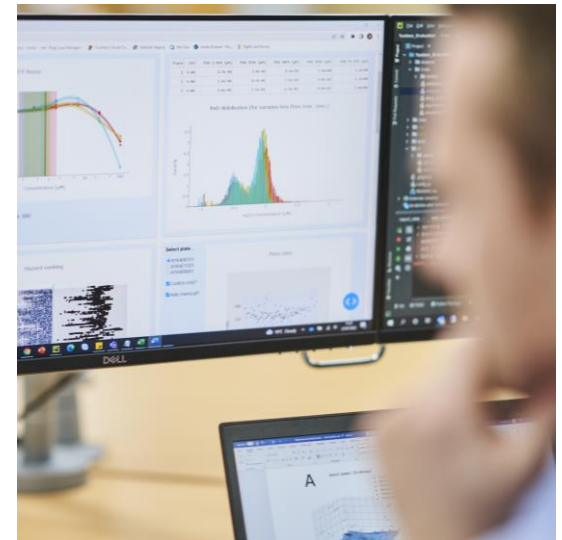


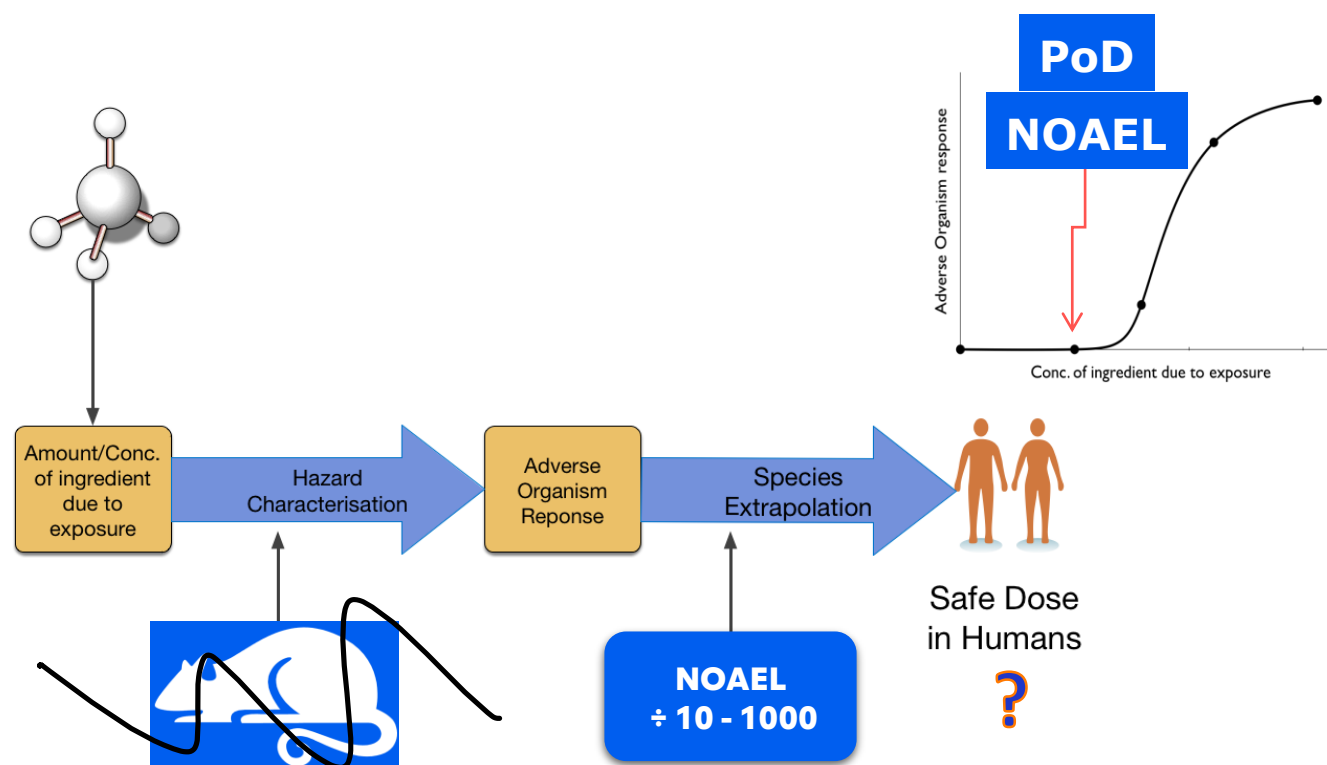
Assessing the protectiveness and utility of a NAM-based toolbox for systemic toxicity

Matt Dent, Unilever Safety and Environmental Assurance Centre, UK



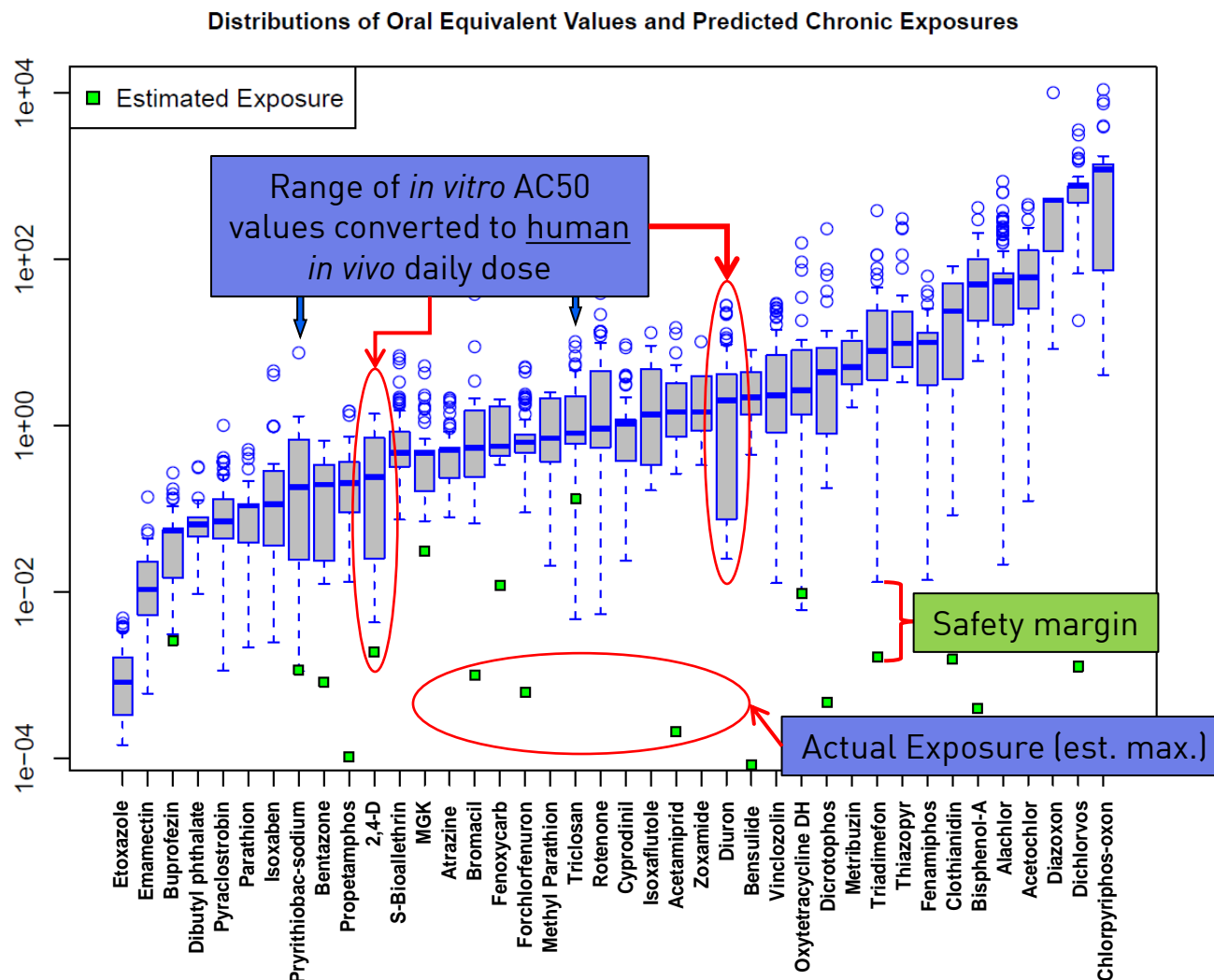
Are non-animal safety assessments even possible for systemic toxicity?

Systemic toxicity isn't like local toxicity



Many possible adversities...ADME considerations...Homeostasis

Paradigm shift for systemic safety - Protection not Prediction



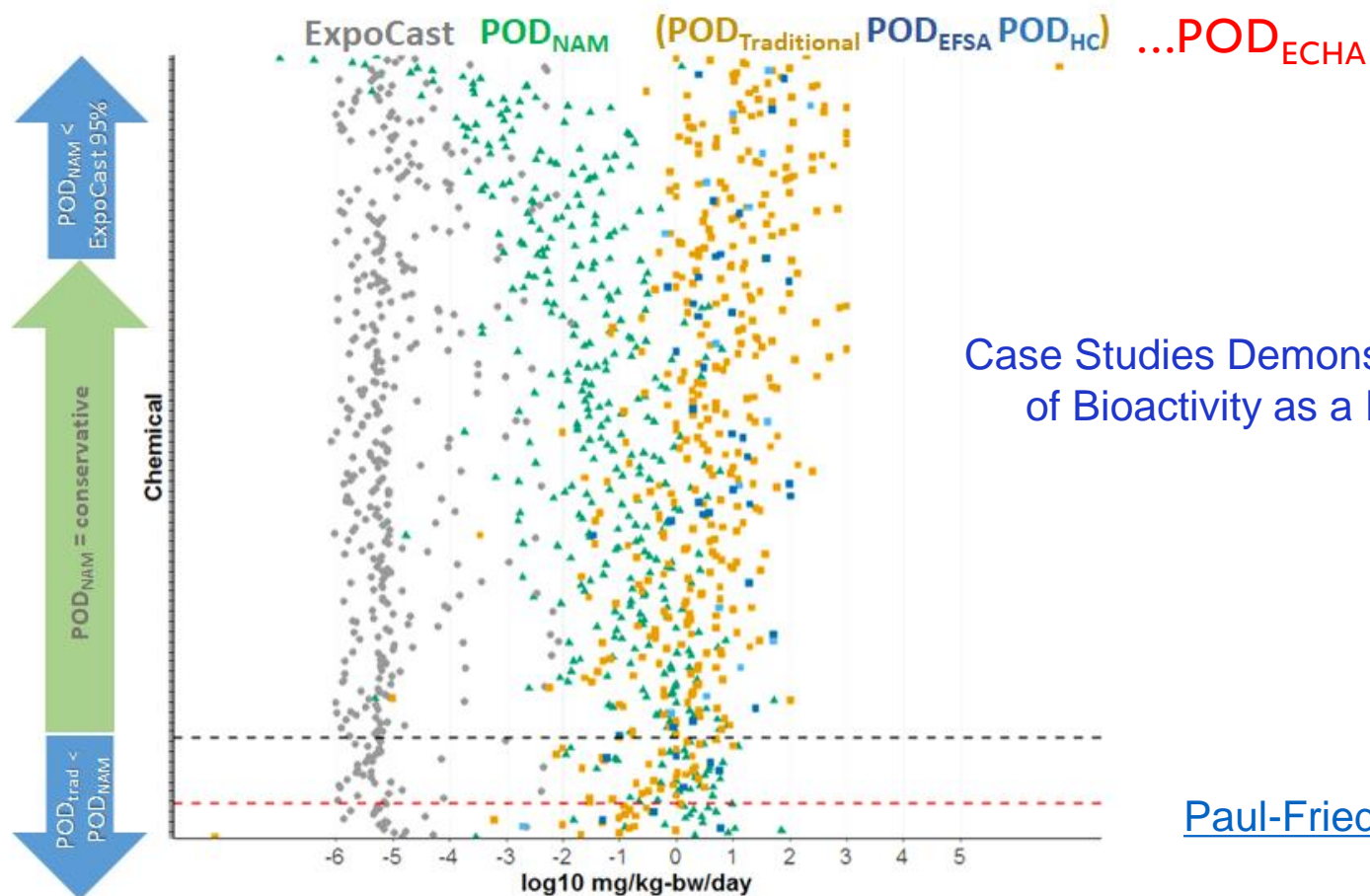
The hypothesis underpinning this type of NGRA is that **if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.**

Rotroff, *et al.* *Tox.Sci* 2010

Graphic from Dr Rusty Thomas, EPA, with thanks



Points of Departure from NAMs can be protective

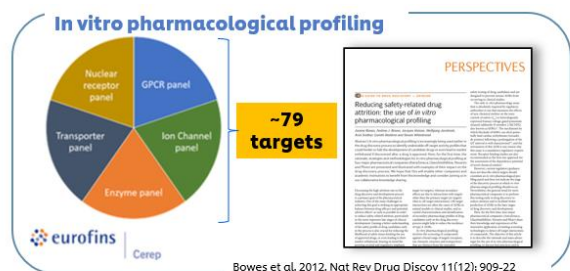


Case Studies Demonstrating Application of Bioactivity as a Protective POD

[Paul-Friedman et al., 2020](#)

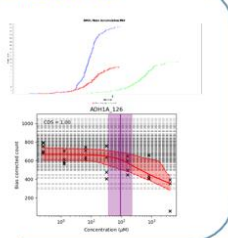
Bioactivity exposure ratios

BIOACTIVITY



High-Throughput transcriptomics (HTTr)

- TempO-seek technology – full gene panel
- 24hr exposure
- 7 concentrations
- Various cell models (e.g. HepG2, MCF7, HepaRG)
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. *Comp Tox* 16: 100138
Baltazar et al. 2020. *Toxicol Sci* 176(1): 236–252

Cell stress panel (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
- Dose-response analysis using BIFROST model

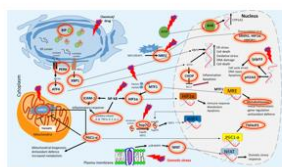
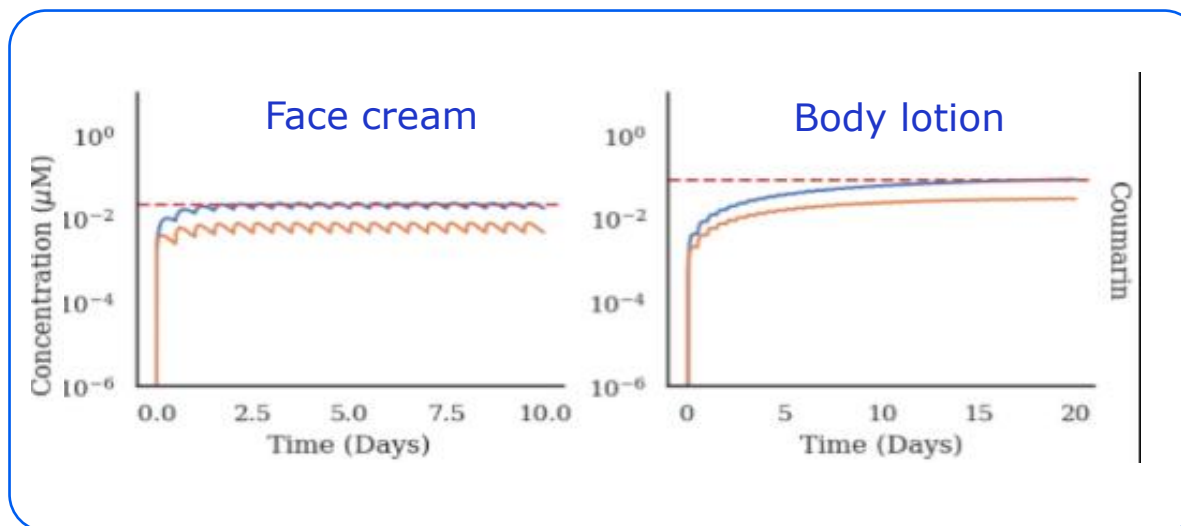


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. *Toxicol Sci* 176(1): 11-33

EXPOSURE



Identify lowest (most sensitive) point of departure, expressed in μM

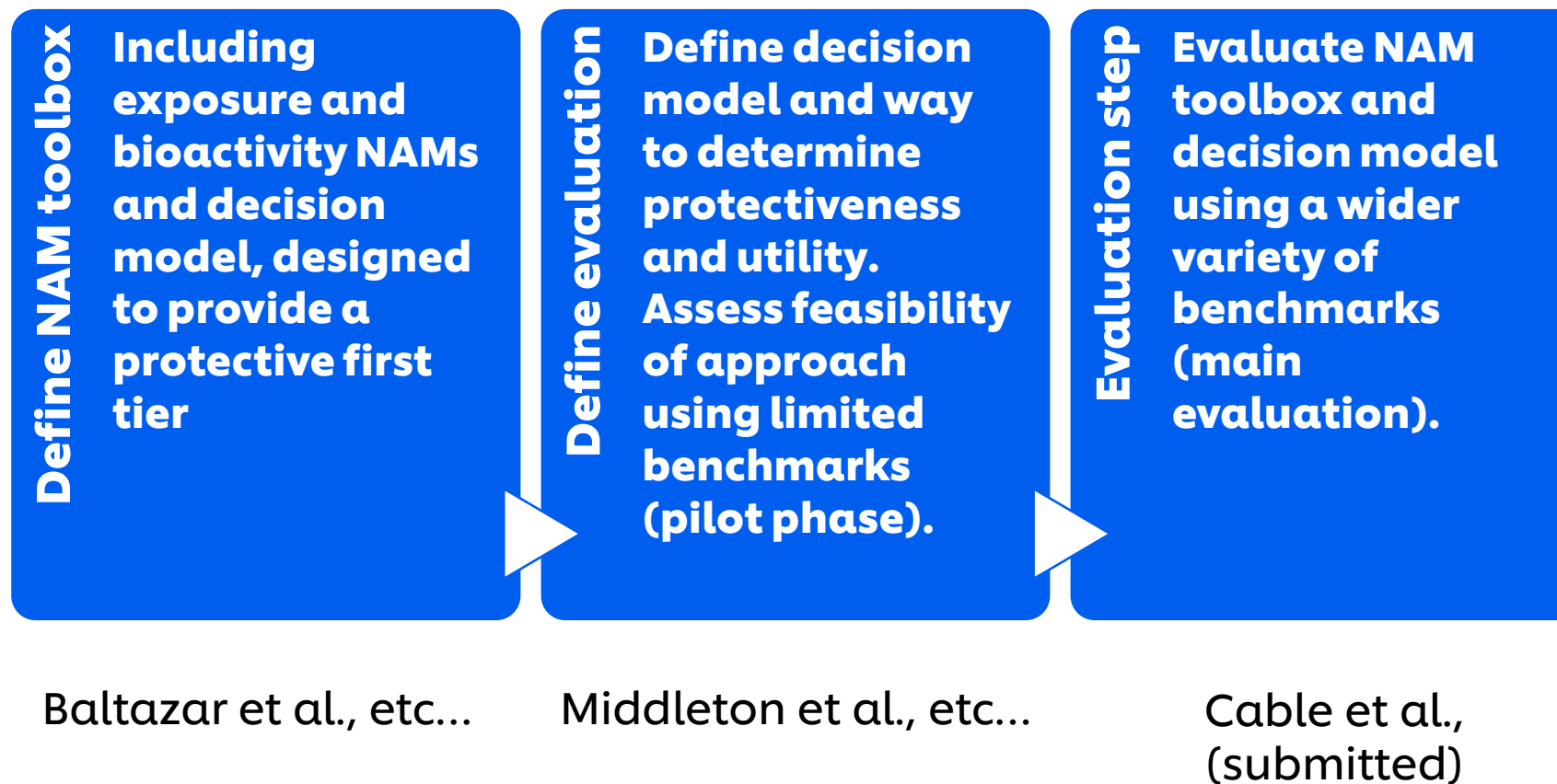
Identify realistic worst-case plasma exposure (C_{max}) expressed as μM

BIOACTIVITY EXPOSURE RATIO =

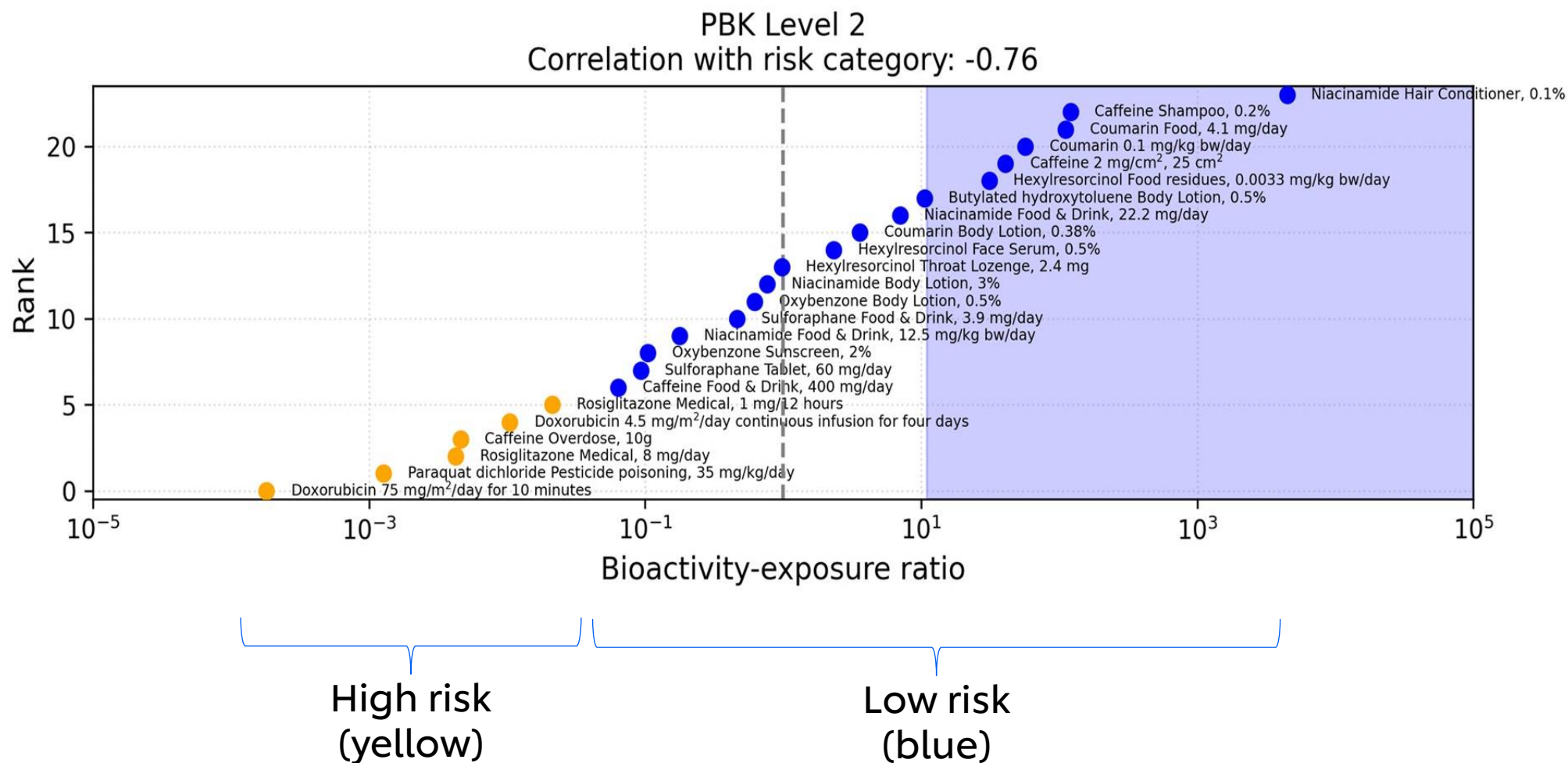
BIOACTIVITY
EXPOSURE

The bigger the BER, the greater the confidence that bioactivity will not occur in exposed consumers

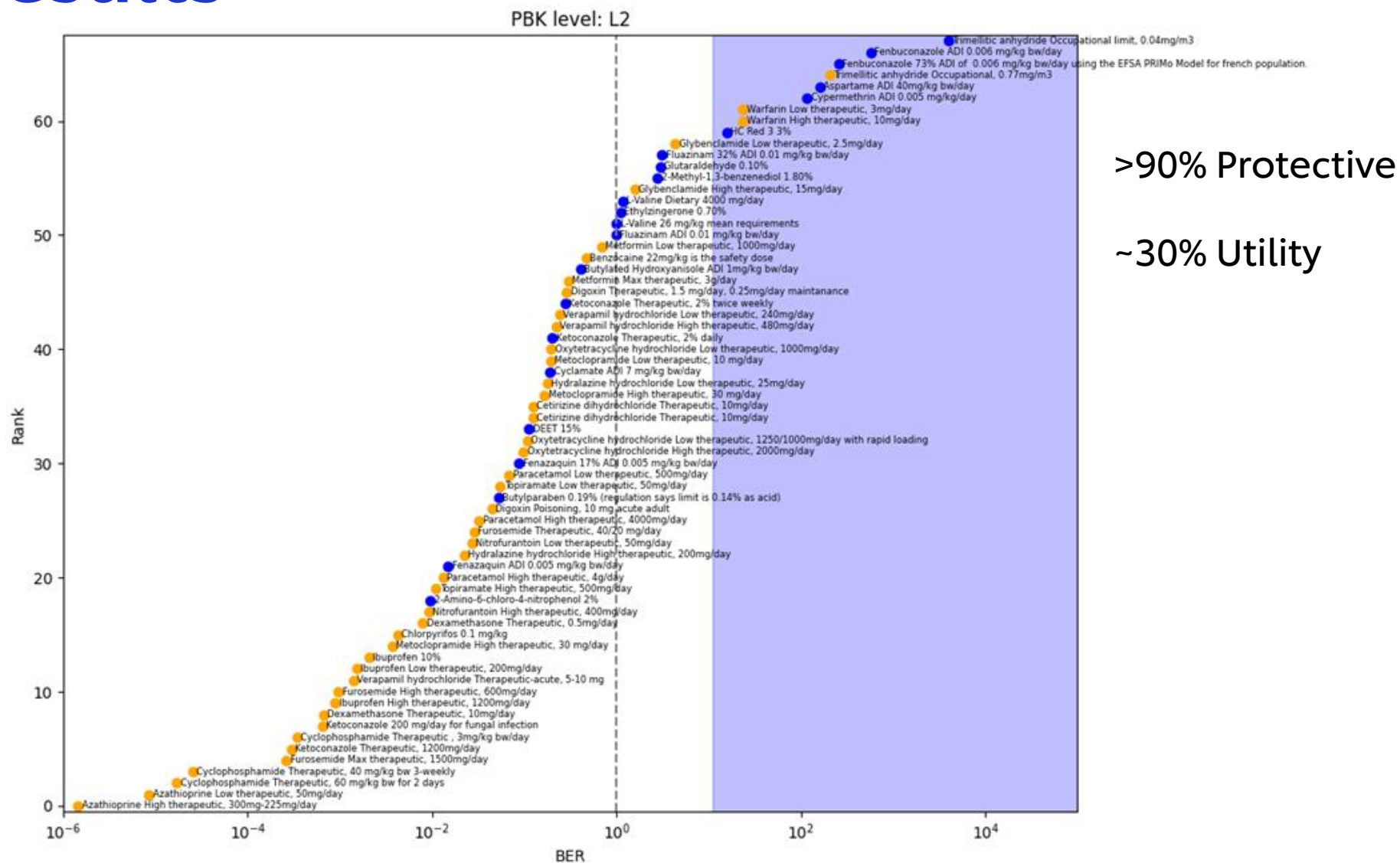
Approach to evaluation of NAM toolbox



Pilot phase results



Main results



Cable et al (Submitted)

CONCLUSIONS

- Pre-defining the evaluation strategy helps prevent bias
- Decisions made using the NAM are generally more protective than those using animal data
- Some modes of action are not covered in this NAM panel – need to integrate other lines of evidence to make a confident decision

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Thank You



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