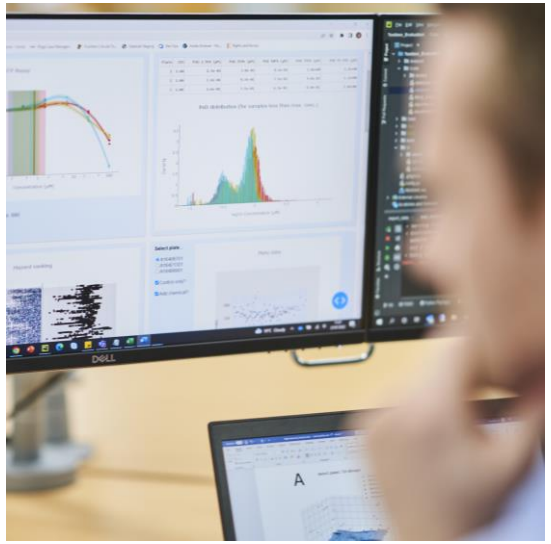
The Role of qAOPs in Exposure-Led NGRA: Benefits and Limitations

Alistair Middleton and Andrew White

12th World Congress on Alternatives and Animal Use in the Life Sciences



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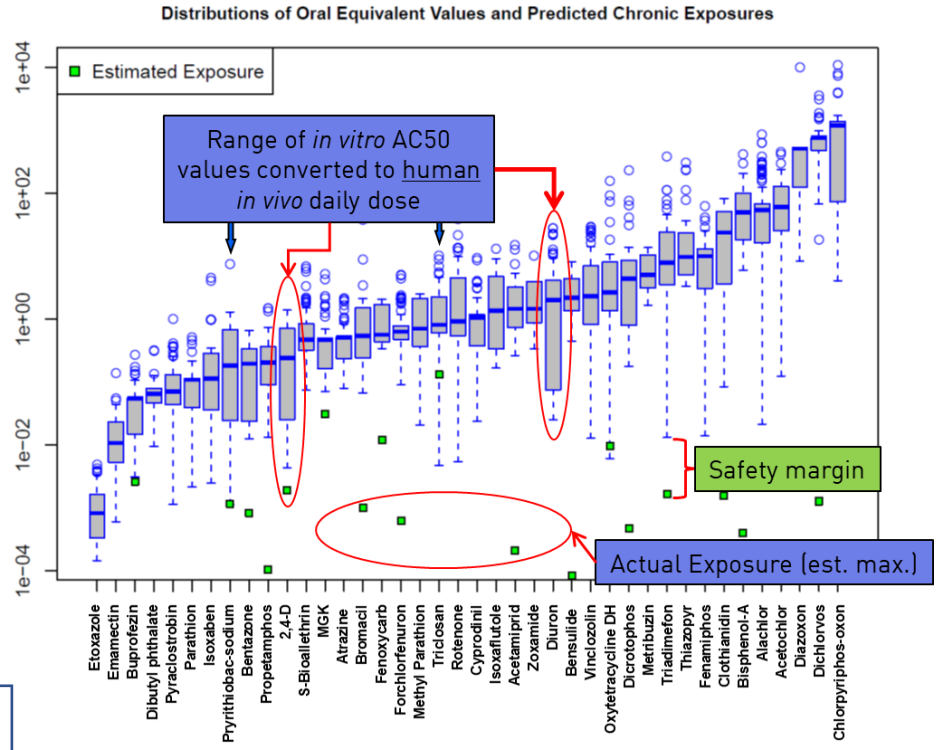
Safety without animal testing - Next Generation Risk Assessment (NGRA)

*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***

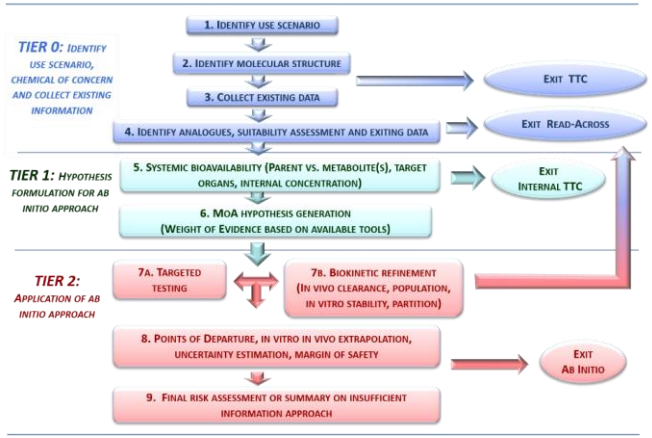


Slide from Dr Rusty Thomas, EPA, with thanks

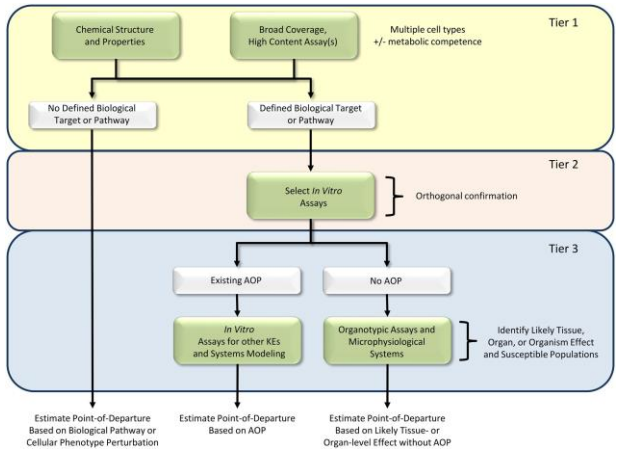
Rotroff, *et al.* Tox.Sci 2010

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.**

Decision frameworks in NGRA

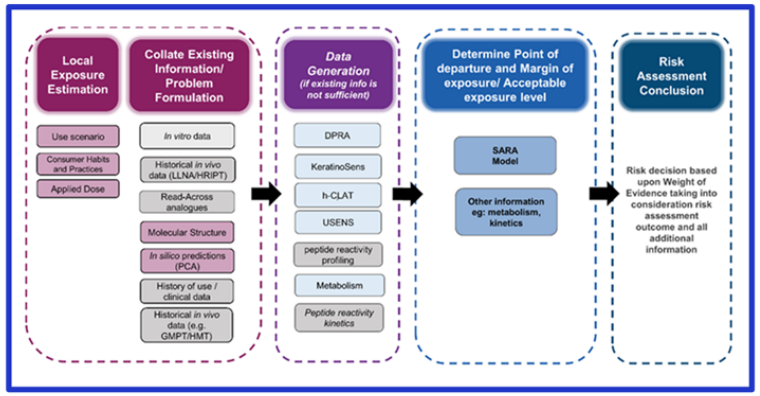


Berggren et al., 2017



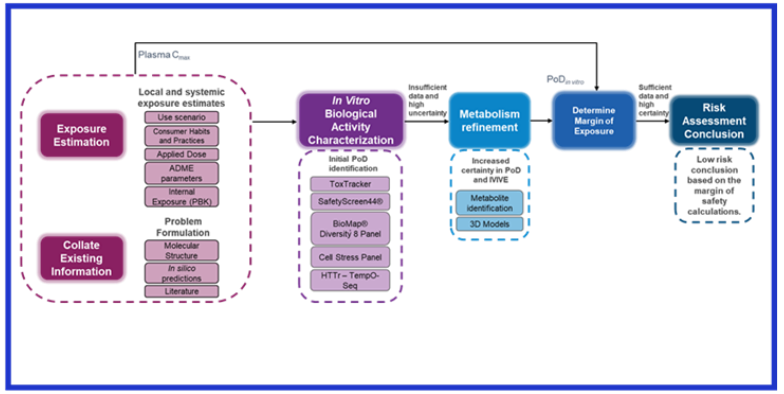
Thomas et al., 2019

Skin Sensitisation



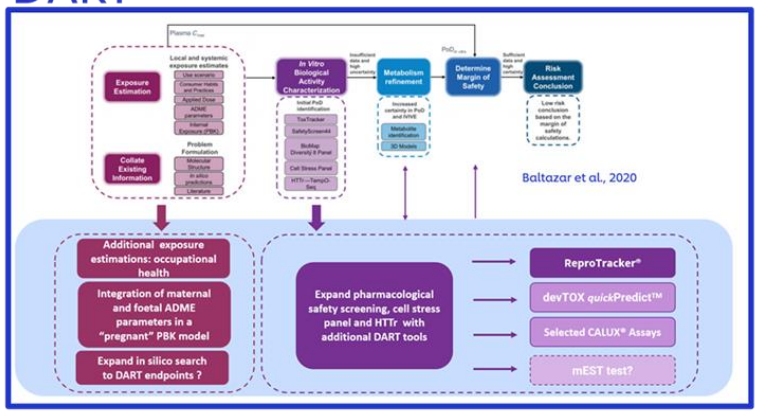
Reynolds et al (2021) Reg Tox Pharmacol, **127**, 105075

Systemic safety



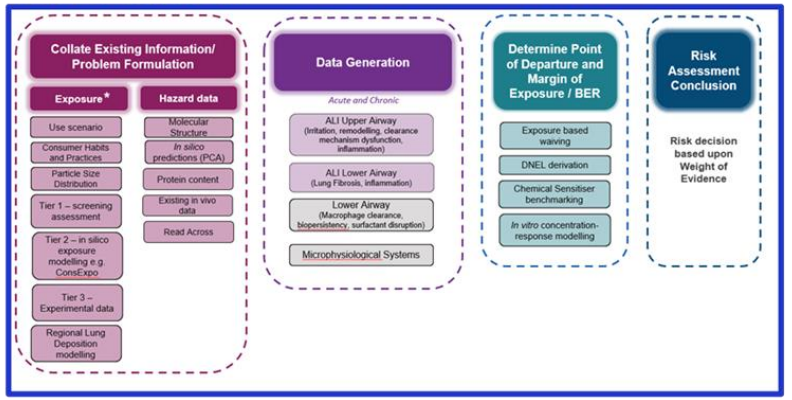
Baltazar *et al.*, (2020) *Tox Sci* , Volume 176, Issue 1, Pages 236–252

DART



Rajagopal et al (2022). Front. Toxicol., 07 March 2022

Inhalation



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qAOPs and NGRA decision frameworks

Maria Baltazar talk
Session S400
(Symposium)
Monday, August 28,
14:00 – 16:00

Problem formulation – Tier 0

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Initial BER estimate – Tier 1

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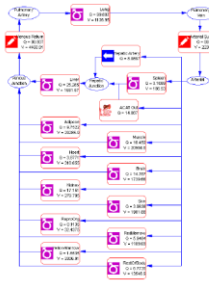
PBK models



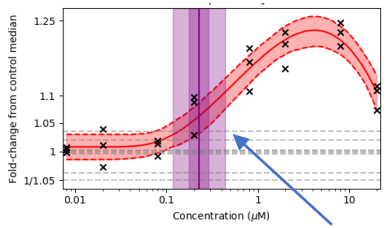
In vitro cells assays

Assay 1

Assay 2

Assay 3

Concentration-response data



POD

Exposure

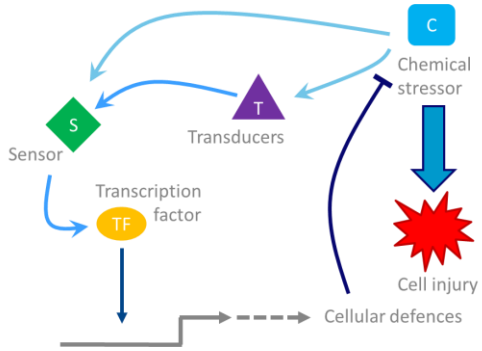
Hazard (points of departure)

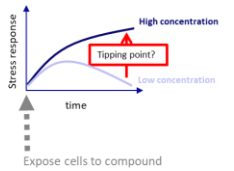
Exposure likely to trigger bioactivity

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

BER refinement – Tier 2

Understanding bioactivity vs adversity





Low risk of exposure causing any bioactivity

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

Safety Decision

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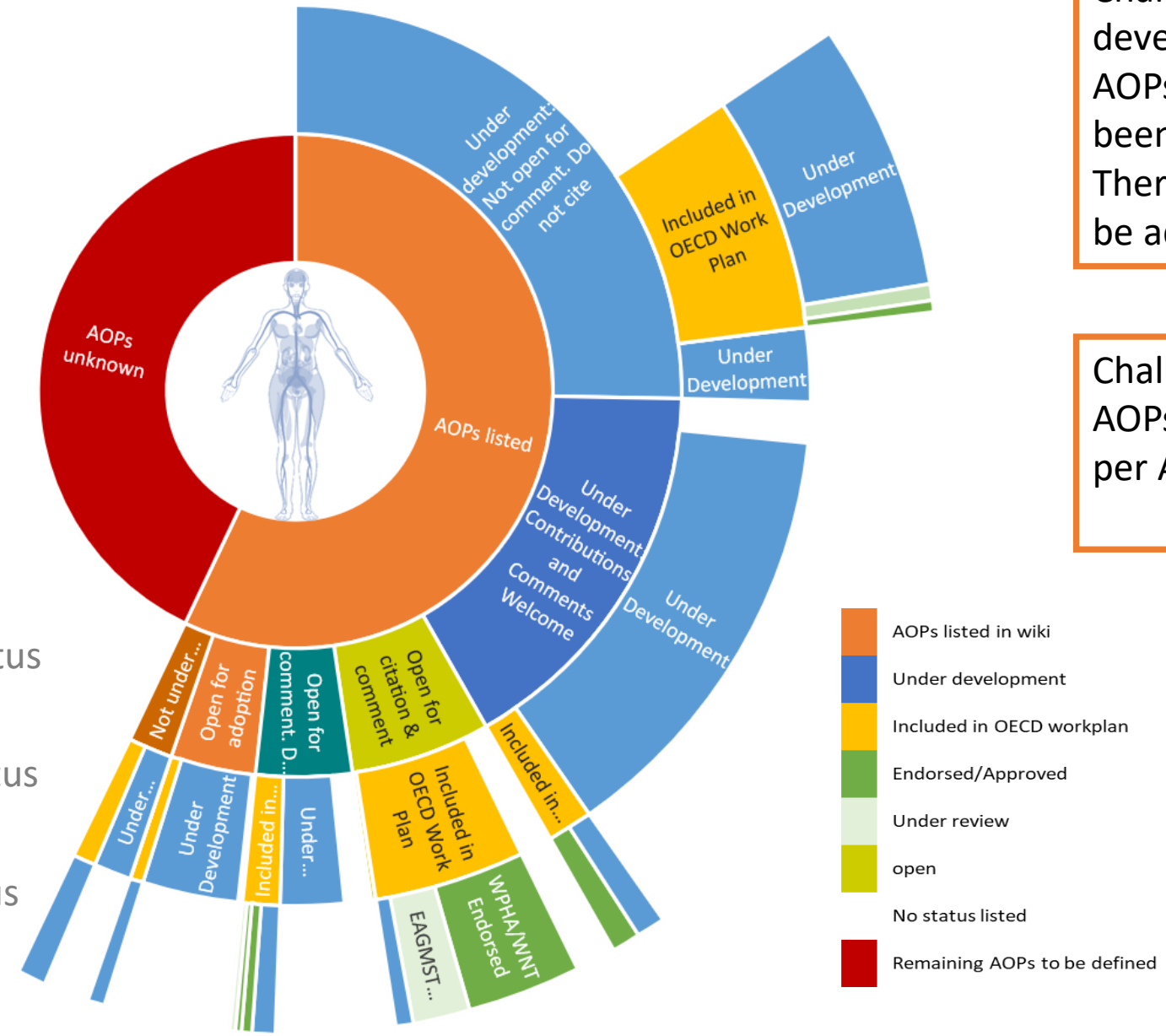
Current status of AOPs



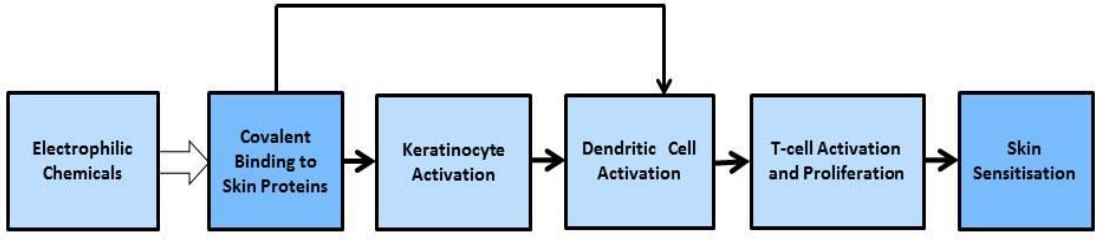
Challenge 1: After ~10 years of development, only limited number of AOPs, many of which have not yet been verified (biological coverage). There's an issue of scale that needs to be addressed.

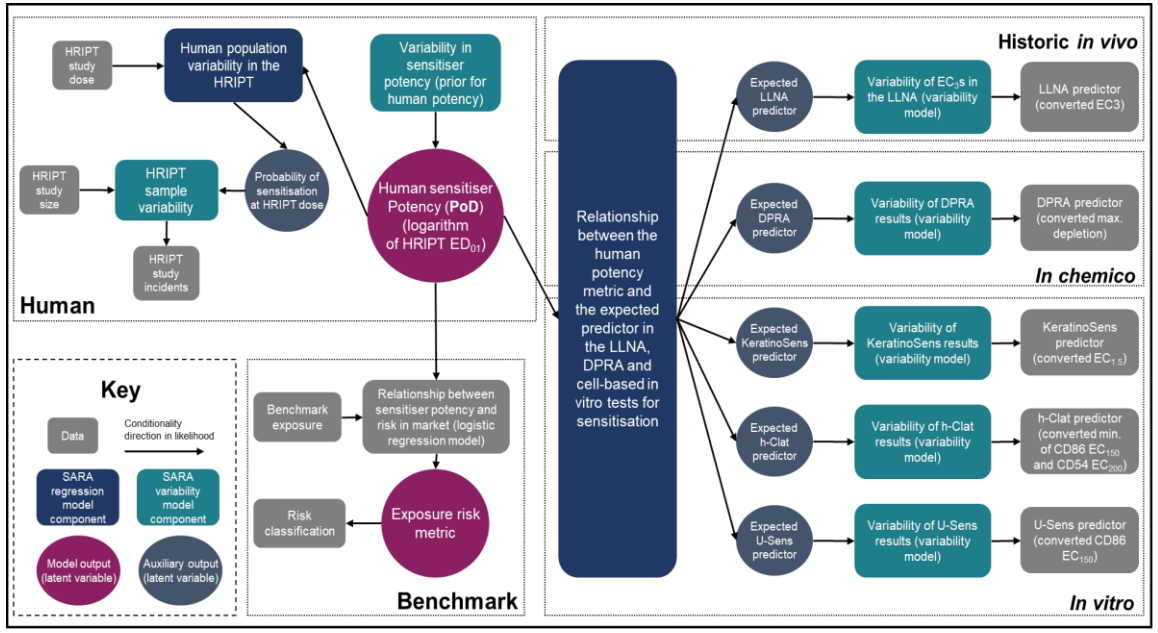
Challenge 2: At present there are 446 AOPs on AOP-Wiki. Assuming 5 KEs per AOP, that's over 2000 assays.

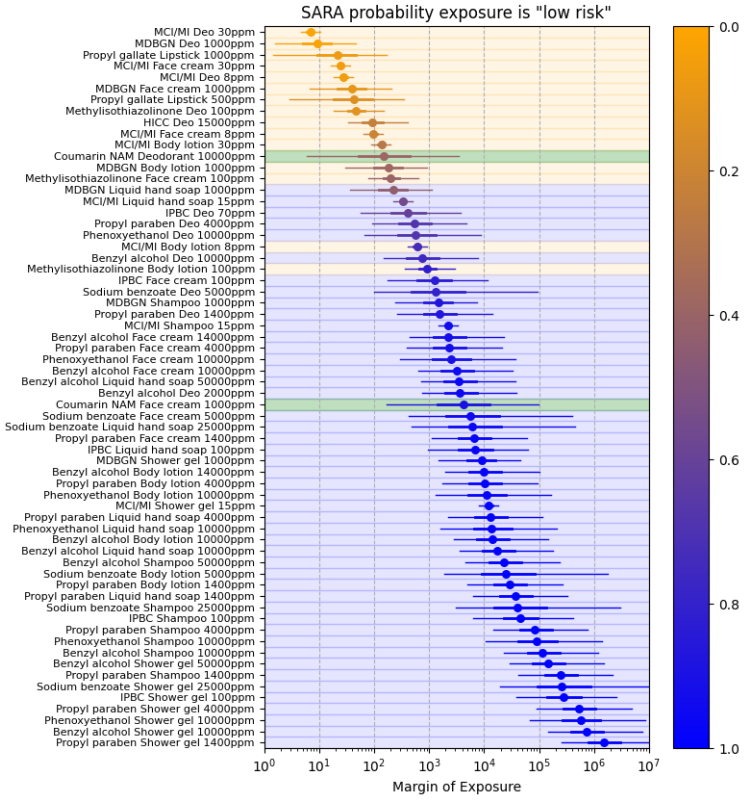
- Toxcast has ~ 700 assays

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

Skin allergy example: AOP-informed testing strategy







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.

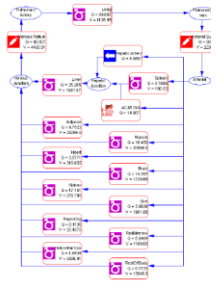
Challenge 3: acceptance and development of AOP-based statistical or machine learning based approaches for quantifying risk

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

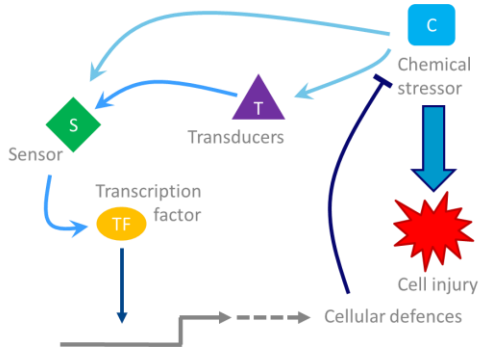
Hazard (points of departure)

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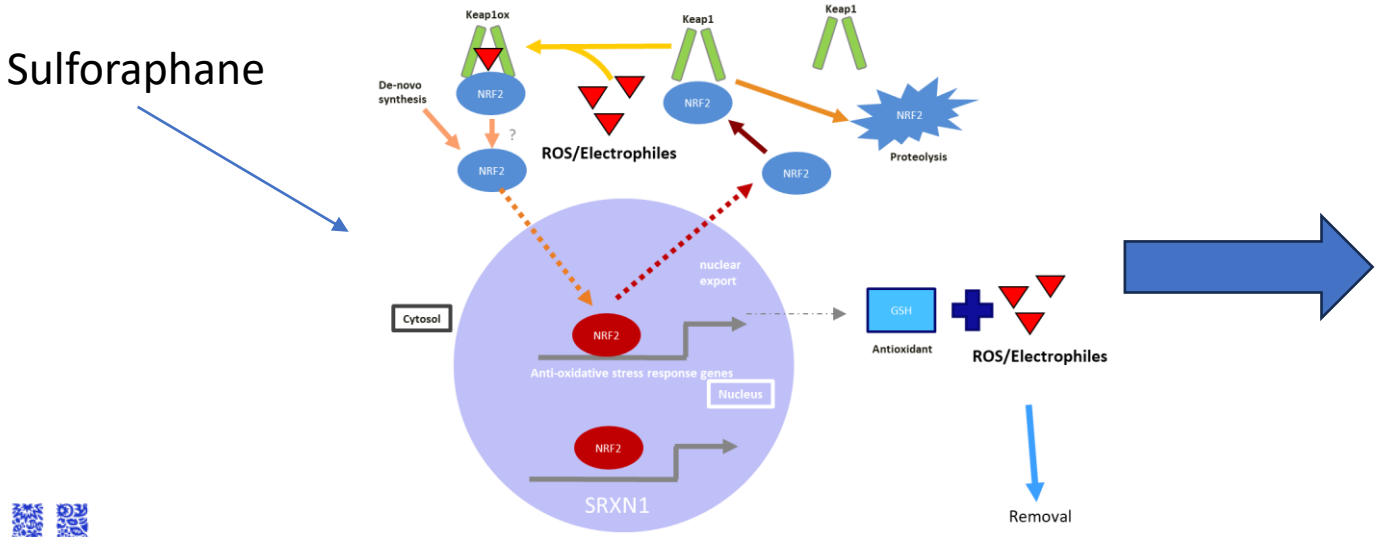
Using qAOPs at tier 2 for distinguishing between adaptive and adverse responses

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?



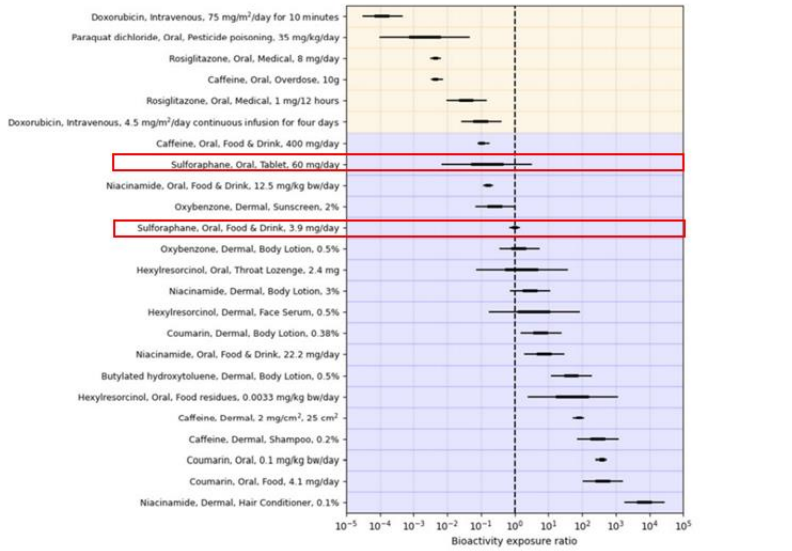
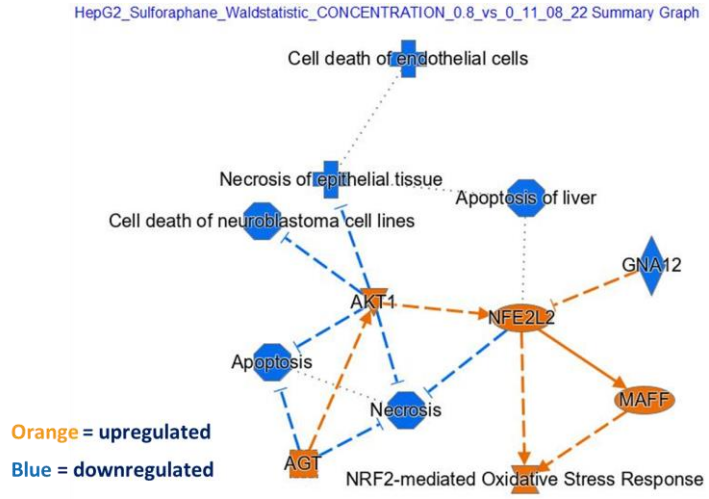


Figure 5. Centered 50% and 95% credible intervals summarizing the distribution of the bioactivity exposure ratio (BER) when using all available predicted C_{max} estimates. Background colors indicate the assigned risk category for each benchmark chemical-exposure scenario assigned at stage 1 (blue—low, yellow—high). The vertical dashed line indicates a BER equal to 1.

Key event in multiple AOPs linked to organ toxicity

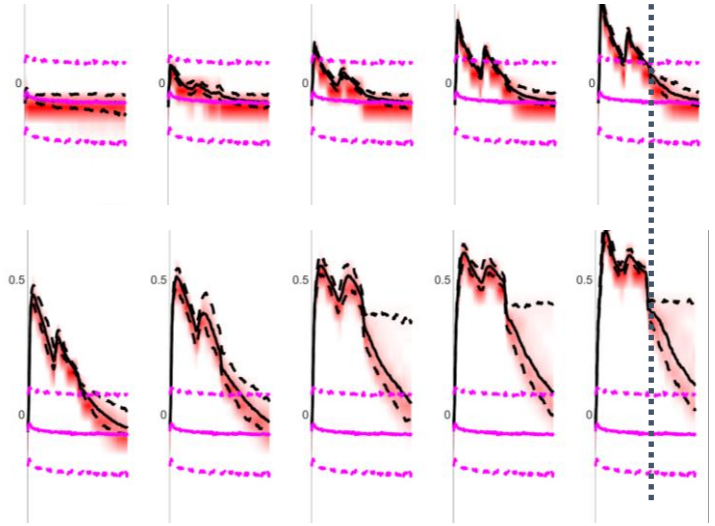


Using qAOPs at tier 2 for distinguishing between adaptive and adverse responses

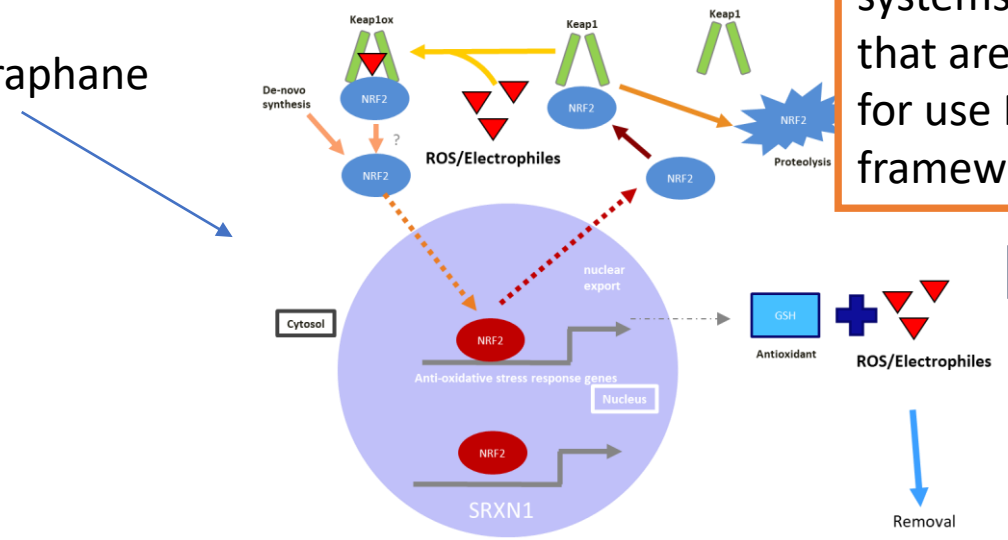
Sulforaphane case study

- Various groups have built ODE-based mechanistic systems biology models of the Nrf2 regulatory network.
- Developing systems that are chemical-agnostic can be very challenging.
- On the other hand, chemically agnostic machine learning based approaches may be useful, but these will not necessarily be mechanistic.

Nrf2 response under increasing concentrations of SFN

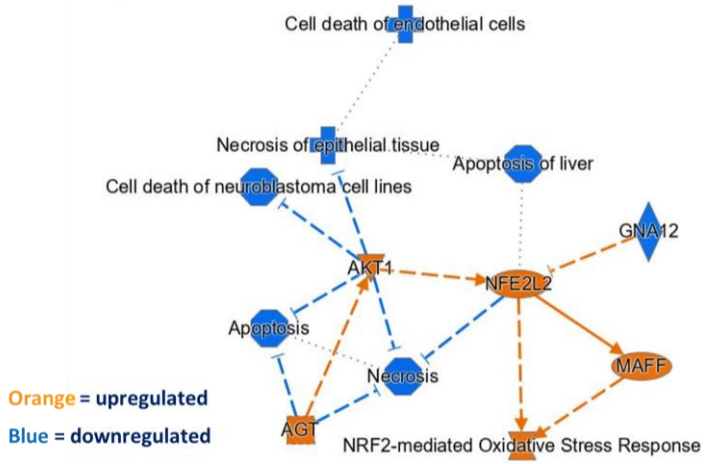


Sulforaphane



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

multiple AOPs linked to organ toxicity



Discussion

- NGRA is 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 …
- … and in the foreseeable future we can foresee use of AOPs to address specific concerns rather than a globally applicable solution, 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).
  - Quantitative AOPs 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).

Thank You

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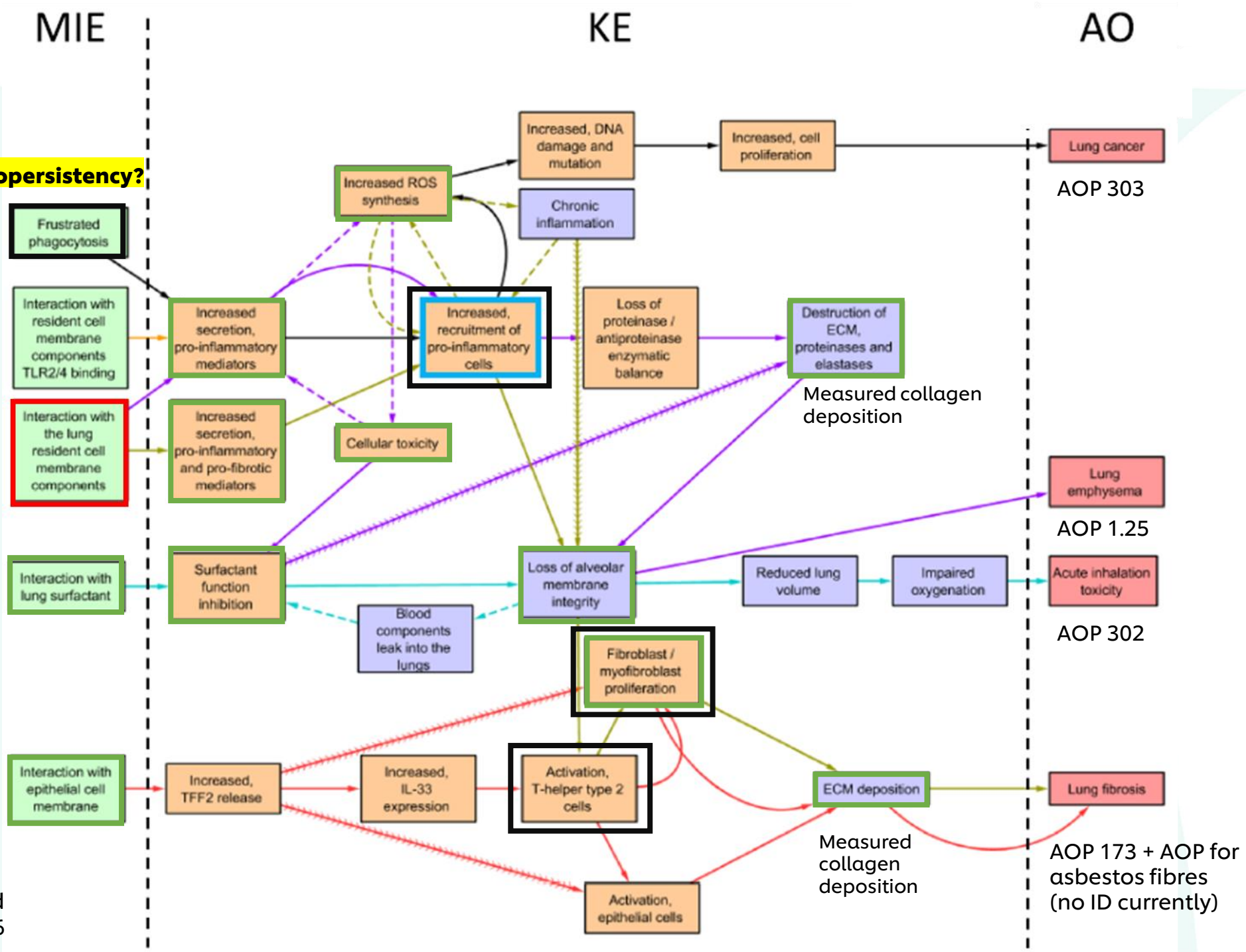
Extras...

From mechanistic point of view our strategy covers multiple MIE, KEs

Ongoing capability build activities

Potential new areas of research?



Halappavar 2020. Particle and Fibre Toxicology volume 17, 16