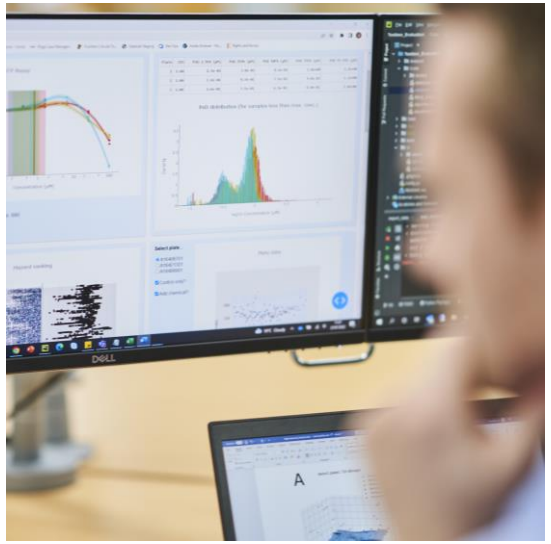
Application of Quantitative Systems Toxicology to support chemical safety assessment in the Cosmetics Industry

Andrew White and Alistair Middleton

Eurotox 2024: S18-02



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Outline

- Drivers for Cosmetic Safety assessment
- Tiered testing Strategies and Exposure led safety assessment NGRA
- Challenges and outcomes using case study examples
- Summary

Ensuring Safe Ingredients for Foods, Drinks, Homecare and Cosmetic Products (not drugs)

Risk Based Approach:
Considers both the hazard and the exposure to evaluate the risk

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

For **consumers**; **workers**; the **environment**

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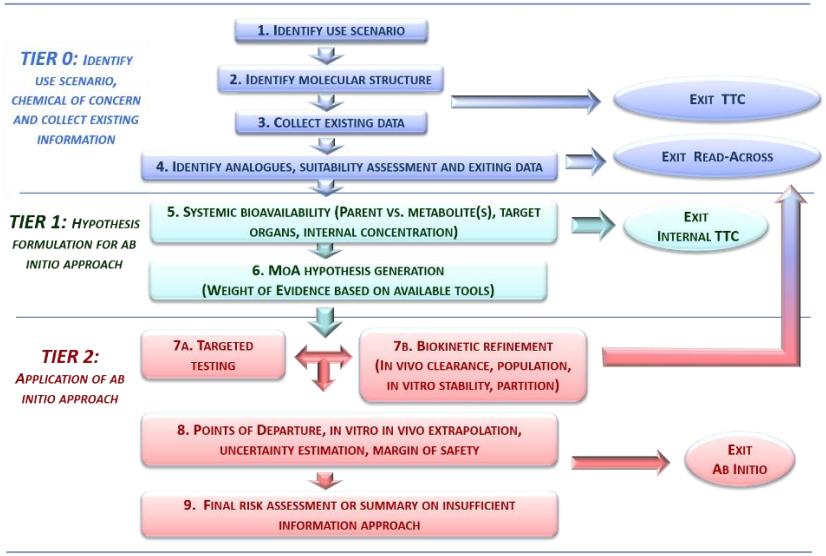
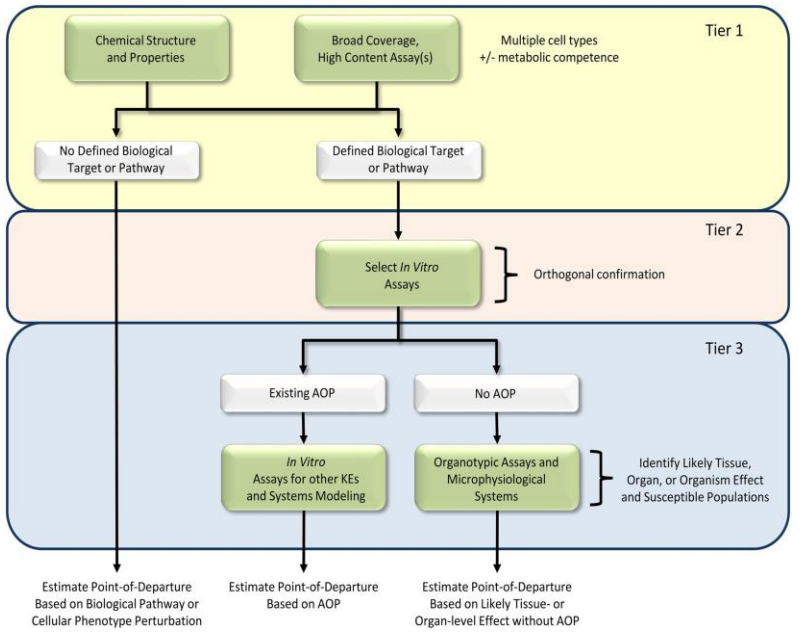
Decision frameworks in NGRA – Tiered approaches

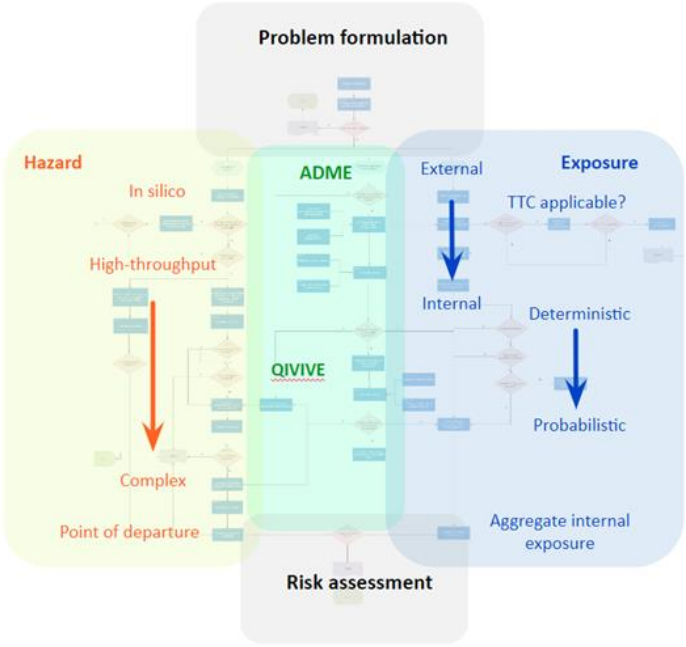
Problem formulation – Tier 0 → **Initial BER estimate – Tier 1** → **BER refinement – Tier 2**



Berggren et al., 2017



Thomas et al., 2019

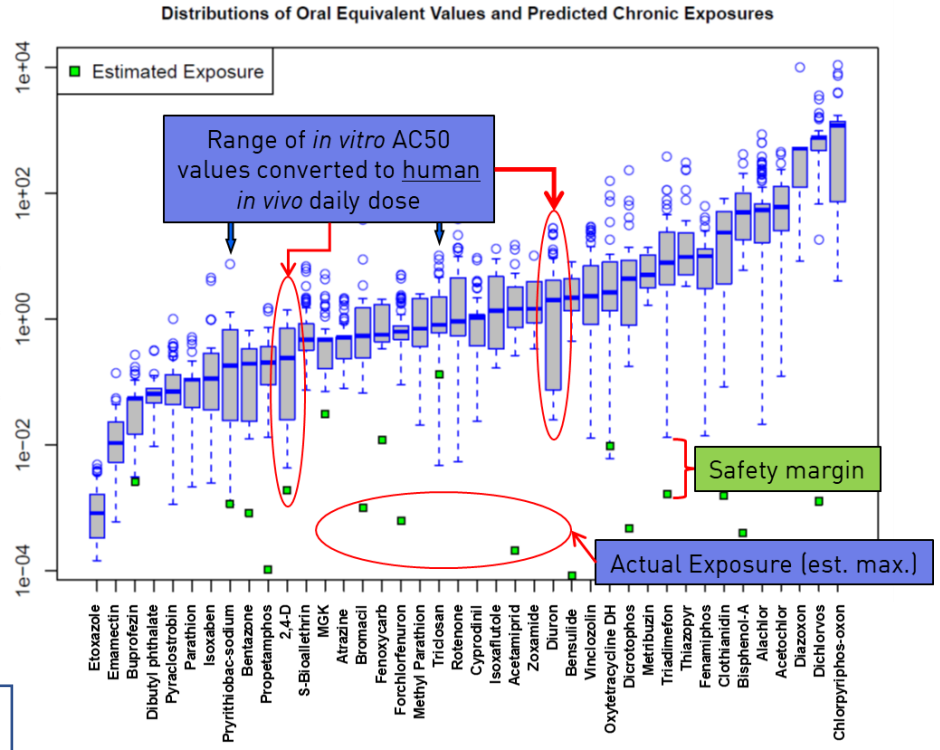


ASPA ver 1.9

Safety Decision

Safety without animal testing - Next Generation Risk Assessment (NGRA)

*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***



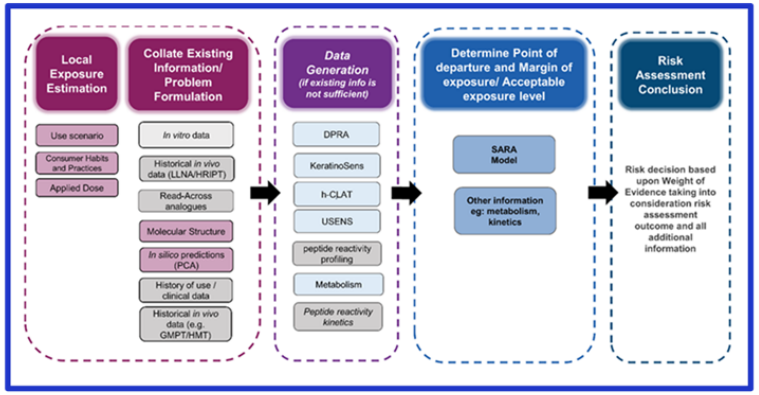
Slide from Dr Rusty Thomas, EPA, with thanks

Rotroff, *et al.* Tox.Sci 2010

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

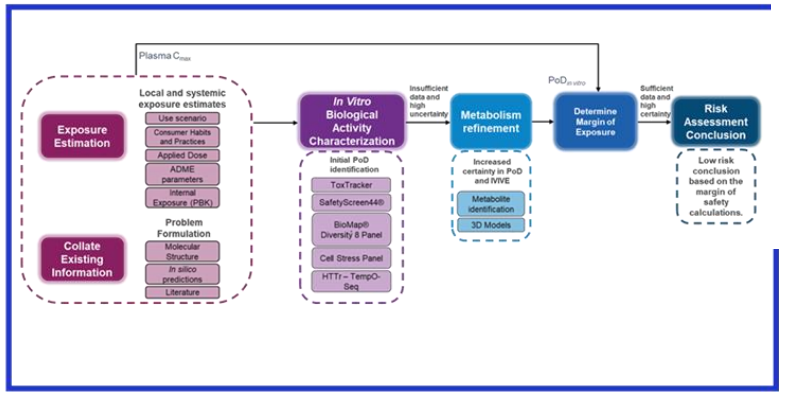
Application of NGRA case studies – Protection Goal

Skin Sensitisation

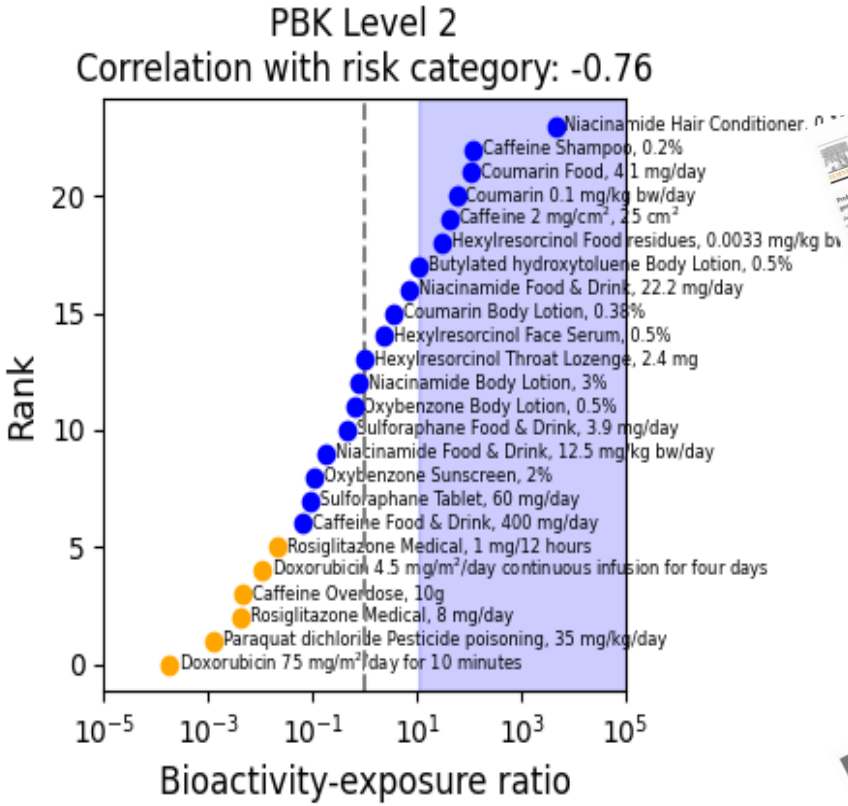


Reynolds et al (2021) Reg Tox Pharmacol, **127**, 105075

Systemic safety



Baltazar *et al.*, (2020) *Tox Sci* , Volume 176, Issue 1, Pages 236–252

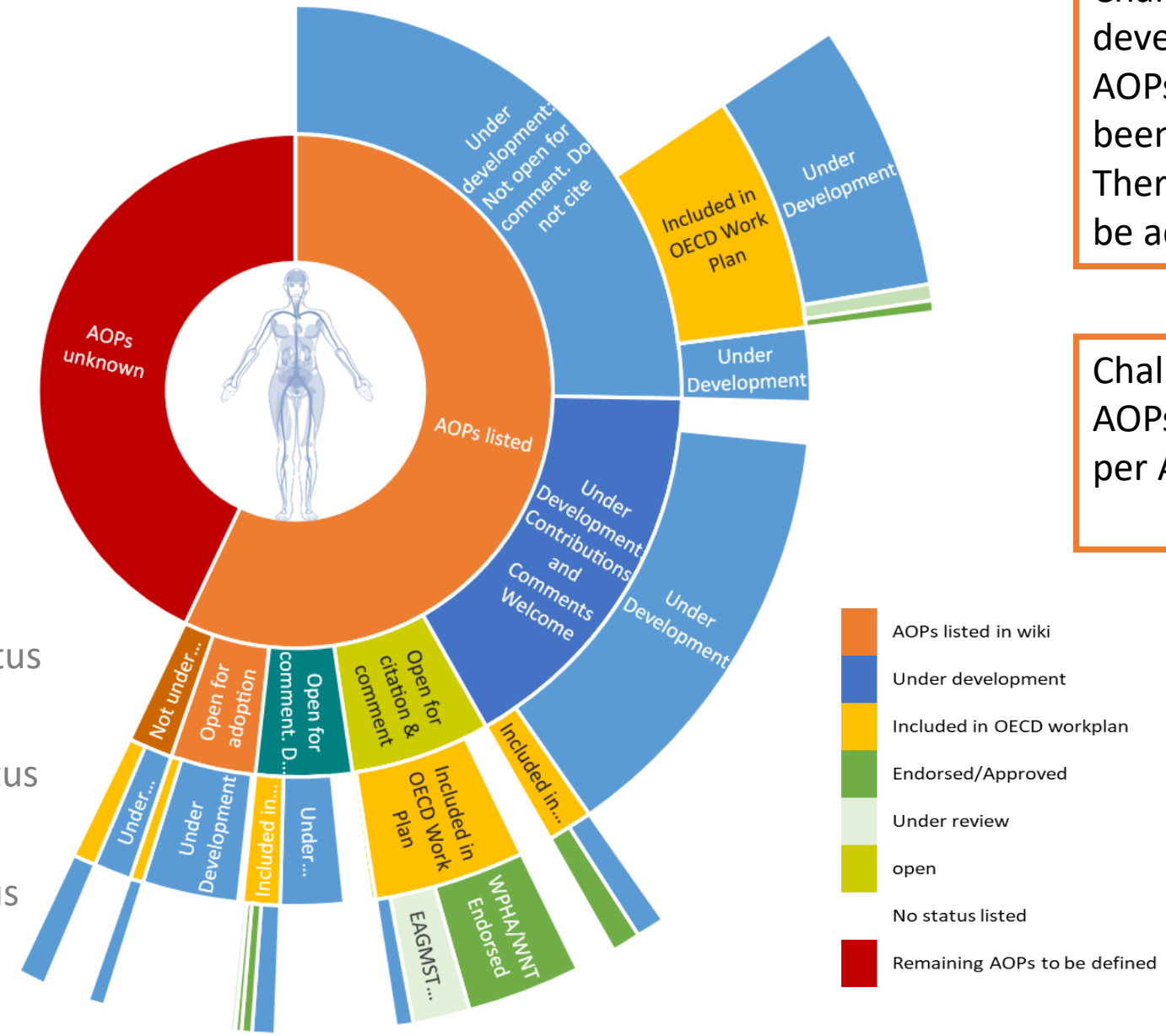


Blue: low risk chemical-exposure scenario

Yellow: high risk chemical-exposure scenario

Exposure scenarios within the **blue shaded region** are identified as **low risk.**

Current status of AOPs



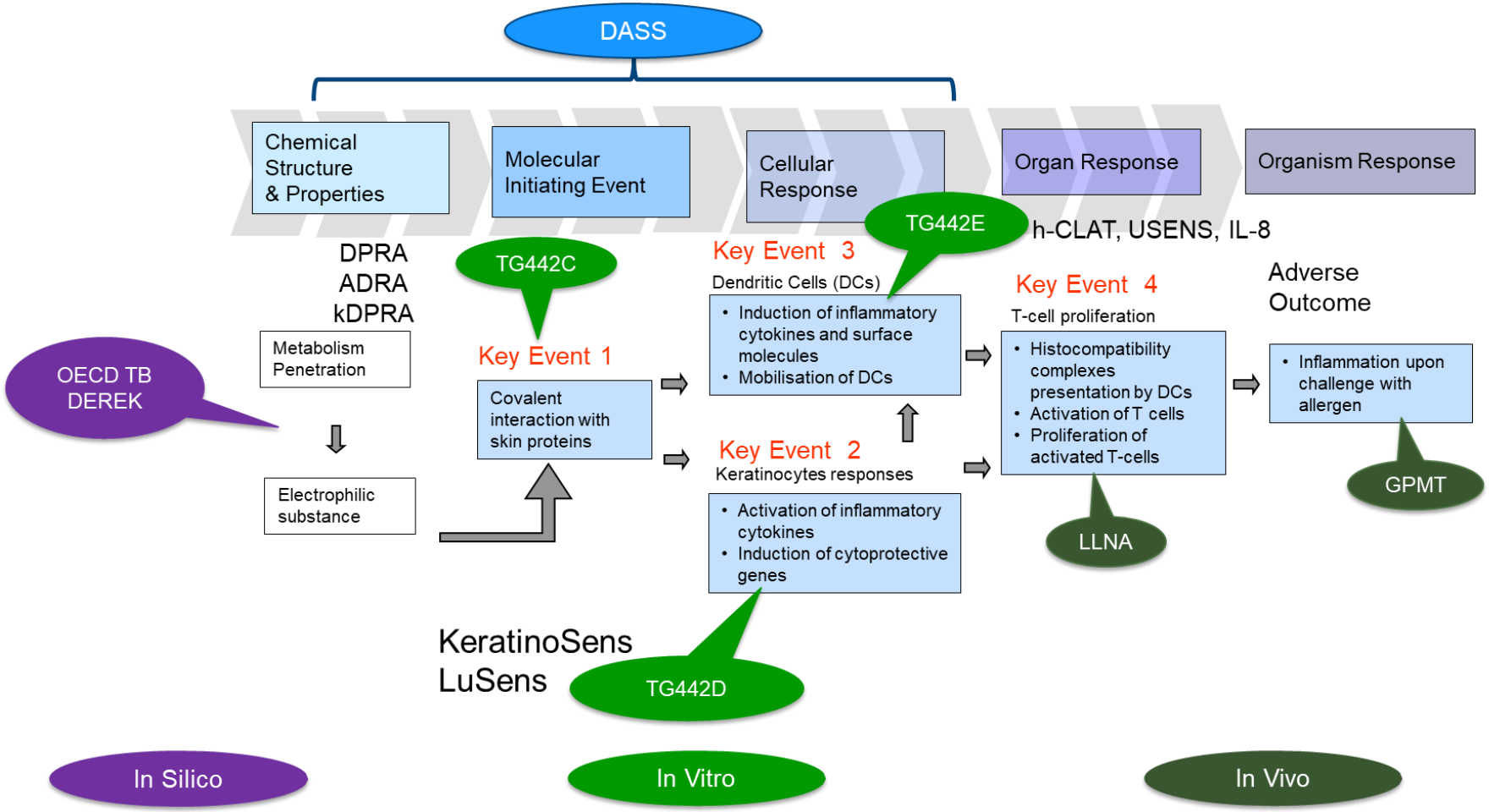
Challenge 1: After ~10 years of development, only limited number of AOPs, many of which have not yet been verified (biological coverage). There's an issue of scale that needs to be addressed.

Challenge 2: At present there are 446 AOPs on AOP-Wiki. Assuming 5 KEs per AOP, that's over 2000 assays.

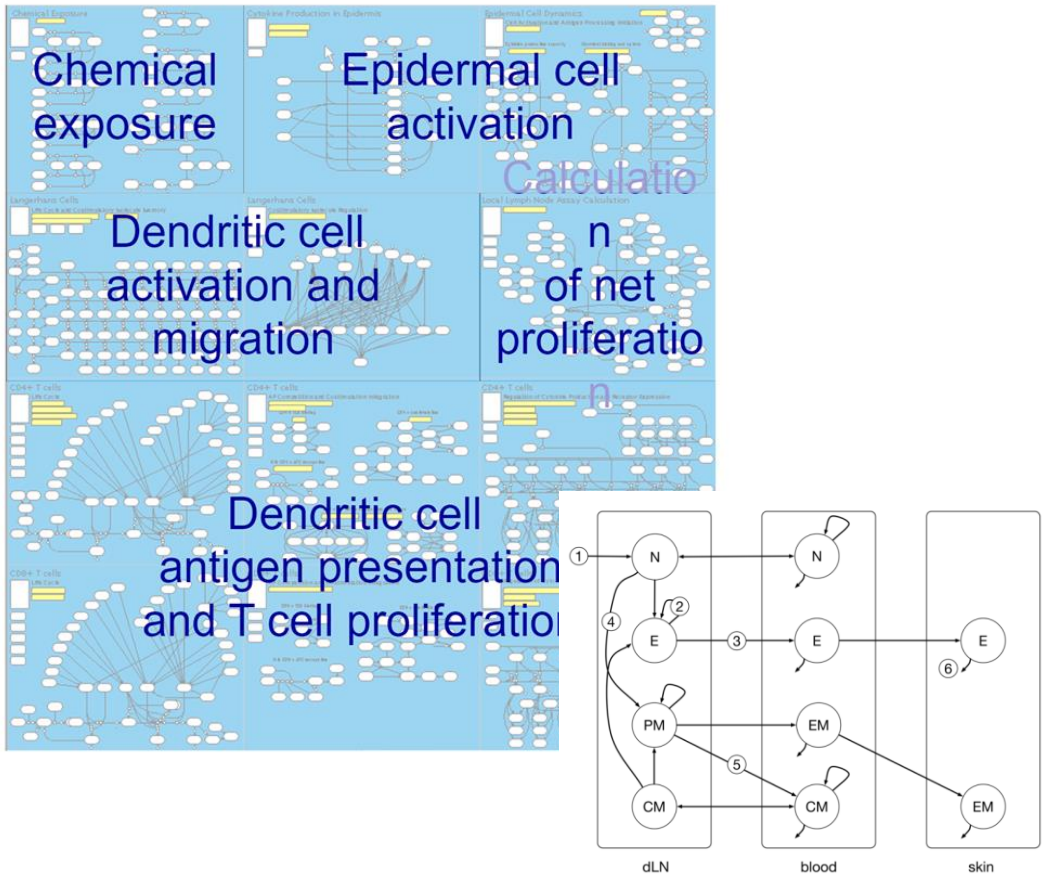
- Toxcast has ~ 700 assays

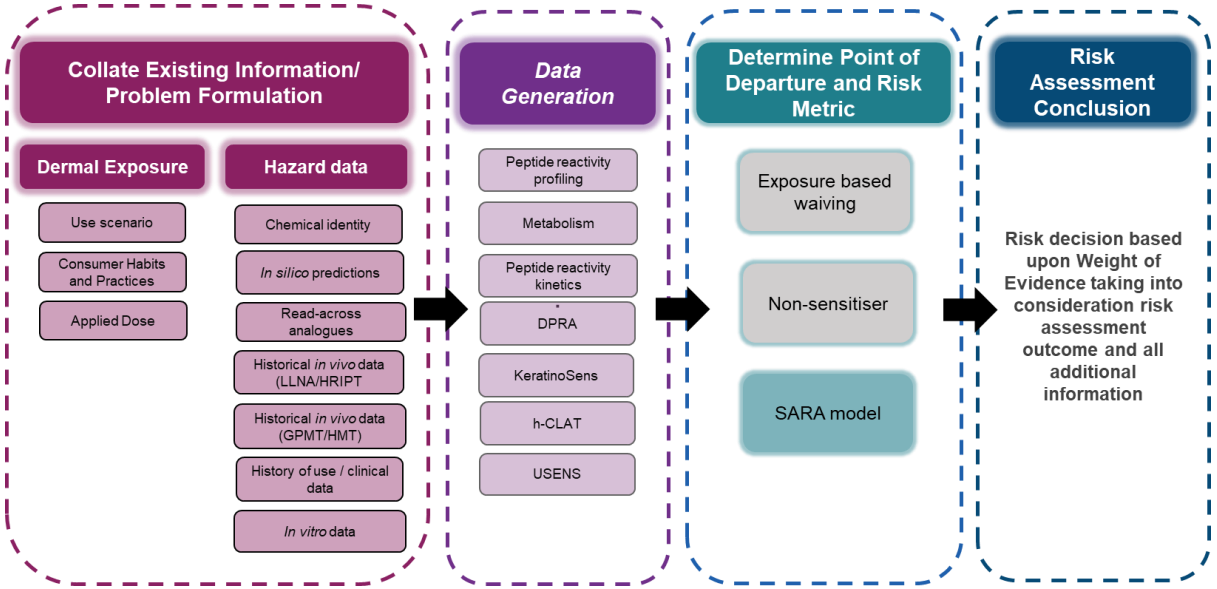
At present, a decision framework based only on AOPs is not feasible. However, AOPs can used as a knowledge base for enhancing a testing strategy

Case study 1. Skin allergy : AOP-informed testing strategy



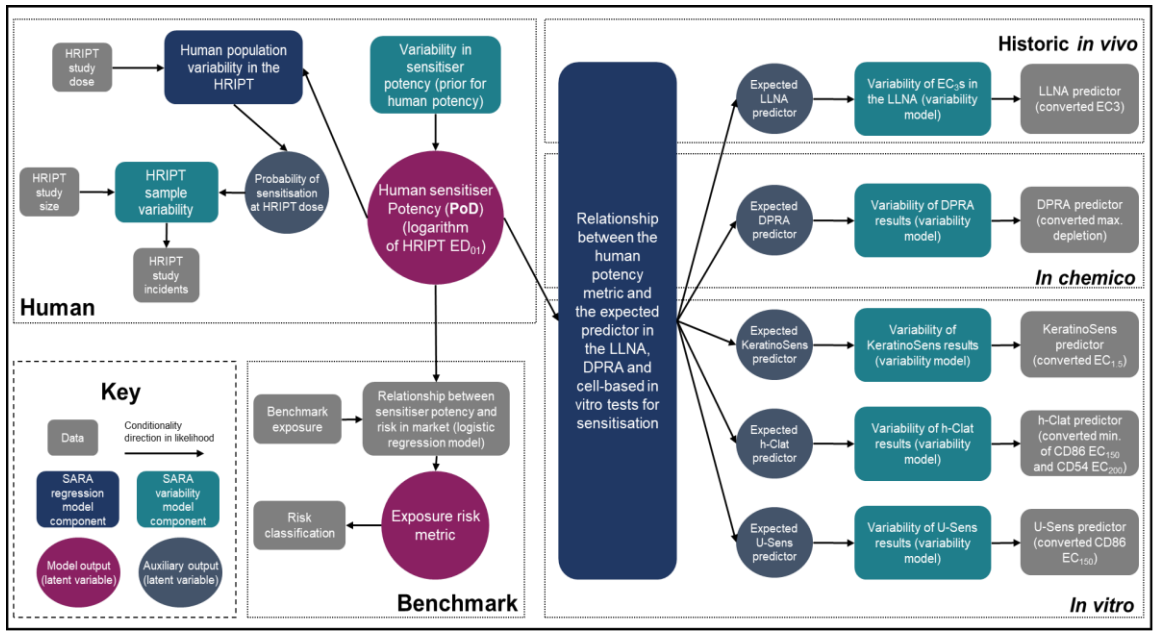
Evolution of approach towards quantitative model of Skin Allergy





- **Unilever NGRA framework for Skin Allergy** was designed to use a tiered WoE based upon all available information, accommodate range of consumer product exposure scenarios and provide a quantitative point of departure and risk metric → **SARA DA**

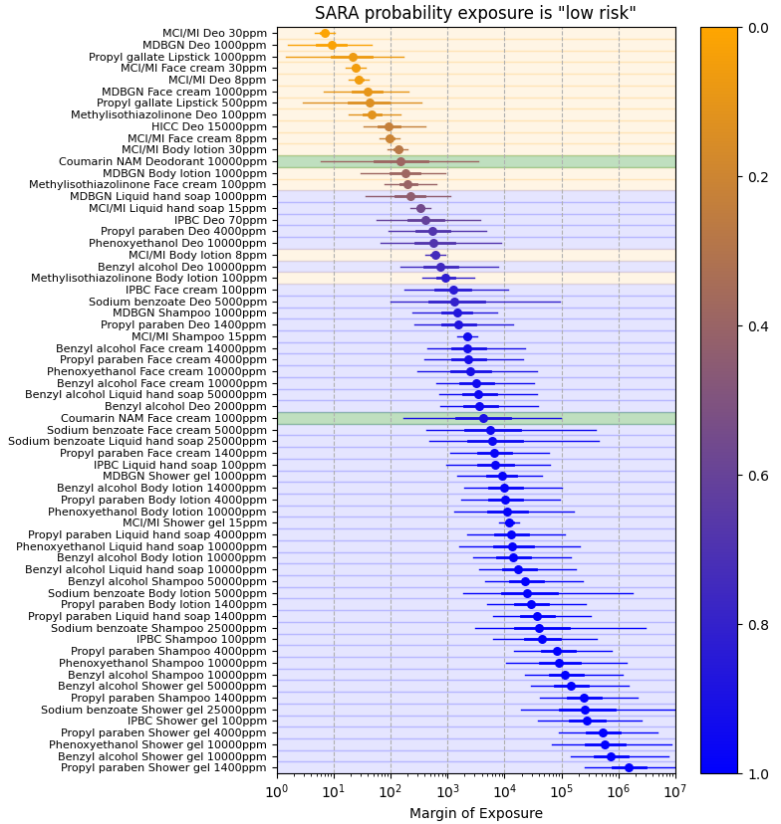
Skin allergy example: AOP-informed testing strategy



The use-case of the SARA DA is to estimate:

1. ED_{01}, the dose at which there is a 1% chance of sensitization in an HPPT-eligible population
2. Probability that a consumer exposure to some chemical is 'low risk', conditional on the available data and the model

Reynolds et al 2022 https://pubmed.ncbi.nlm.nih.gov/35835397/



SARA: A Bayesian model describing statistical relationships between data associated with different KE, which can be used to predict the Margin of Exposure for a given scenario.

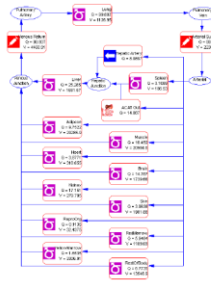
Challenge 3: acceptance and development of AOP-based statistical or machine learning based approaches for quantifying risk

qAOPs and NGRA decision frameworks

Problem formulation – Tier 0

Initial BER estimate – Tier 1

PBK models



AOP-informed (where possible)

Broad biological coverage

- Receptor binding assays
- Cellular stress assays
- Phenotypic profiling
- Transcriptomics

Exposure

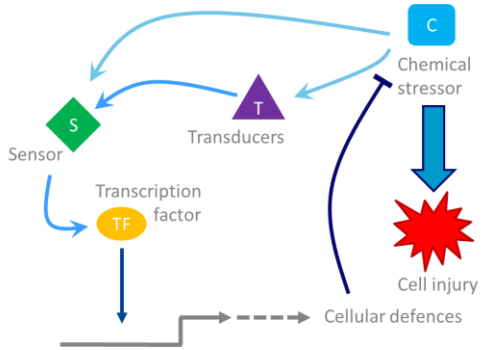
Hazard (points of departure)

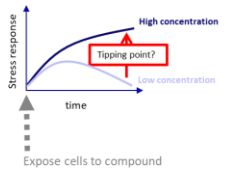
Exposure likely to trigger bioactivity

Small BER (i.e., Exposure close to POD)

BER refinement – Tier 2

Understanding bioactivity vs adversity





Low risk of exposure causing any bioactivity

Large BER (i.e., Exposure << POD)

Safety Decision

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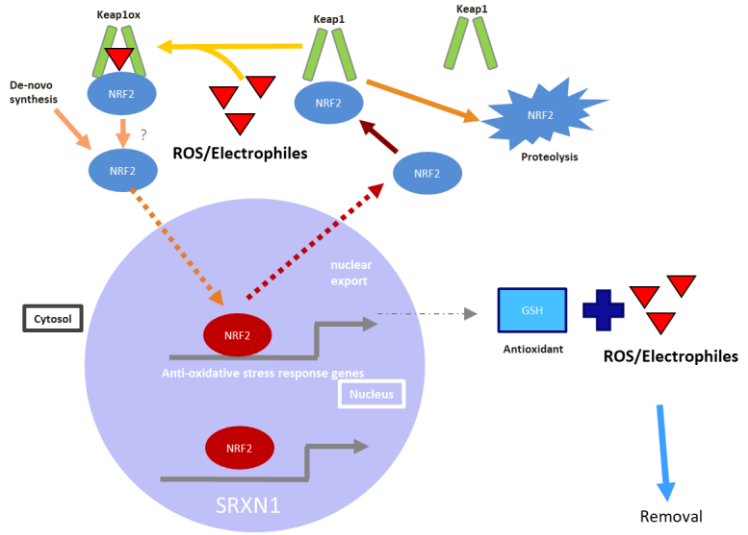
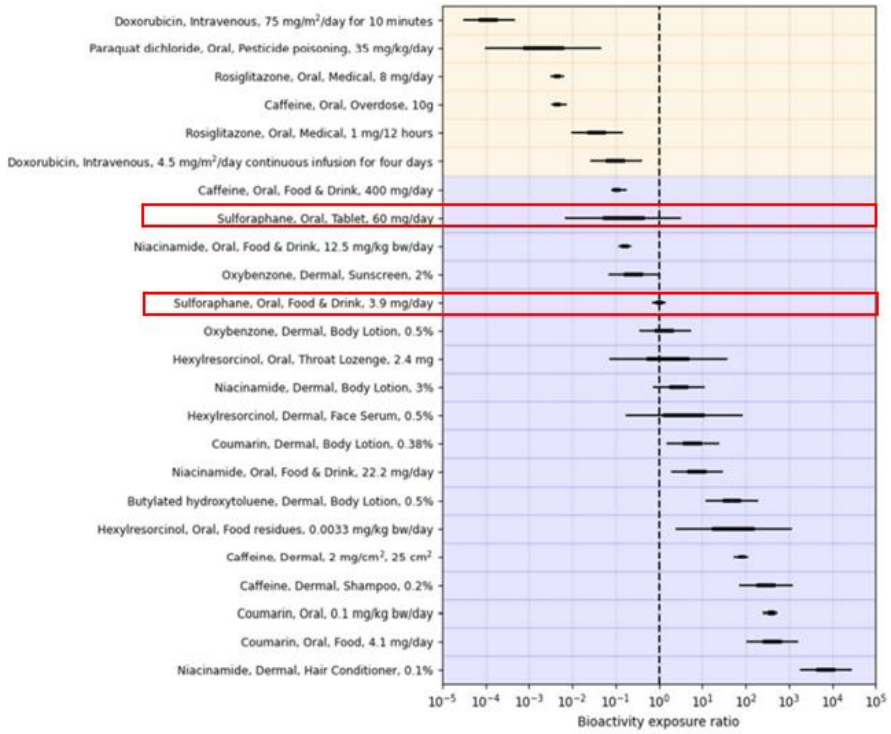
Case study 2. Using qAOPs at tier 2 for distinguishing between adaptive and adverse responses

Sulforaphane case study

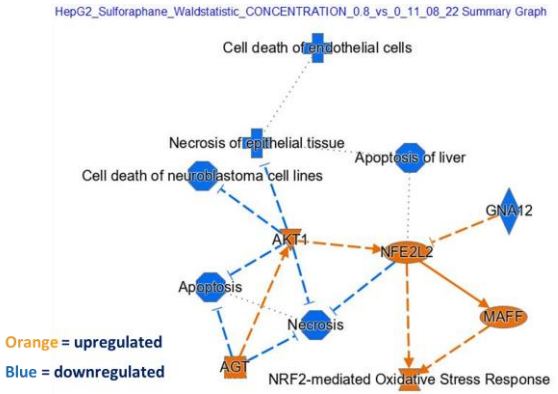
- Sulforaphane is a plant compound found in cruciferous vegetables like broccoli, cabbage, cauliflower, and kale.
- Under normal consumption, the BER<1 indicating exposure is likely to trigger bioactivity.
- Sulforaphane is an activator of Nrf2.
- Is the sulforaphane triggering an adverse effect?

Sulforaphane



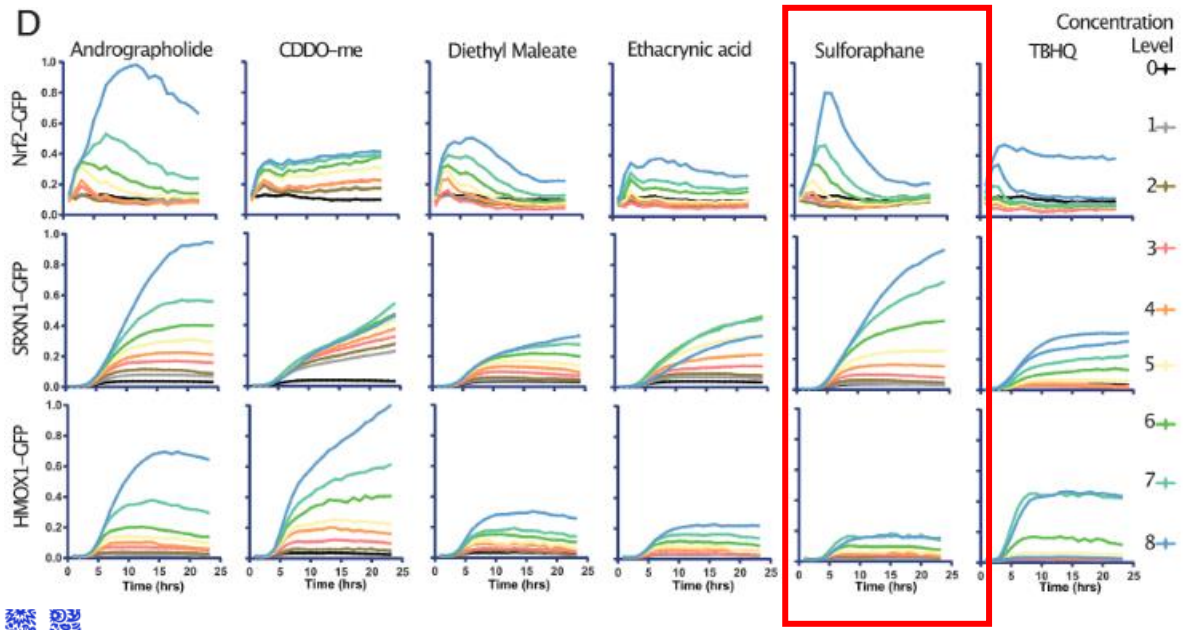


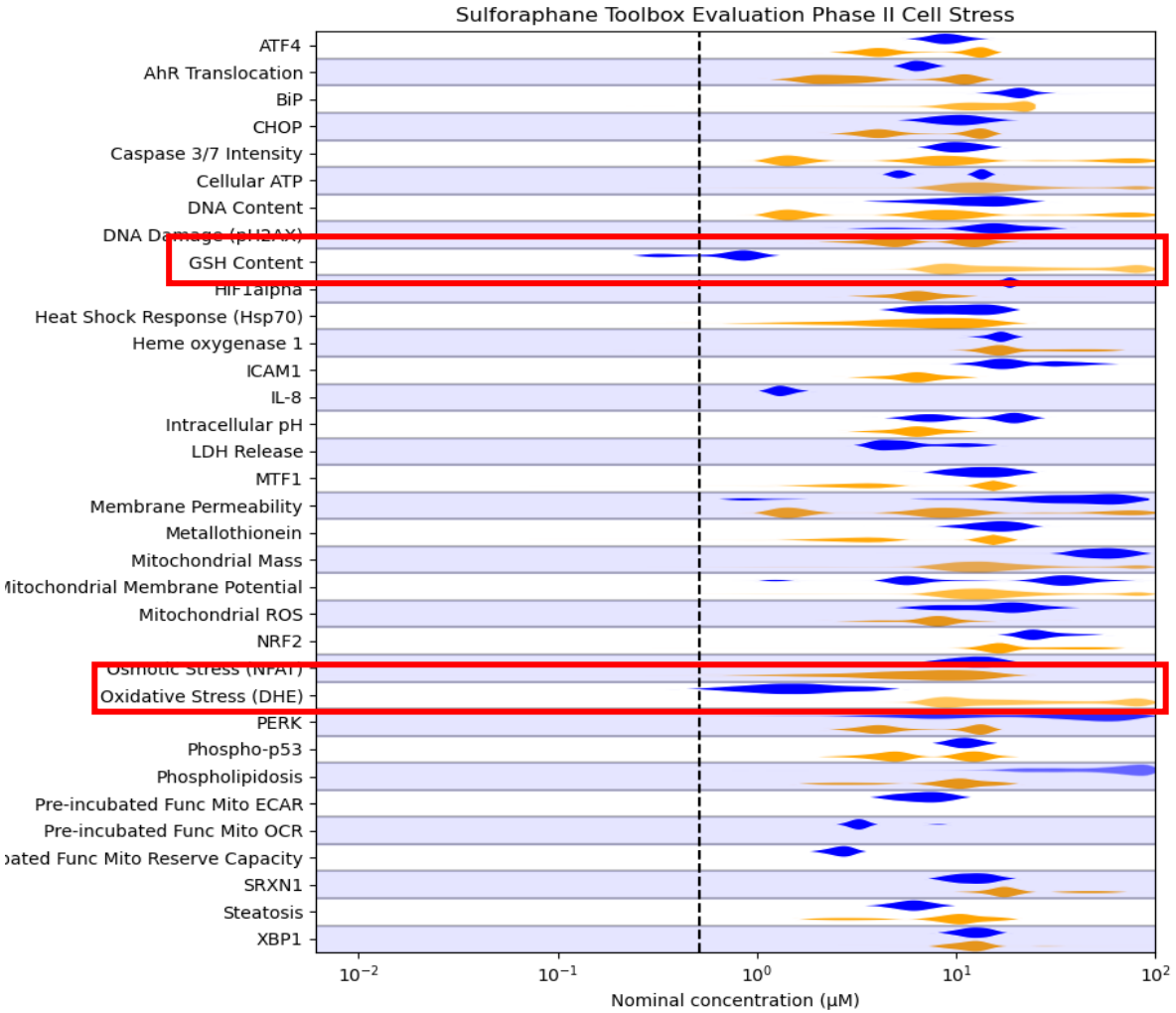
Key event in multiple AOPs linked to organ toxicity



CSP Bioactivity Summary Plot

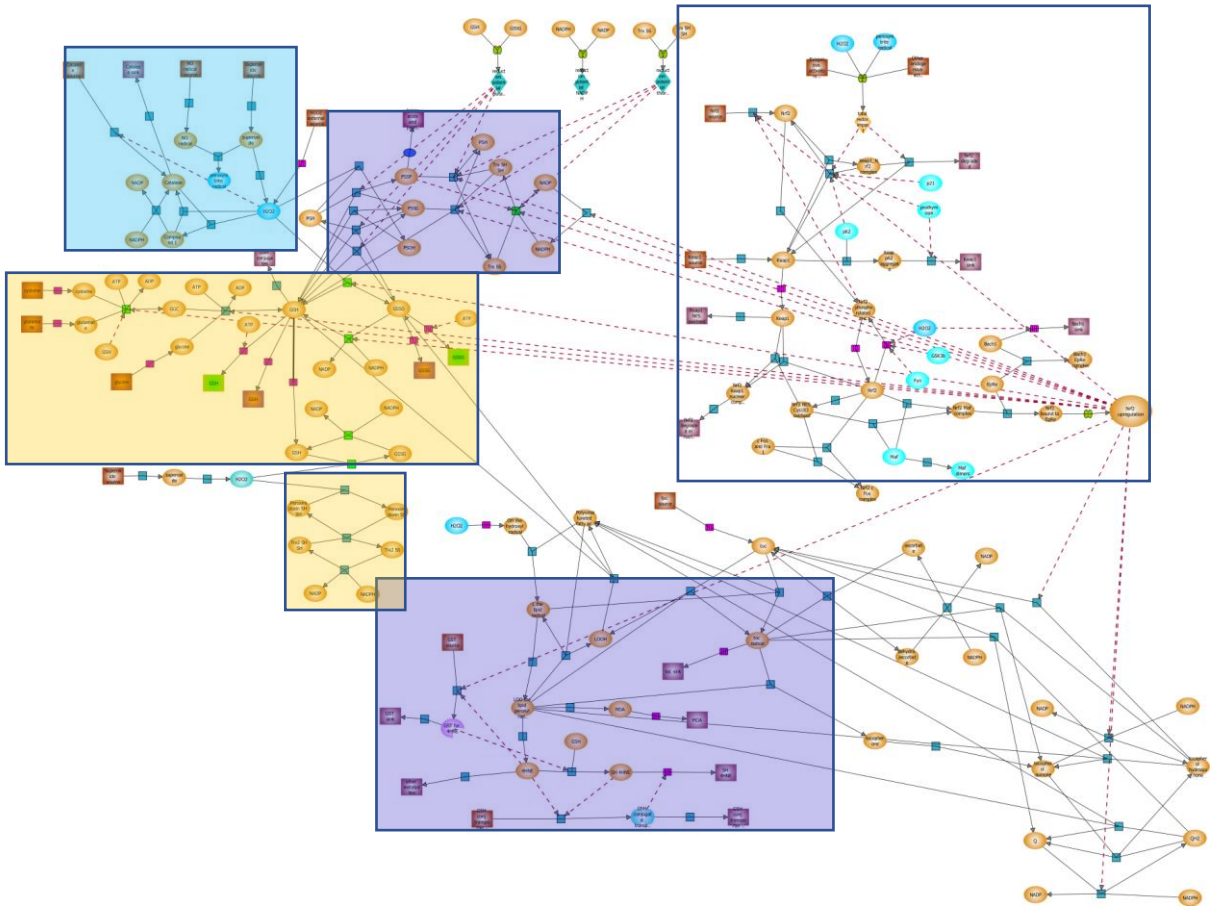
- **Blue** = PoDs for assay-specific biomarkers.
- **Orange** = pooled PoDs for assay-specific cell health.
- **GSH content** = lowest Platform PoD (0.51 µM)
- **Lowest PoDs related to Oxidative Stress & Inflammation**



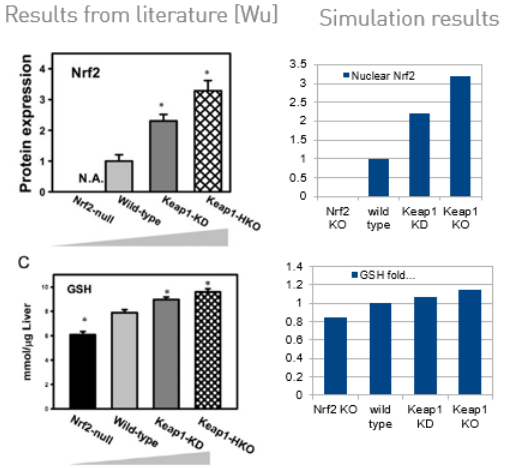


Taken from Braak et al, Toxicology in vitro 84 (2022)
https://doi.org/10.1016/j.tiv.2022.105419

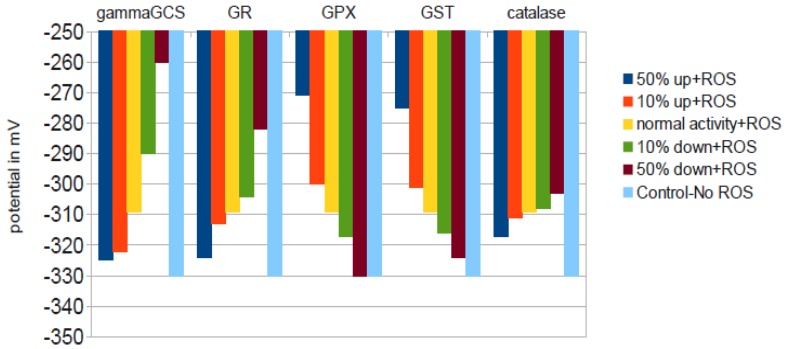
Early Oxidative stress systems model



Challenge 4: Developing qAOP systems toxicology approaches that are truly chemical agnostic for use NGRA decision frameworks.



Comparative analysis of model simulation results to literature and experimental findings..



Determination of Redox Sensitive components of the model – Glutathione redox potential

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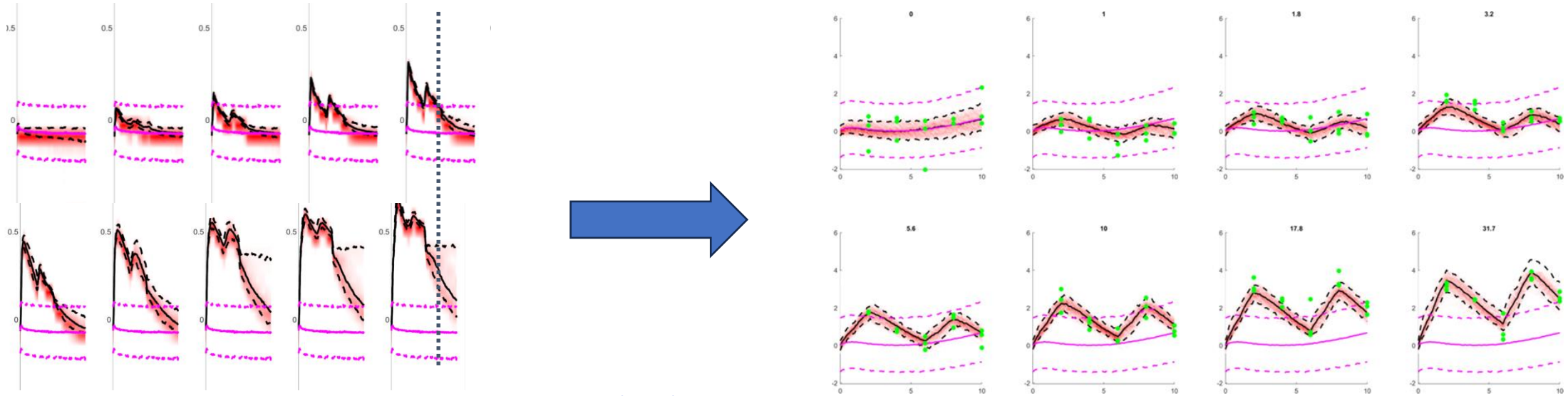
Using qAOPs at tier 2 for distinguishing between adaptive and adverse responses

- Various groups have built ODE-based mechanistic systems biology models of the Nrf2 regulatory network such as in kidney, liver
- On the other hand, chemically agnostic machine learning based approaches may be useful, but these will not necessarily be mechanistic.
- Leads to additional challenges around acceptance
- Focus on understanding homeostatic control of system to return to baseline - understand interplay between exposure and response
- Use repeat dose data generated in Leiden University

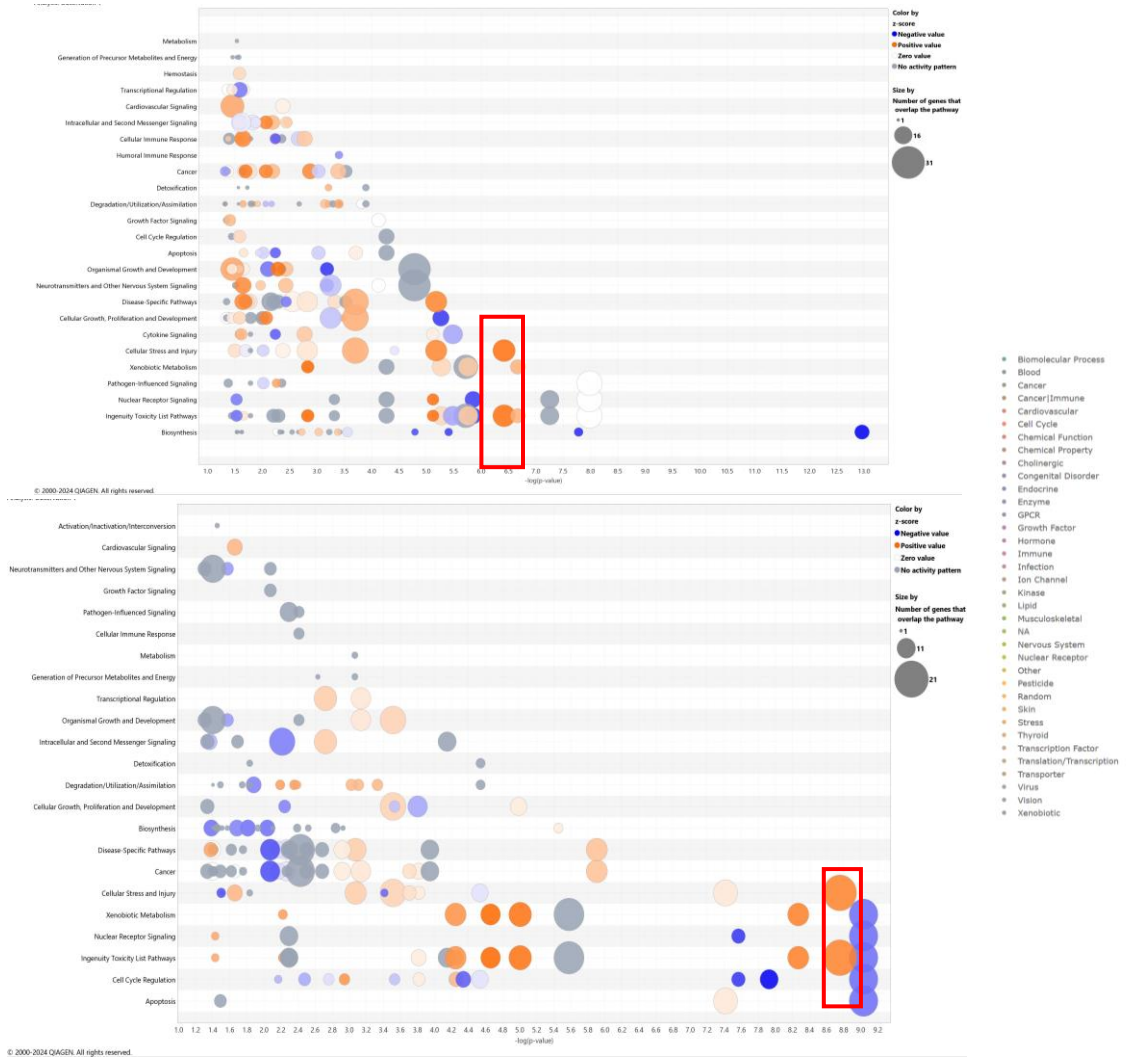
Chemical	Use scenario	Route	PBK L1 Cmax (µM)	PBK L2 Cmax (µM)	PBK L3 Cmax (µM)	Measured Cmax (µM)
Sulforaphane	Food & Drink, 3.9 mg/day	Oral	0.23	0.15	N/A	0.070
Sulforaphane	Tablet, 60 mg/day	Oral	1.2	0.77	N/A	N/A

Nrf2 response under increasing concentrations of SFN



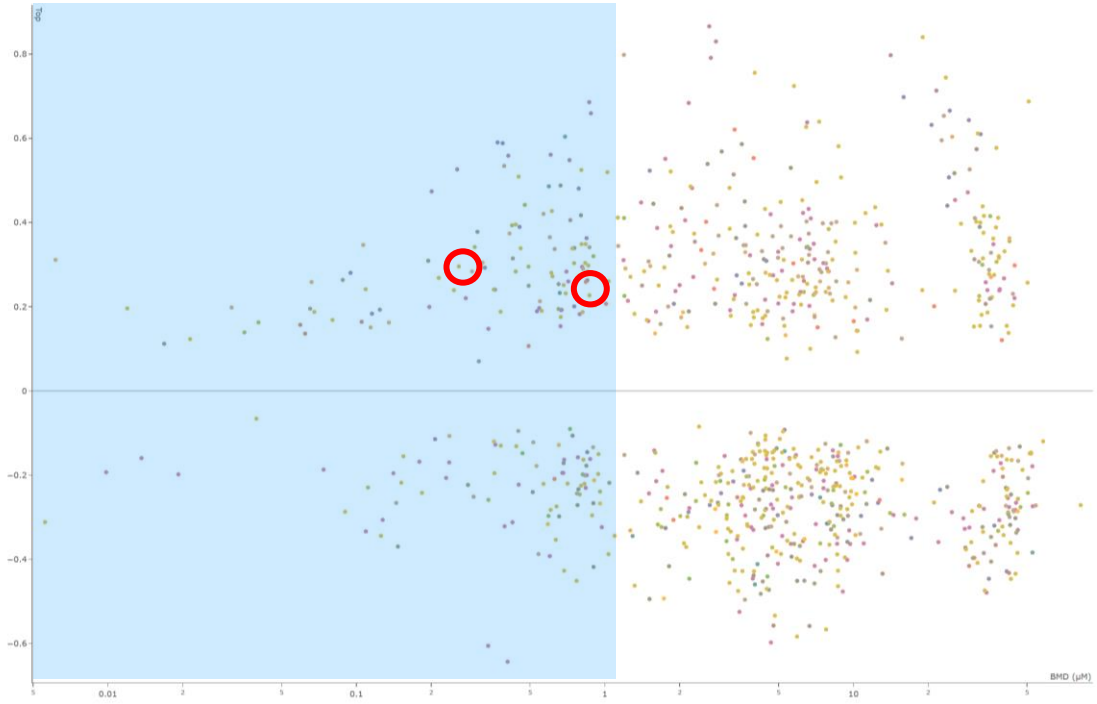
Data generated Leiden University

Challenge –secondary non-specific effects occurring within same dose range



IPA Plots from internal HTTr analysis of sulforaphane
In 2 cell lines – Nrf2 response gene sets highlighted in red

Data from Toxcast Dashboard for Sulforaphane showing HTTr gene sets plotted against dose

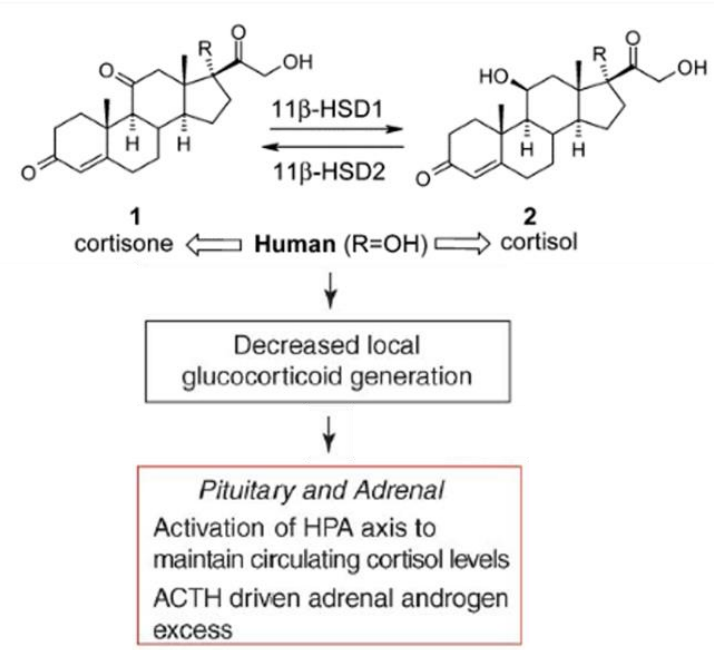


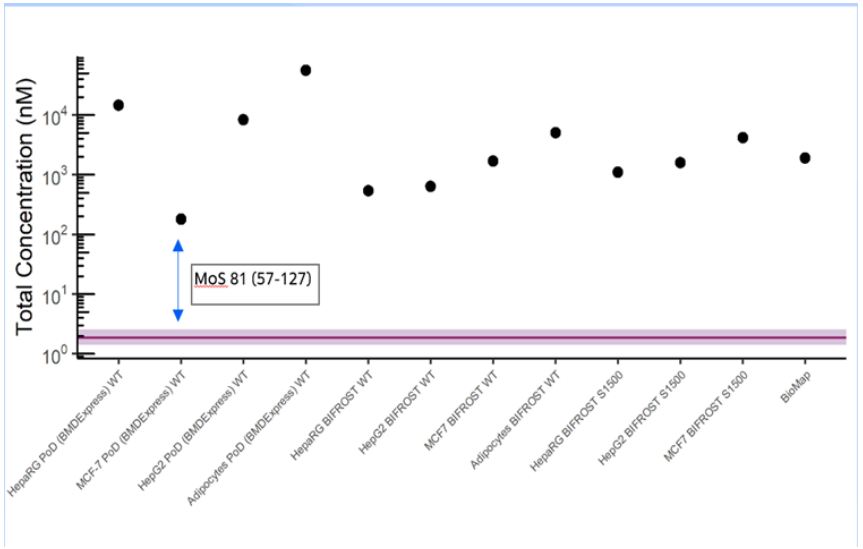
Dose

Chemical	Use scenario	Route	PBK L1 Cmax (μM)	PBK L2 Cmax (μM)	PBK L3 Cmax (μM)	Measured Cmax (μM)
Sulforaphane	Food & Drink, 3.9 mg/day	Oral	0.23	0.15	N/A	0.070
Sulforaphane	Tablet, 60 mg/day	Oral	1.2	0.77	N/A	N/A

Case study 3: Support consideration when specific mode of action identified

- Example when specific modality has been identified with other non-specific effects
- Focus on Systemic toxicity consideration
- Identified impact resulting in inhibition of 11B-HSD1 – no AOP identified
- Advantage human clinical relevant data identified

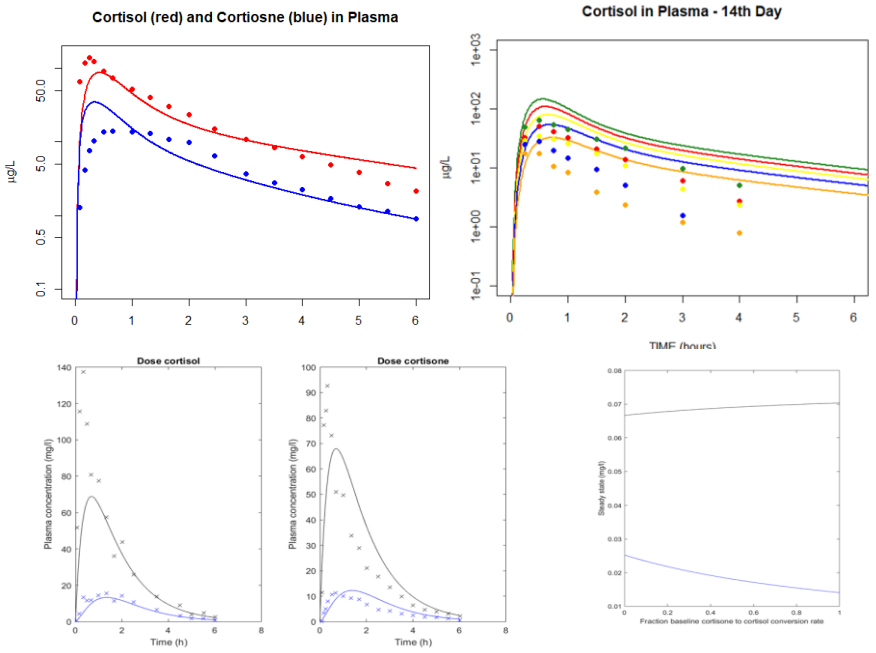


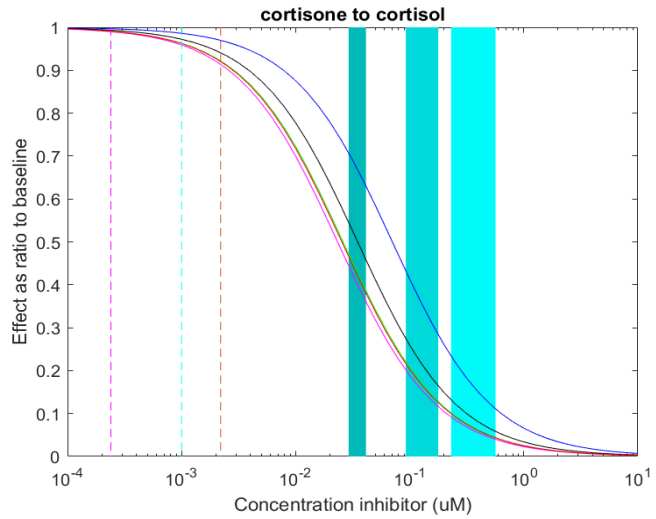


Bioactivity: exposure (BER) plot for consumer use scenario. Magenta line indicates the predicted systemic exposure (2.2nM). pale pink region indicates the uncertainty
No specific hits from MIE panel including CERUP targets

Case study 3 cont.

- Build a mechanistic model of systemic concentrations of cortisol, cortisone and an inhibitor of 11bHSD1 – utilised to predict the corresponding impact on levels of cortisol from H11bHSD1 inhibitors
- Initially replicating published clinical data parametrised in vitro findings and subsequently to support predictions of compound of interest.
- model produces predictions of cortisol and cortisone plasma concentrations that agree reasonably well with clinical measurements of baseline but underestimates reduction in cortisol
- A second simplified model build subsequently improved in replicating cortisone plasma kinetics and understand impact of steady state levels by following inclusion of a cortisol production rate.
- Final image brings together in vitro inhibition to clinical data and predicted systemic exposure
- Low amounts of inhibition produced only minor changes in systemic concentrations of cortisol and cortisone





Discussion

- NGRA is a tiered approach for making decisions without the use of animal data
- In many cases, protective safety decisions can be made without the use of AOPs e.g
    - For chemicals where no lead MoA can be identified or where multiple targets of activity are observed in a narrow dose range this is a more pragmatic solution
- For the foreseeable future we can foresee use of AOPs to address specific concerns rather than a globally applicable solution for more complex endpoints, e.g.
    - AOPs can be useful in designing either a tier 1 or 2 testing strategy when enough is known about an endpoint of concern (e.g. skin sensitisation).
    - qAOPs may also be helpful at tier 2 in distinguishing between adaptive and adverse effects
- qAOPs do not necessarily have to be fully mechanistic (i.e., systems biology) models, and other approaches should be considered (e.g., statistical or machine-learning based).
- The determination of what is required for acceptance for these models especially those predictive models less reliant on mechanistic basis has yet to be defined.

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Acknowledgements

- Alistair Middleton, Maria Baltazar, Sophie Cable, Paul Carmichael, Tom Cull, Matthew Dent, Nicky Gilmour, Sarah Hatherall, Predrag Kukic, Cameron MacKay, Gavin Maxwell, Sophie Malcomber, Claire Peart, Georgia Reynolds, Joe Reynolds, Adam Wood

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Thank You

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