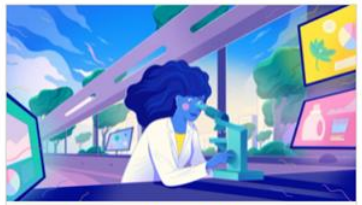
Safety & Environmental Assurance Centre (SEAC)

Ensuring Unilever's Innovations & Products are Safe & Sustainable by Design



Leading safety and environmental sustainability sciences
The scientists behind our safe and sustainable products

Safe and sustainable by design
How we build safety and sustainability into every product innovation.



Keeping people and the environment safe
The science-based approaches we use to keep our consumers, workers and the environment safe.

Reducing our environmental impact
How we harness the latest science to minimise our environmental footprint.

Unilever Product / Ingredient Safety Governance

- Provide scientific evidence to manage safety risks & environmental impacts

应用科学的证据管理安全风险和环境影响

业界领先的安全，环境以及可持续科学能力

Industry-leading Safety & Environmental Sustainability Science Capability

- Deploy expertise on higher risk business projects
- Collaborate with leading external research teams to develop & apply new capability
- Leverage our science & global networks for consumer trust & freedom to operate

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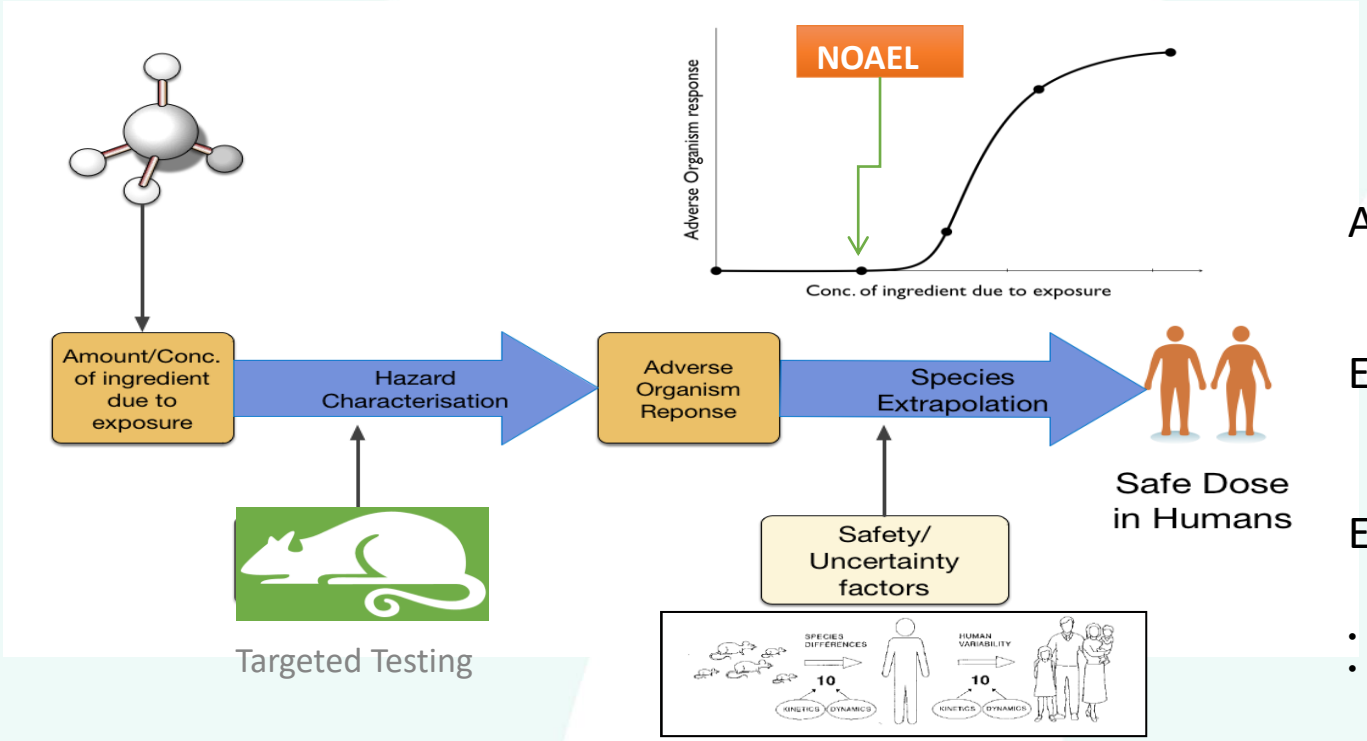
Traditional risk assessment, limitations and opportunities for NAM



ADI/TDI* = NOAEL ÷ 100

Exposure < ADI/TDI ☺

Exposure > ADI/TDI ☹

- Acceptable Daily Intake
- Tolerable Daily Intake

Limitations

- Value of animal test being challenged
- Lack of mechanistic understanding
- Consumer drive:
  - Animal welfare
  - Vegan and plant based

Opportunities

- Rapid advances in scientific knowledge e.g. exposure science, genomics
- Huge technological advances e.g. HTS, informatics, computational toxicology
- Speed of innovation creating novel materials e.g. nano, biotechnology

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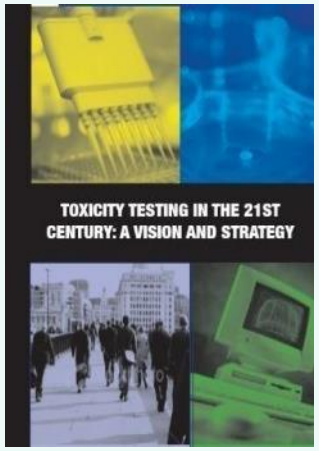
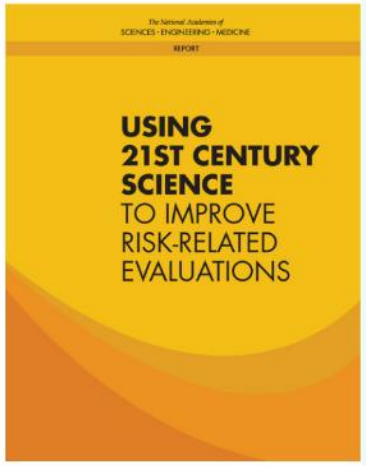
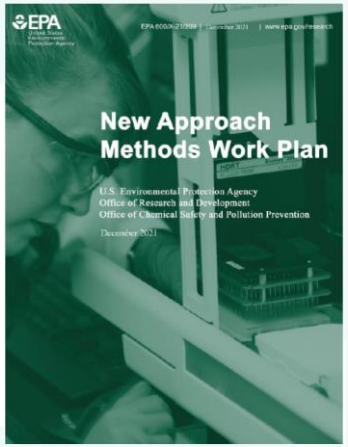
Next Generation Risk Assessment (NGRA) (下一代风险评估方法)







NGRA is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing

暴露引导，假设驱动　　整合各种新一代的方法　　不使用动物测试

我们使用科学，不是动物

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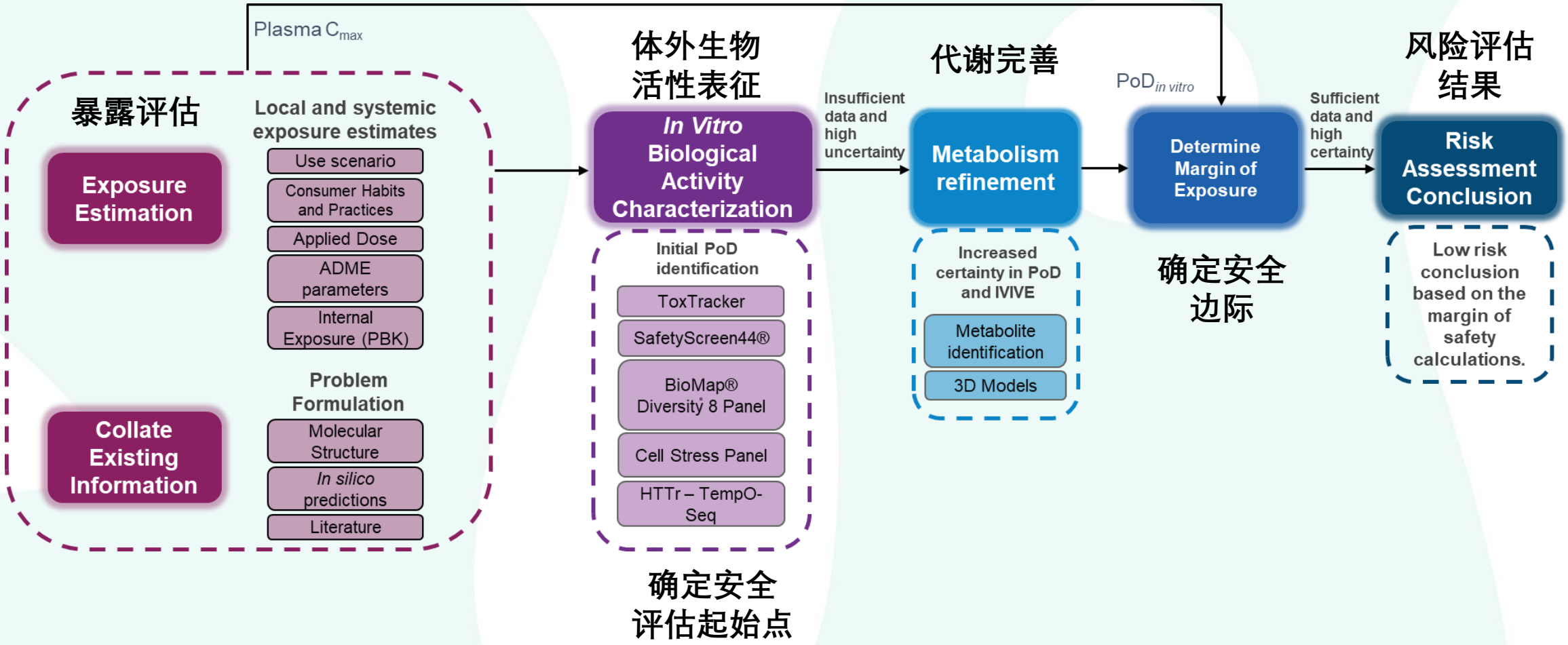
NGRA toolbox framework

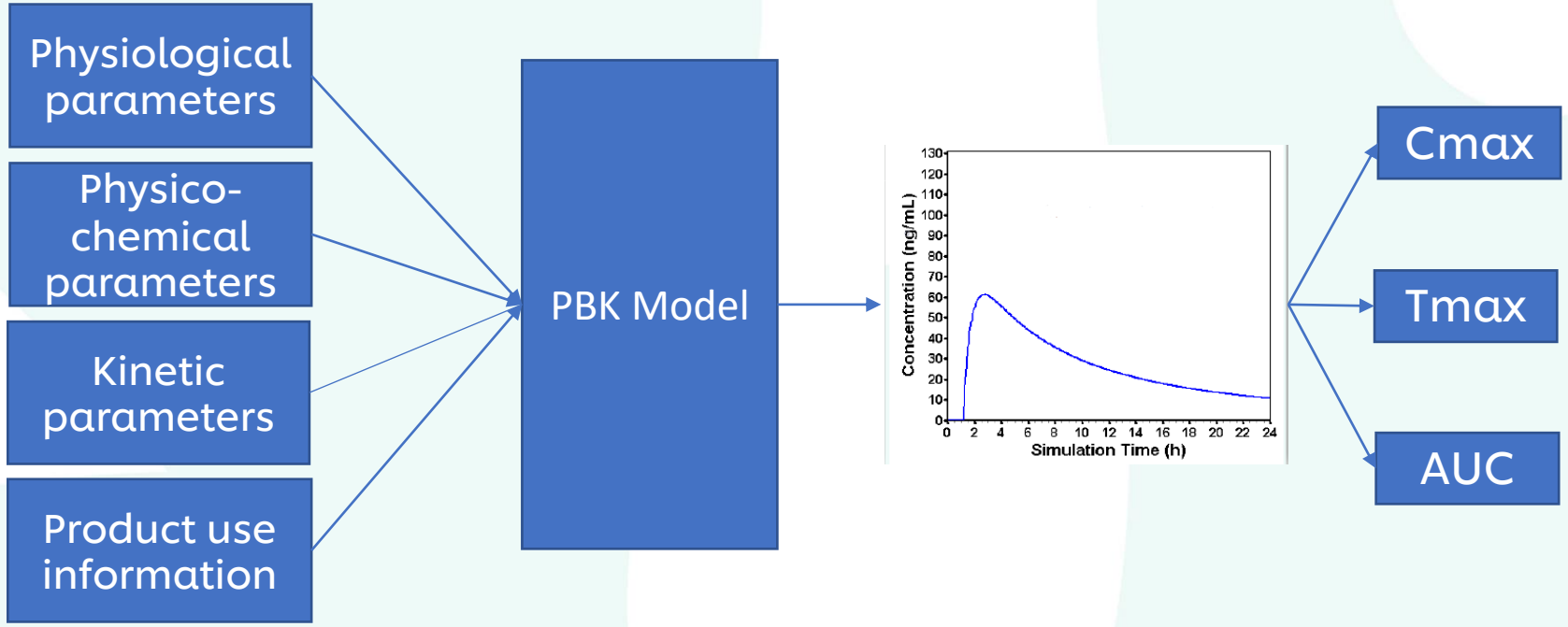


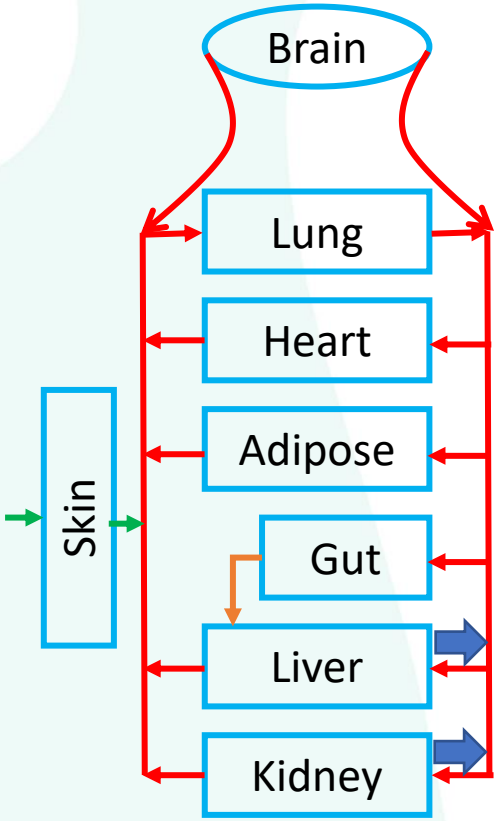
Baltazar et al., (2020) Toxicol Sci 176, 236–252

Physiologically Based Kinetic (PBK) modelling

Aim:

According to ADME properties of a certain chemical, predict its concentration in different organs/tissues in human body after exposure to the chemical via different exposure route, e.g., oral, skin and inhalation





Key challenges:

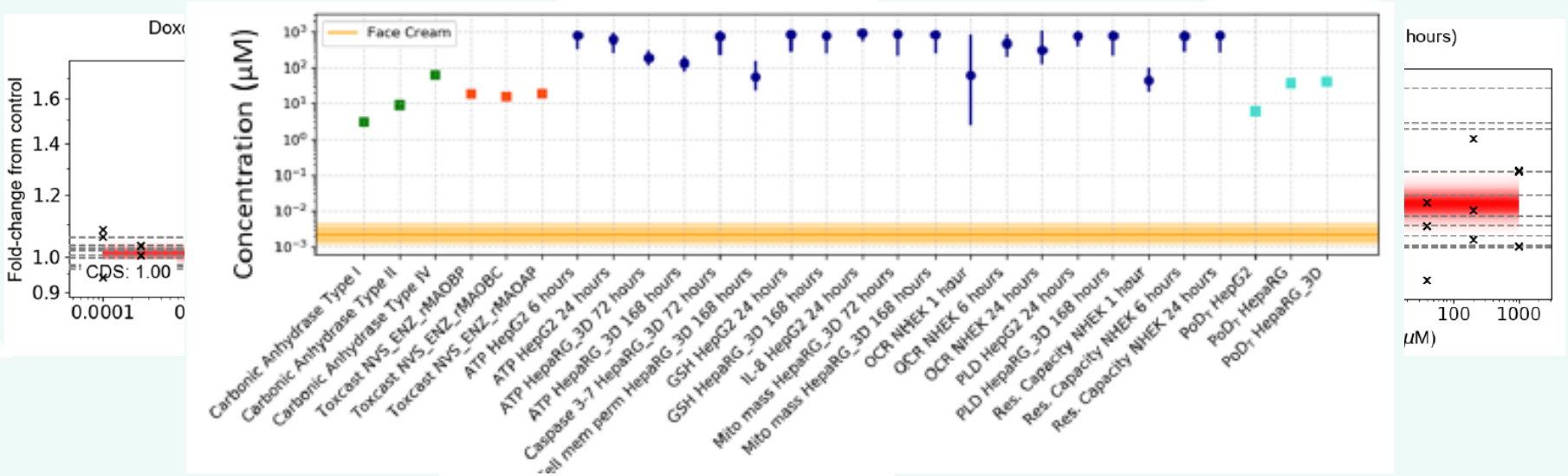
- Understanding ADME mechanism
- Parameterisation

Li *et al* (2022) *Toxicology and Applied Pharmacology*, **442**, 115992

Dose Response Modelling

Aim:

- Using the dose and response data from a certain in vitro assay to derive a Point of Departure (PoD) regarding a certain biomarker after exposure to a certain chemical.
- By combing PoDs from different assays regarding different biomarkers, the overall bioactivity of the chemical can be described, which is then compared with exposure derived from PBK modelling, so that a safety decision can be informed.



Key challenges:

- Whether there is a response?
- At what dose there is a response?
- Uncertainty

Baltazar *et al.*, (2020) *ToxicolSci***176**, 236–252

Sulforaphane (萝卜硫素) Case study – introduction

- Sulforaphane is a naturally occurring compound in cruciferous vegetables like broccoli and cabbage.
- In the food, it is in the inactive form of glucoraphanin. When vegetables are chopped or chewed, myrosinase (enzyme) is released, comes into contact with glucoraphanin, and sulforaphane is formed.
- Sulforaphane has been associated with various health benefits and may beneficially affect cancer, heart disease, diabetes, and digestion
- The aim of the case study is to find out whether a hypothetical sulforaphane food supplement with the dose of 60mg sulforaphane is safe.

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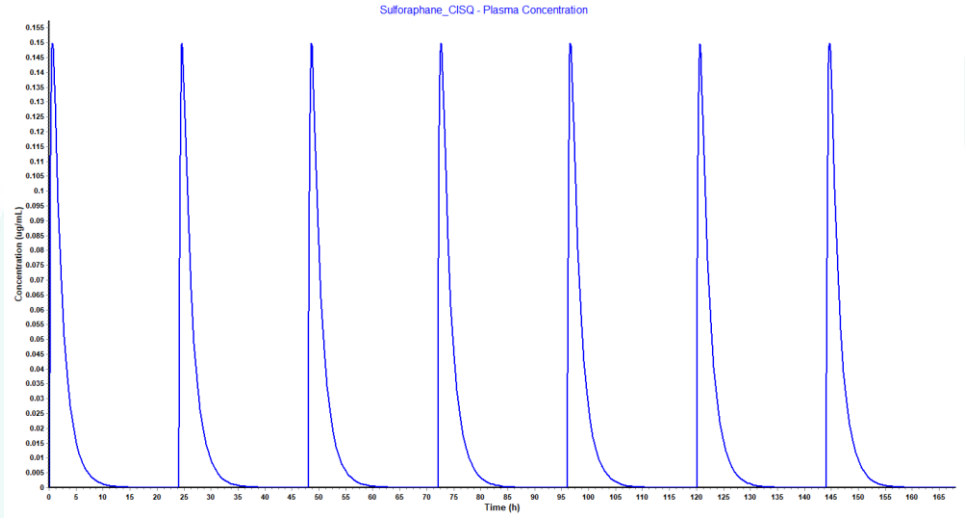
Sulforaphane case study – risk assessment

Exposure

- Assume the supplement that contains 60mg sulforaphane per tablet is taken once per day
- A PBK model is built to estimate the corresponding plasma concentration
- Most parameters needed for PBK are based on in silico predictions, except fup* and Papp*, which are based on in vitro assays
- The simulation is run over 7 days

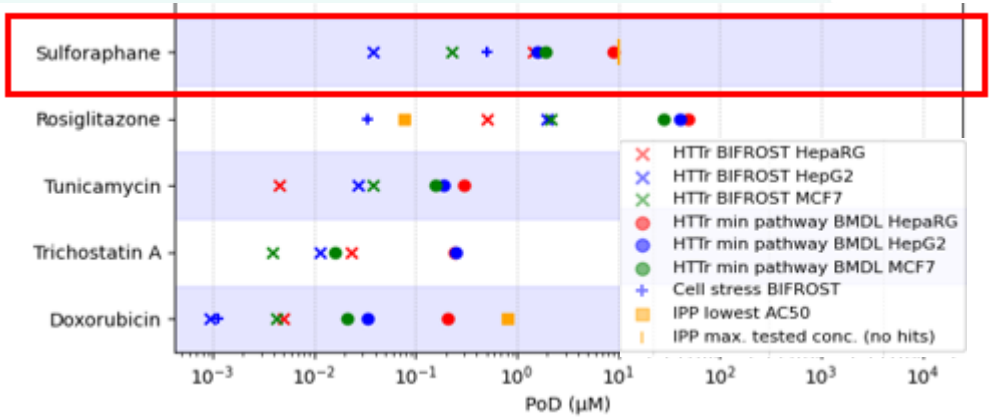


Cmax = 0.84 uM

Hazard

Estimating the various Points of Departure (PODs) based on *in vitro* bioactivity data using three of the *in vitro* bioactivity platforms

- High-throughput transcriptomics
- A cell stress panel
- *In vitro* pharmacological profiling



Lowest PoD = 0.072 uM

Conclusion

- The proposed dose could not be supported
- Next tier risk assessment is needed, such as:
  - Refining clearance in PBK model
  - Identify relevant pathways to investigate further
  - Incorporating uncertainty analysis

Fup: fraction unbound in plasma
Papp: apparent permeability coefficient in Caco-2 assay

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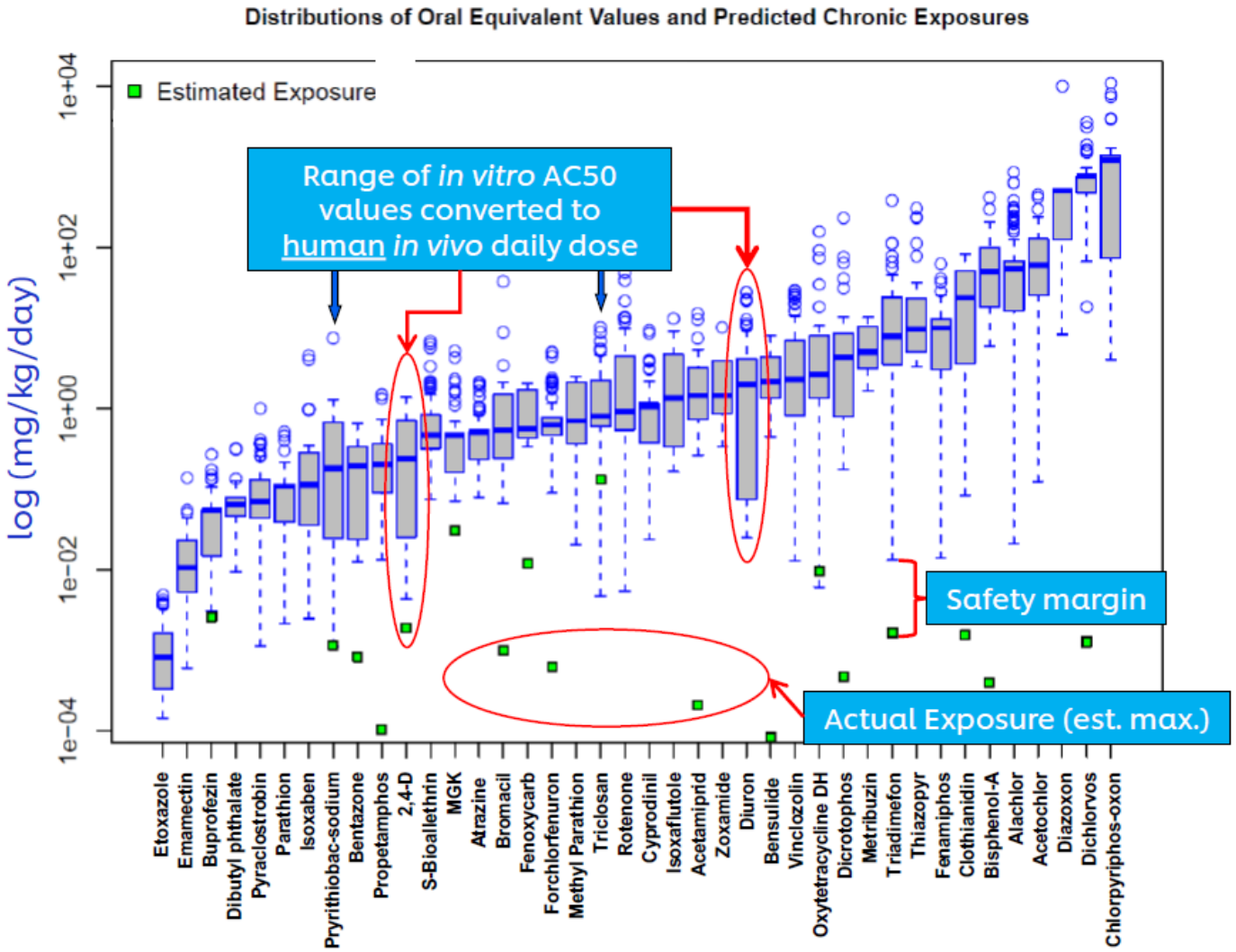
NGRA: Protection not Prediction (保护而不是预测)



The hypothesis underpinning this NGRA is that if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.

At no point does NGRA attempt to predict the results of high dose toxicology studies in animals

NGRA uses new exposure science and understanding of human biology

Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

Way forward

- Science and technology:
  - Develop mechanistic understanding of interaction between food/food ingredients and human:
    - In vitro assays (体外测试): such as cell viability, genotoxicity, complex cellular toxicity assays, etc.
    - In silico tools (计算机工具): including QSAR, Read-across and mathematical modelling to study the ADME of chemicals, such as PBPK models
    - Other technologies: such as organs-on-chips (器官芯片)
  - Weight of Evidence approach: combine different lines of evidence according to their weight
  - Uncertainty analysis

- Communication and improving acceptance
  - Reproducible and transparent in vitro assays and data analysis
  - Clear documentation of applicability domain, uncertainties and limitations
  - Multistakeholder sharing and evaluation of safety decision making using NAM approaches in food ingredients risk assessment, identifying their strength and weakness
  - Developing networks of organisations with common interests
  - Advocating, education and upskilling

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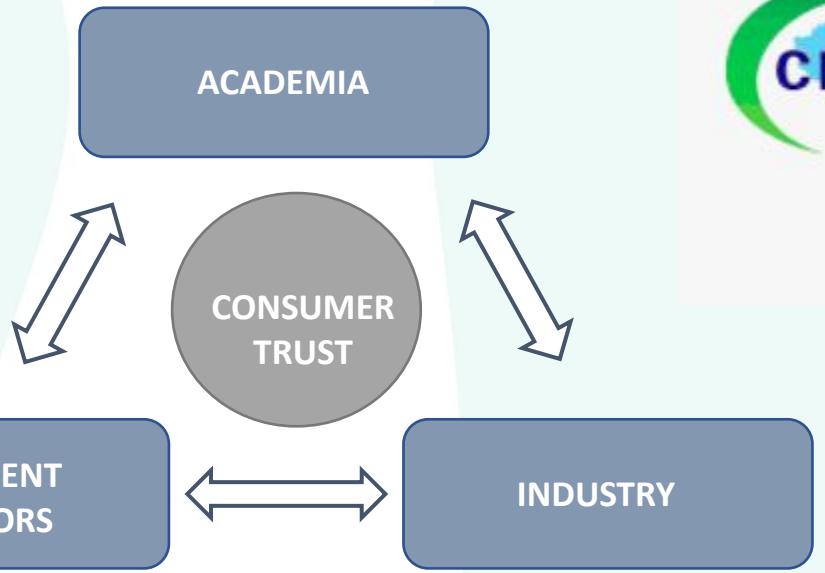
Important to collaborate and form stakeholder partnerships

ILSI

南方醫科大學 Southern Medical University

CFSA 国家食品风险评估中心



中国毒理学会 Chinese Society of Toxicology

广东省疾病预防控制中心 Guangdong Provincial Center for Disease Control and Prevention

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UCCPSCC

The Unilever China Consumer Product Safety Collaboration Center has been established at our Unilever Global R&D Center in Shanghai to partner with public and private stakeholders in China and to collaborate in key areas underpinning the safety of consumer products such as foods, personal and homecare products

Why this Centre? | Themes and Programs | Partners and Partnerships | Unilever Expert Resources | Calendar of Events | Contact and Directions

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Acknowledgement

Nora Aptula
Maja Aleksic
Maria Baltazar
Trina Barritt
Danilo Basili
Sophie Cable
Paul Carmichael
Tom Cull
Matt Dent
Ellen Edwards
Julia Fentem
Nicky Gilmour
Steve Gutsell
Sarah Hatherell
Jade Houghton
Lucy Ingram
Predrag Kukic
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