Application of computational models in Next Generation Risk Assessment activities at Unilever

Dawei Tang, Andrew White

Dawei.tang@unilever.com

Outline

- Introduction

- Computational models applied in NGRA in Unilever
  - Physiologically Based Kinetic (PBK) modelling
  - Dose Response Modelling
  - High Throughput Transcriptomics (HTTr) Dose response analysis
  - Bayesian Method
  - Expert Knowledge Elicitation

- An example

- Summary and discussion

Can we use a new ingredient safely and how do we know?

Can we safely use x% of ingredient y in product z?

NGRA is defined as an <u>exposure-led, hypothesis-driven</u> risk assessment approach that integrates <u>New Approach Methodologies (NAMs)</u> to assure safety <u>without the use of animal testing</u>
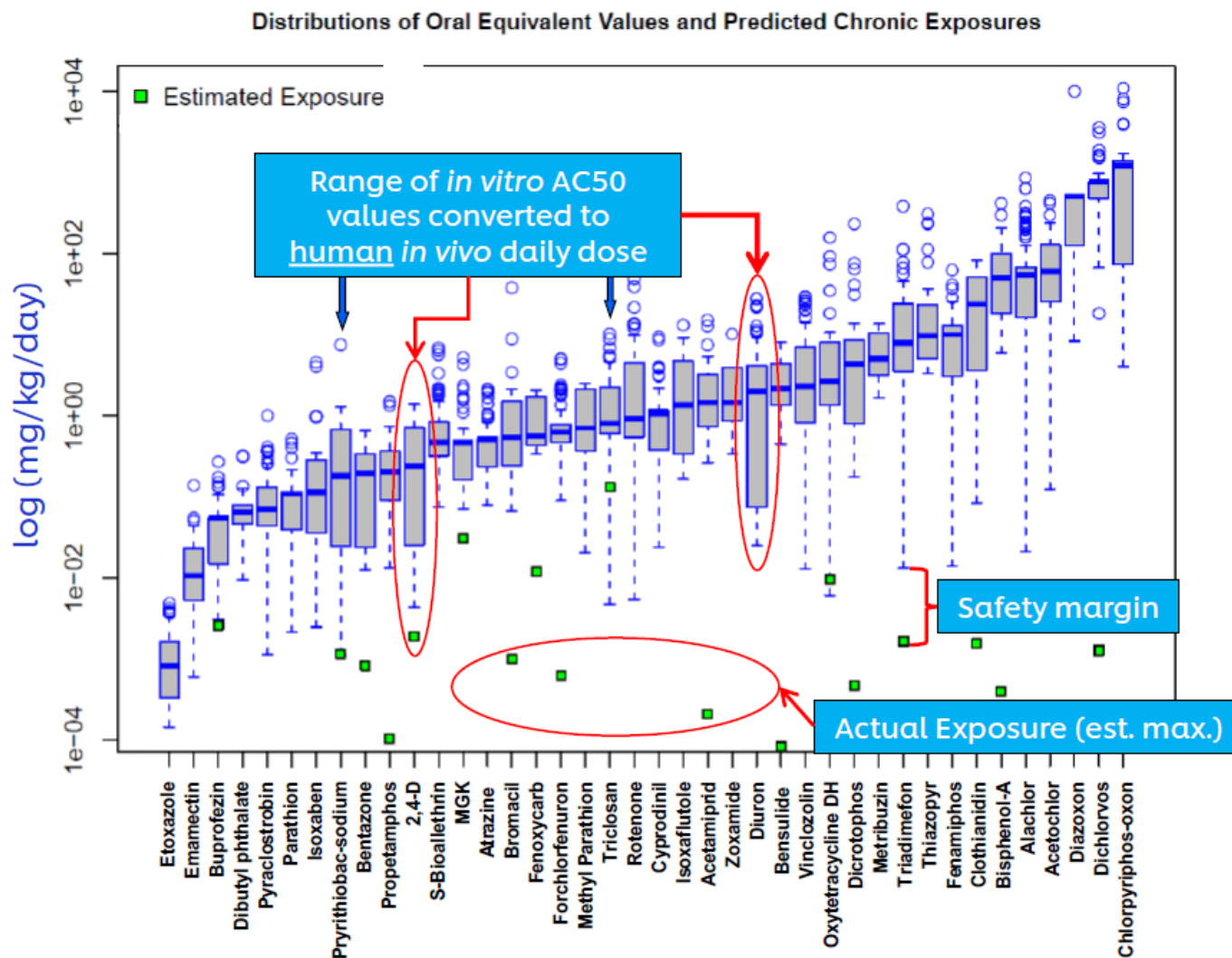
We address the above question using Next Generation Risk Assessment
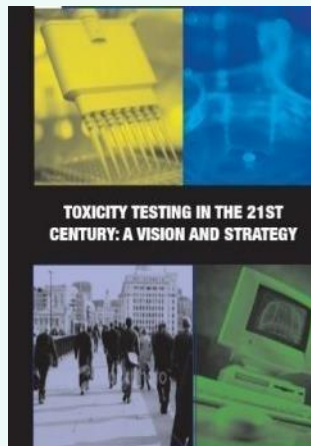
NGRA: Protection not Prediction

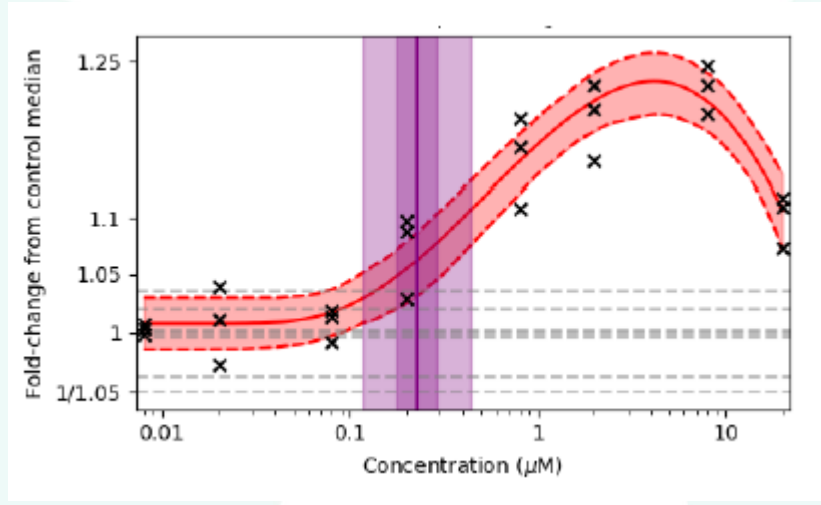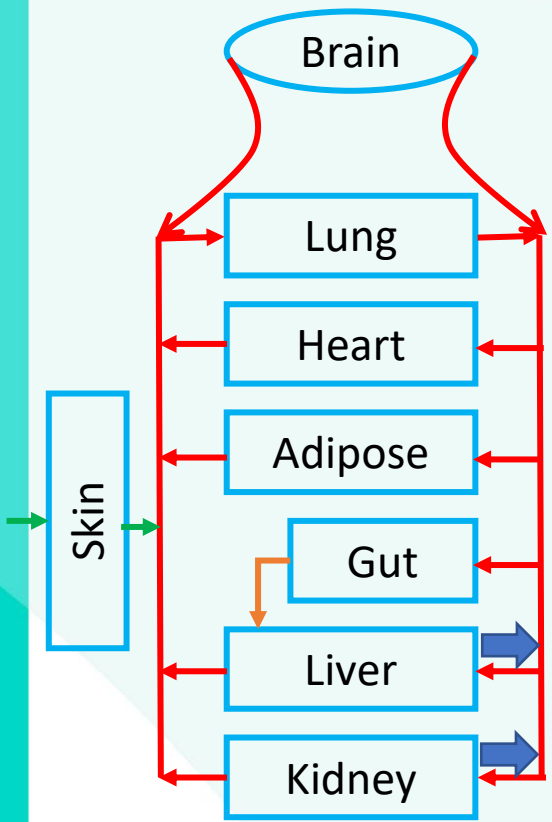Distributions of Oral Equivalent Values and Predicted Chronic Exposures

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

Computational models in NGRA – some examples

Bayesian Statistics

$$P(\theta|Data) \propto P(\theta) * P(Data|\theta)$$

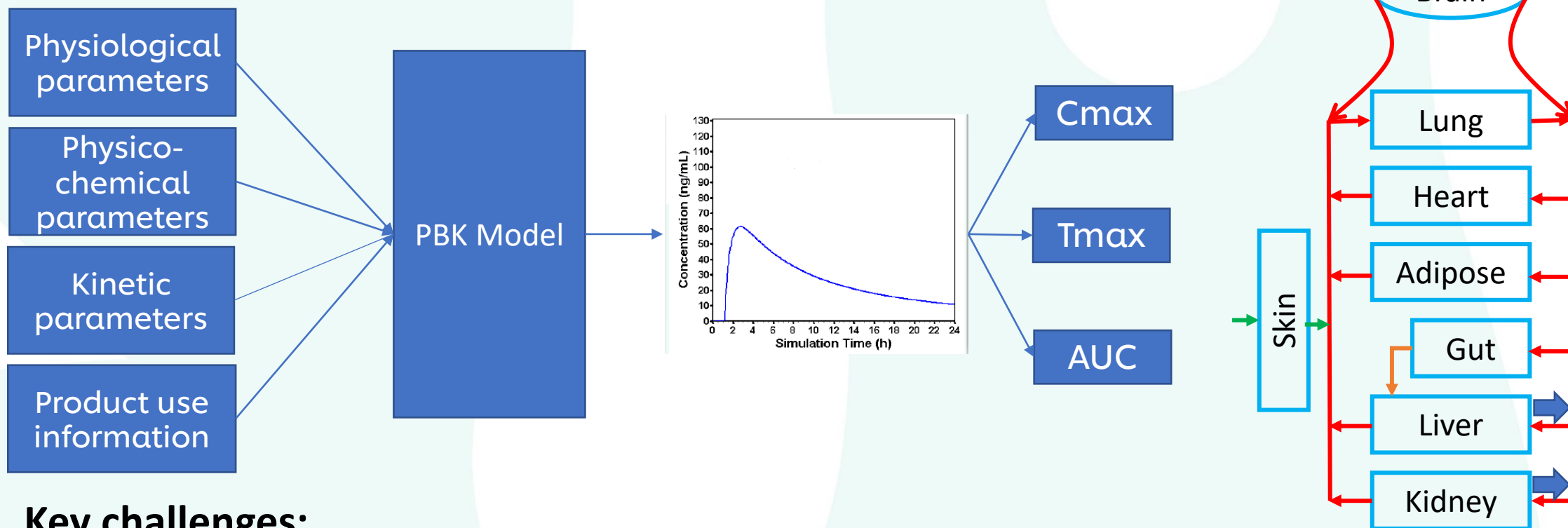# Computational models 1- Physiologically Based Kinetic (PBK) modelling

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
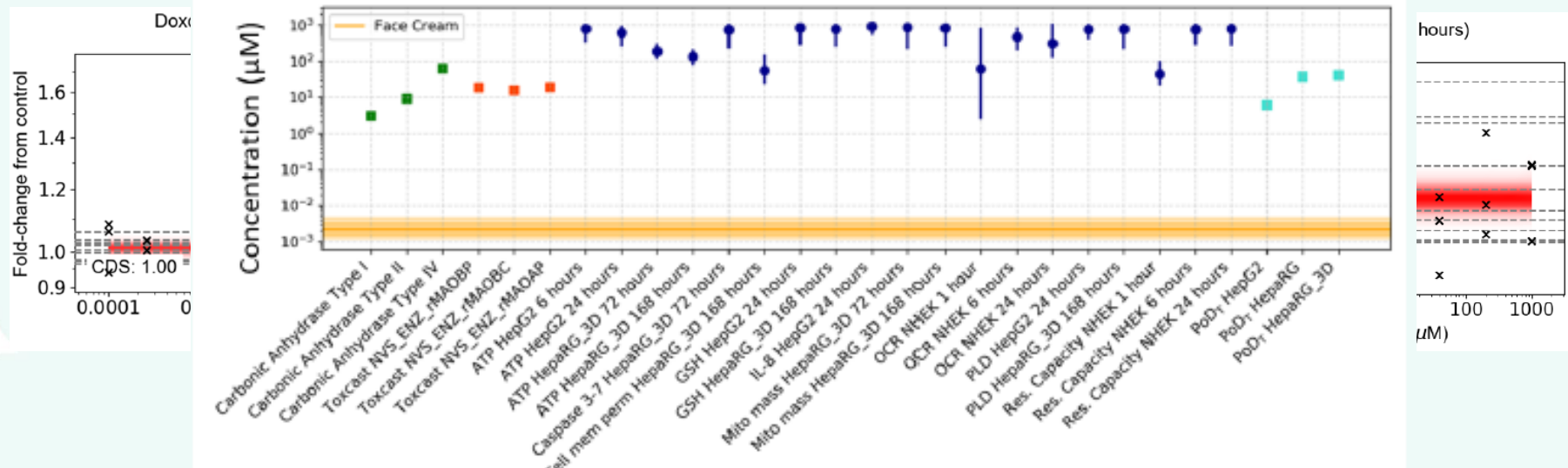

Key challenges:
- Understanding ADME mechanism
- Parameterisation

Computational models 2 - 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

Computational models 3 - High Throughput Transcriptomics (HTTr) Dose response analysis

Aim: based on the gene expression data, provide a broad biological perturbation concentration response measure (POD) and indicate mechanistic information as a hazard characterisation. **Assumption:** there is no adverse effect without gene expression changes

Challenges:
- Multiple parameter thresholds need to be defined that impact on overall analysis and sensitivity, e.g.,
    - depth of sequencing & replicates impact power of experiment
    - No. of cell lines – overall biological coverage
    - fold change/p-value/BMR factor filters, choice of models for dose response, genes vs pathways – a matrix of options with best set(s) still currently being assessed.
- Transparency in sharing complex assay with complex bioinformatic workflows to enable replication. OECD Transcriptomic Reporting Framework (TRF)

Computational models 4 – Bayesian statistics

Aim:
- Using (newly) observed/available data to update the probability distribution of parameters in a mathematical model based on
  - 1) the prior probability distribution of the parameters before observing the data, and
  - 2) a likelihood function describing how likely the data can be observed given certain values that the parameters take.
- Can be used in many different areas, such as analysing dose response relations.

Bayesian Statistics

$$P (\theta | Data) \propto P(\theta)*P(Data|\theta)$$

Bayesian linear regression

Y=aX + b
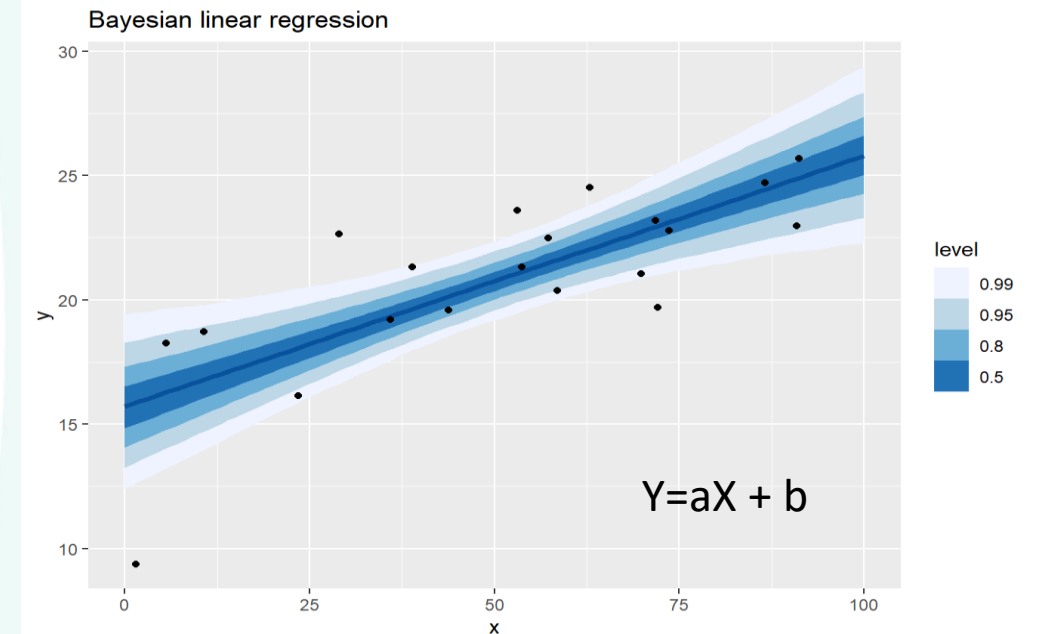
Key challenges:
- Specify prior distribution of parameters and a likelihood function

Computational models 5 - Expert Knowledge Elicitation

Aim:

- Handling the situation where there is not enough data to adequately inform the risk assessment decision but there is some extent of data and knowledge exist which can be used to inform the decision.

- Elicit experts' knowledge in a way that common cognitive and psychological biases are minimised by following a strict protocol with rational of the experts' judgment explicitly justified and documented.

Literature information

Relevant figure

Expert Interpretation

Consensus Distribution after Step 1

Individual Judgement of PoD of DNA Damage (uM) given MN assay data
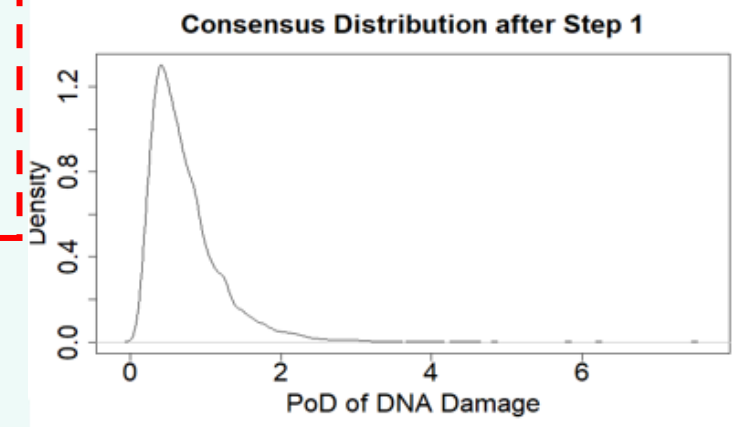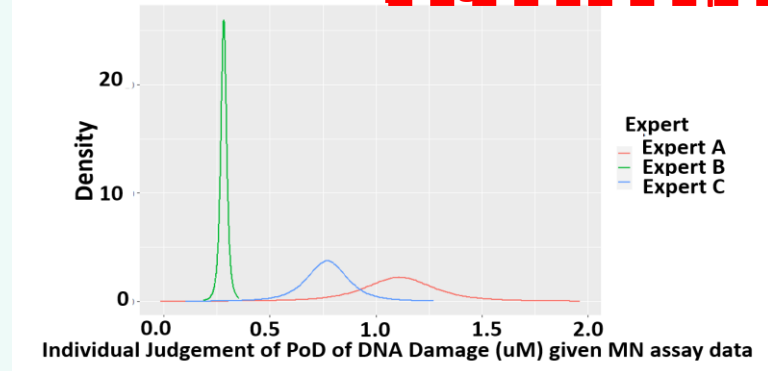
Key challenges:

- Elicitation process design and facilitation

Example – evaluating protectiveness of safety assessment using non animal methods
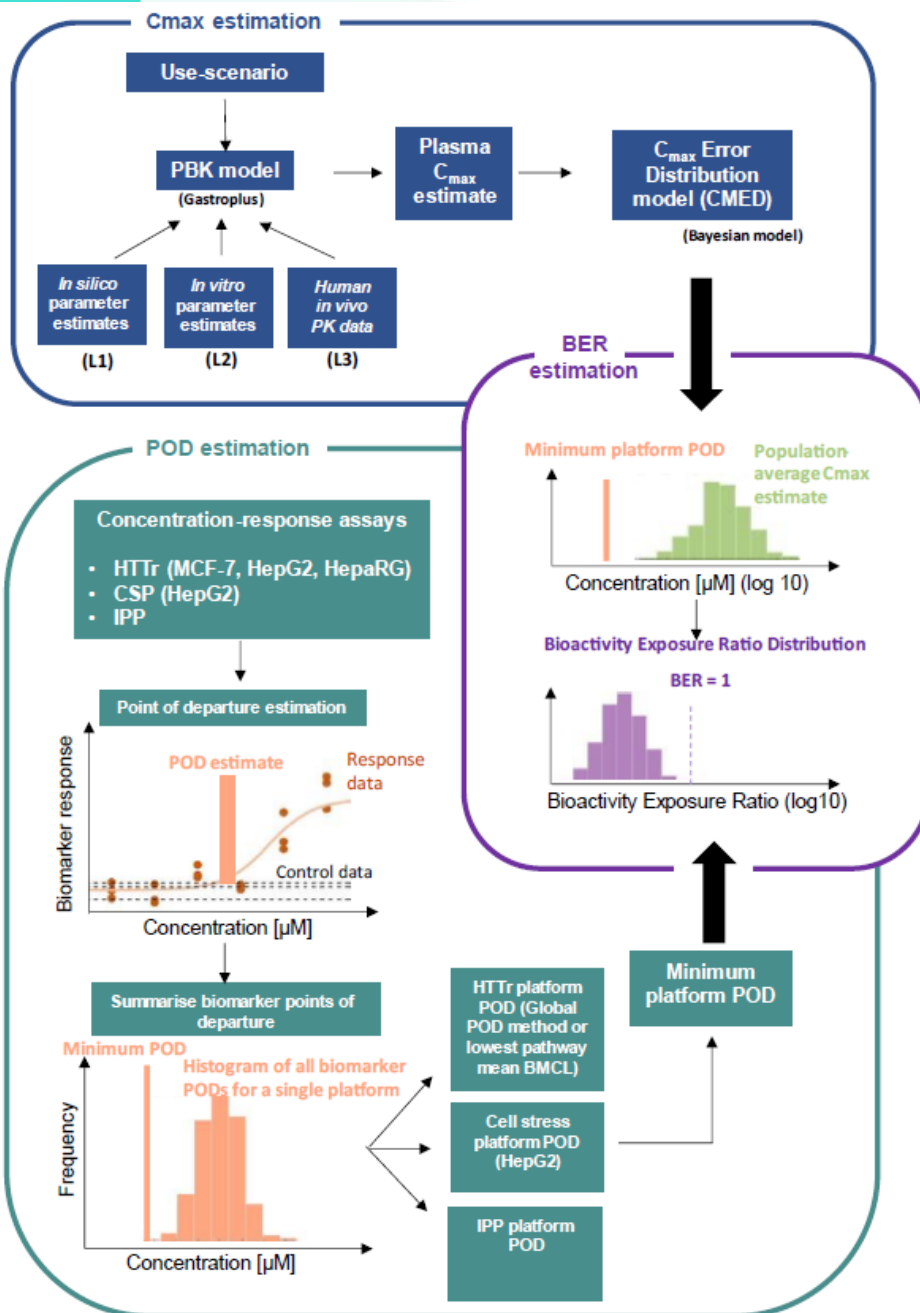
Estimating the internal exposure of a chemical based on a given use-case scenario, using 3 different levels of information:

- In silico informed parameters only
- + some in vitro informed parameters
- + some in vivo informed parameters

Outputs from these modules are combined in the third module to estimate the Bioactivity Exposure Ratio (BER)

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

Middleton *et al.,* (2022) *ToxicolSci*, **189(1)**, 124-147

Example – evaluating protectiveness of safety assessment using non animal methods

Step 1: Define Benchmark chemical-exposure scenarios

| Chemical	Exposure scenario	Risk category
Chem X_1	Scenario Y_1	Low/High
…	…	…
Chem X_n	Scenario Y_m	Low/High

Step 2: Apply NAM tools to generate bioactivity and exposure data for PoD and Cmax estimation

Step 3: estimate minimum platform PoD and the Cmax to calculate the BER

Step 4: benchmark BER against risk category for each exposure scenario in Step 1

Middleton *et al.,* (2022) *ToxicolSci,* **189(1)**, 124-147
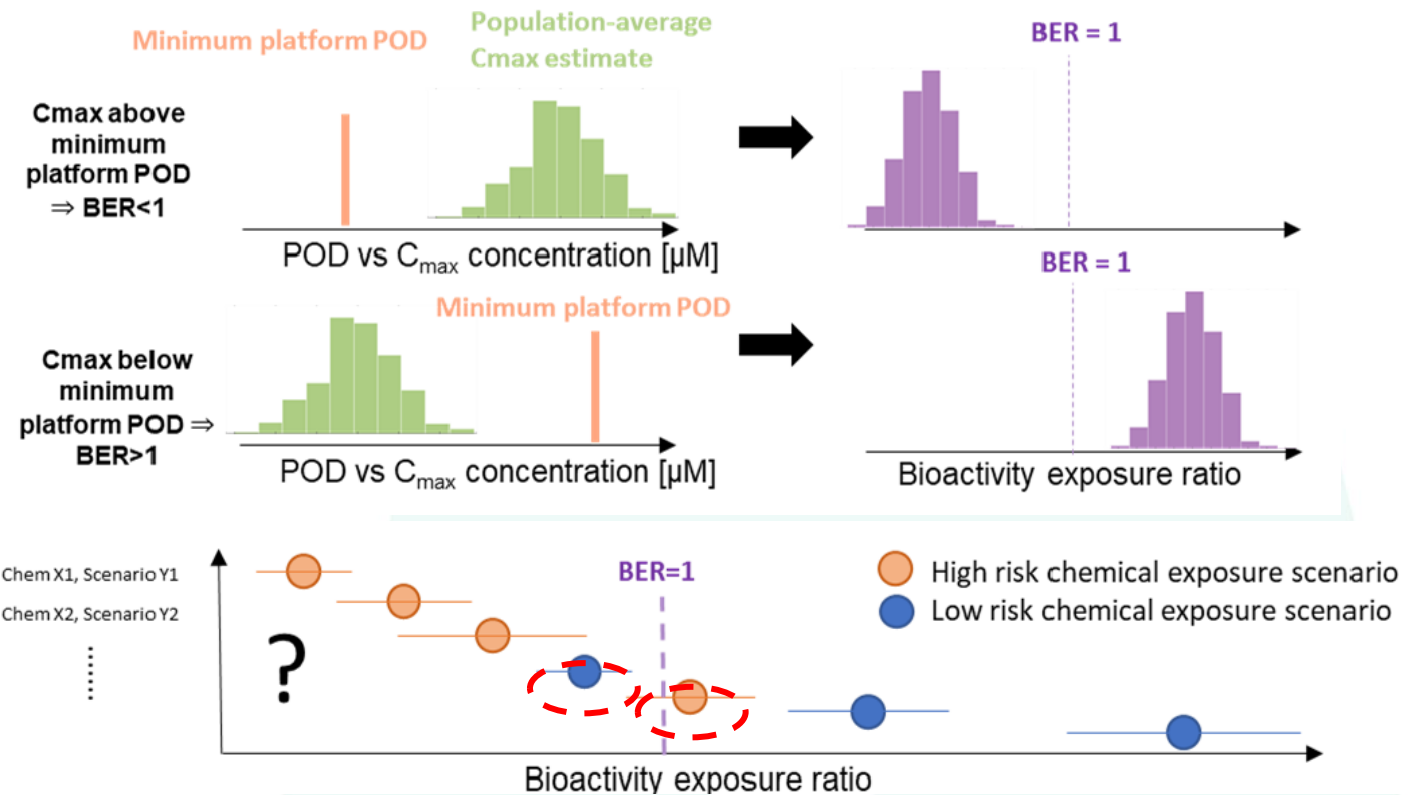
Example - evaluating protectiveness of safety assessment using non animal methods
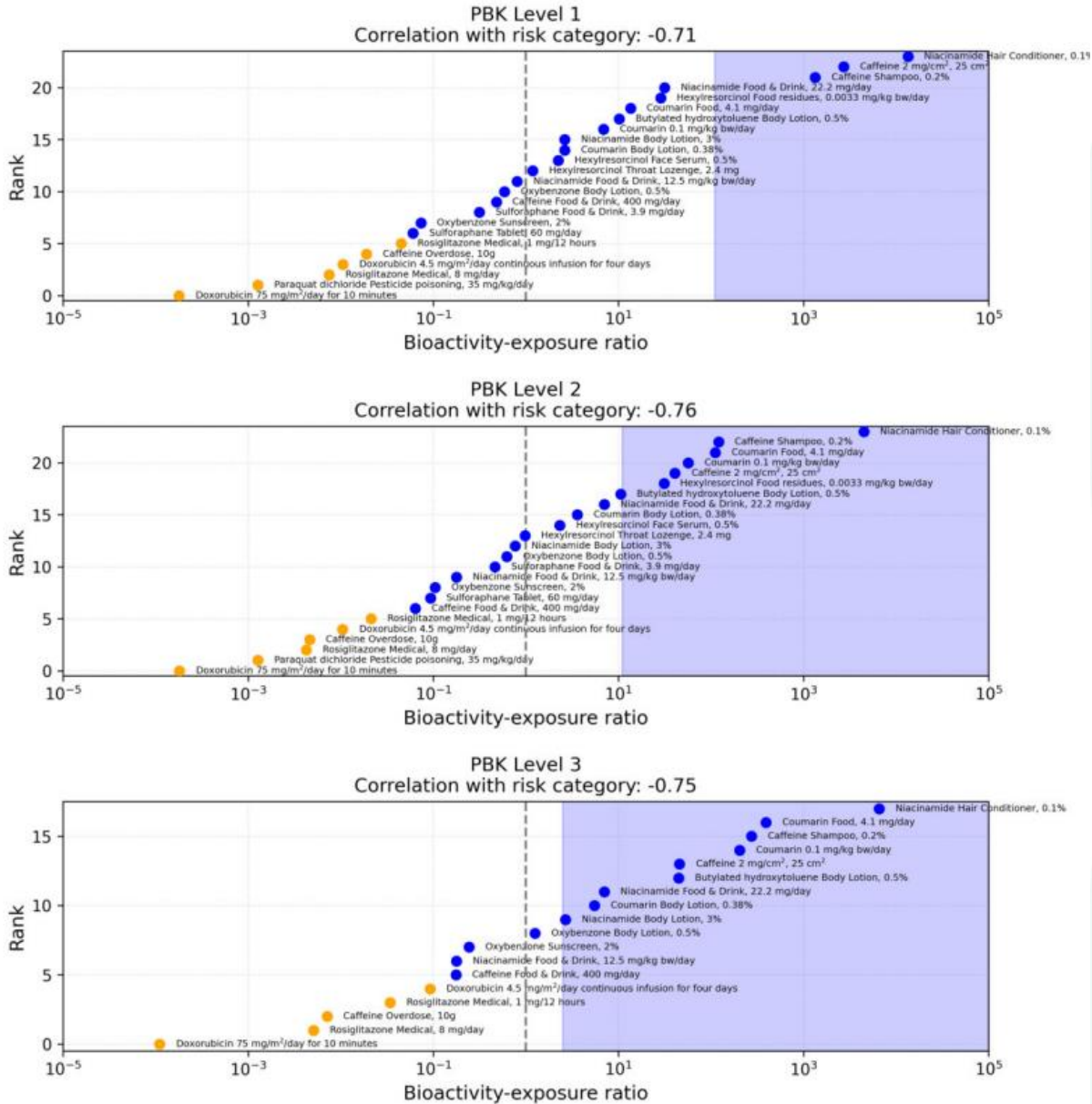
Protectiveness: The proportion of high-risk scenarios not identified as low risk

Utility: The proportion of low-risk benchmark chemical scenarios correctly identified as such

PBK Level	Empirical Utility	Empirical Protectiveness
1	3/18 (17%)	6/6 (100%)
2	6/18 (33%)	6/6 (100%)
3	9/13 (69%)	5/5 (100%)

Middleton *et al.,* (2022) *ToxicolSci*, **189(1)**, 124-147

Discussion

- A number of computational methods have been applied to NGRA

- An example is briefly introduced which applies some of the methods above to demonstrate the protectiveness of systemic safety assessment using non animal methods

- In general, computational models are increasingly applied across different areas (bioactivity and exposure) within NGRA.

- We need to work hard to ensure methods are robust and acceptable

Reproducible and transparent data analysis, with uncertainty properly characterised and communicated

Clear documentation of applicability domain and limitations

Targeted communication to different audiences

Building Trust and Confidence

Multistakeholder evaluation of approaches, which should be available for people to use

Advocating, education and upskilling

Developing networks of organisations with common interests

Acknowledgement

Unilever