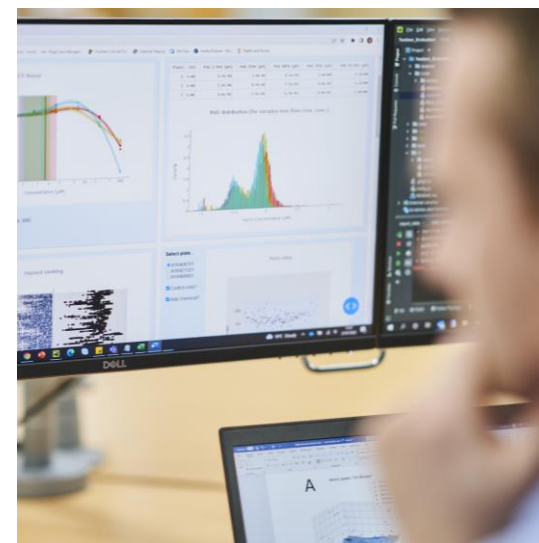
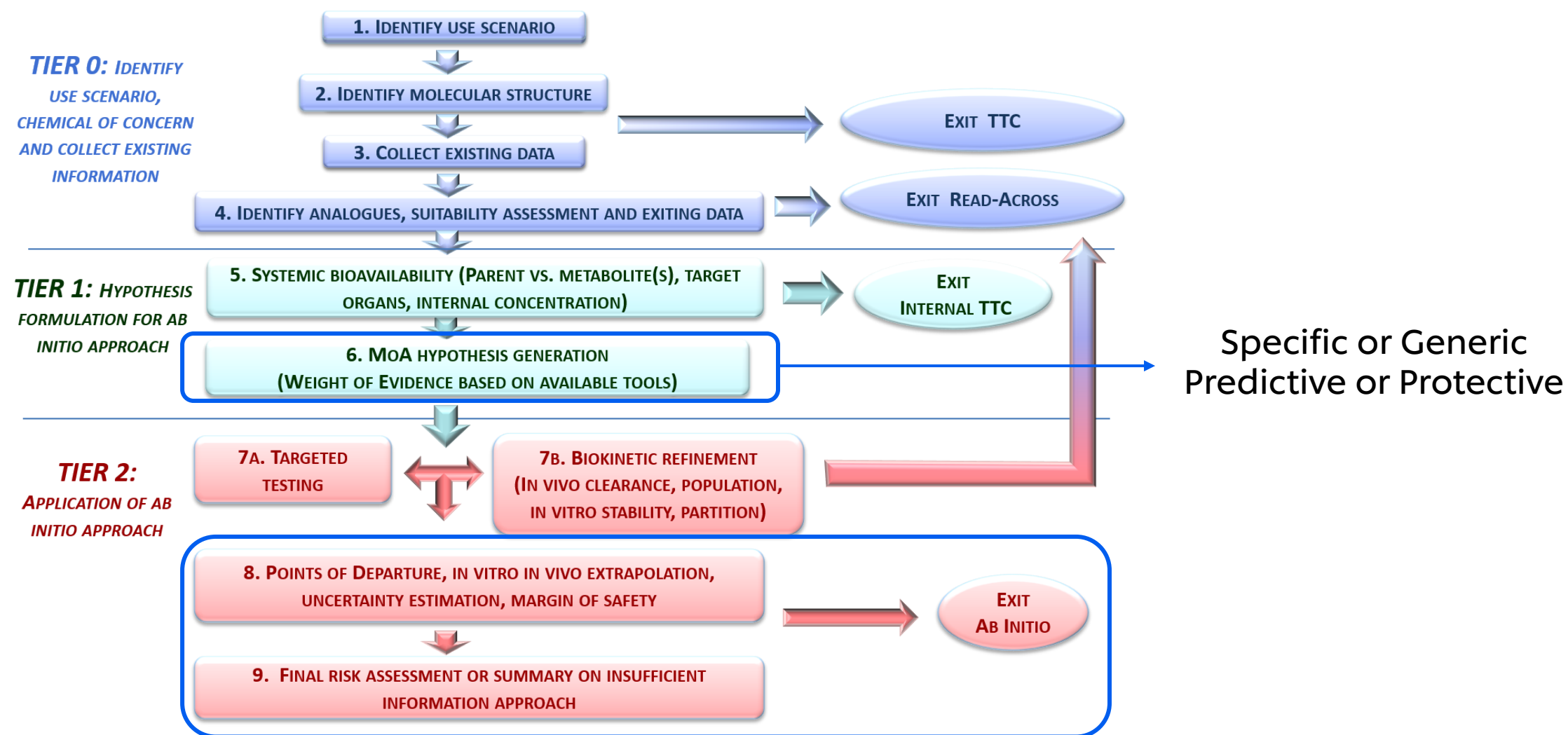


Practical use of Bioactivity Exposure Ratio (BER) in animal-free cosmetic ingredient risk assessment:

Matt Dent, Unilever Safety and Environmental Assurance Centre, UK



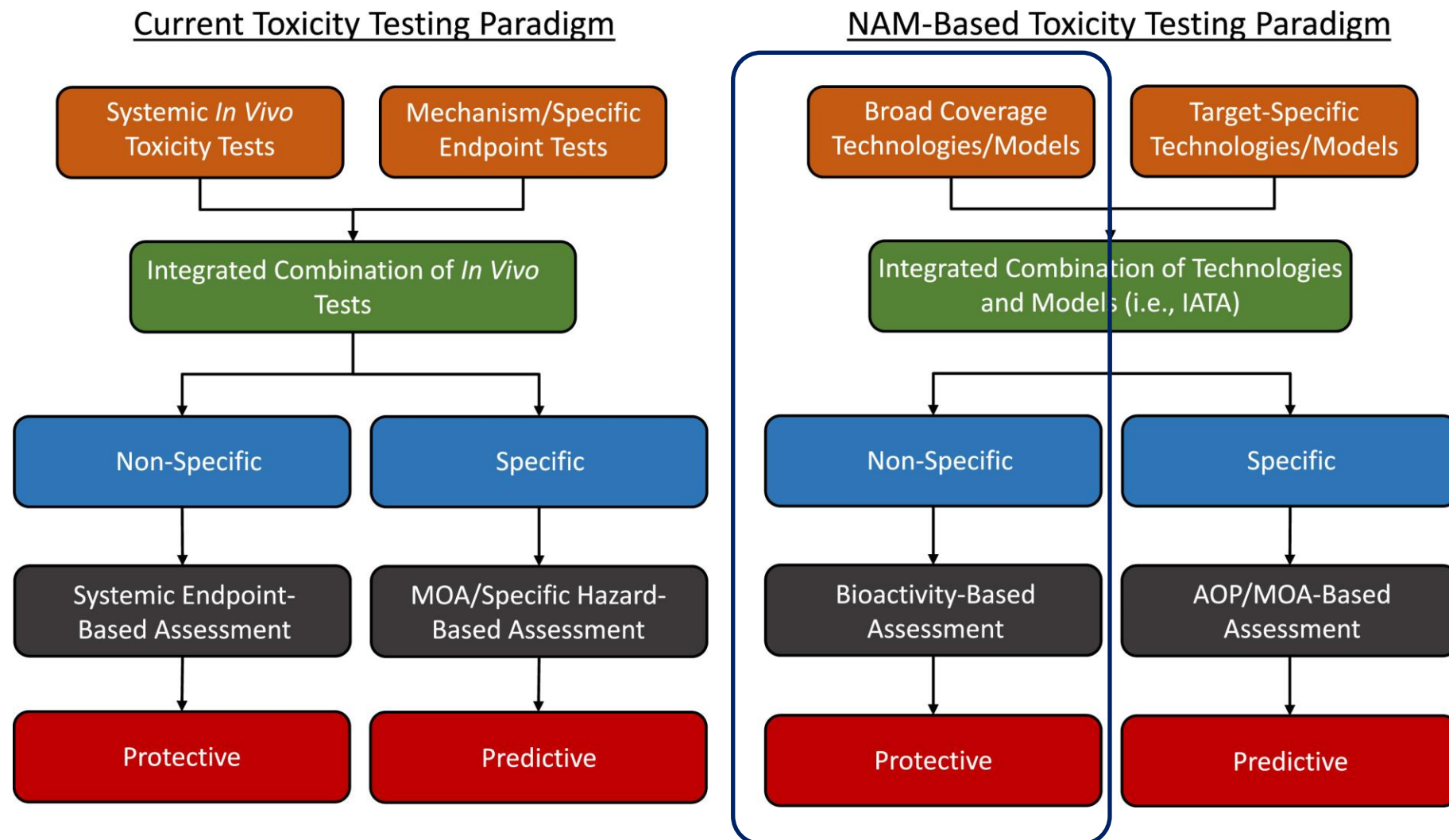
Practicality of BERs in a tiered approach



Berggren et al., (2017)

<https://doi.org/10.1016/j.comtox.2017.10.001>

Protection and prediction in current and future assessment approaches



Browne et al., (2024) <https://doi.org/10.1016/j.yrtph.2024.105579>

Practical considerations

- Confidence in exposure predictions (including role of metabolism)
- Breadth of biological coverage (how much is enough?)
- Common understanding of the meaning of the BER
...and its place in a tiered NGRA

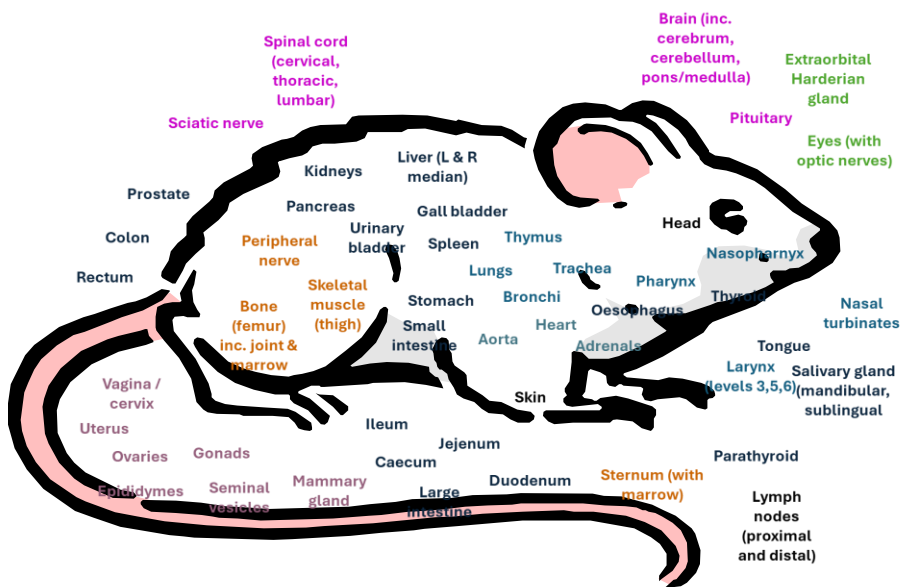
Practical considerations

- Confidence in exposure predictions (including role of metabolism)
- Breadth of biological coverage (how much is enough?)
- Common understanding of the meaning of the BER
...and its place in a tiered NGRA
- *How confident can you be in the use of BER for safety decision making?*

Breadth of biological coverage

Historical: animal *in vivo*

New: human-derived *in vitro*



In vitro pharmacological profiling

Cell stress panel (CSP)

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

High-Throughput transcriptomics (HTTr)

- TempO-seq technology: full gene panel
- 24hr exposure
- 7 concentrations
- Variability in HepG2
- Dose-response BMD modeling

Other targeted assays

REPROTRACKER®

Animal-free developmental toxicity predictions

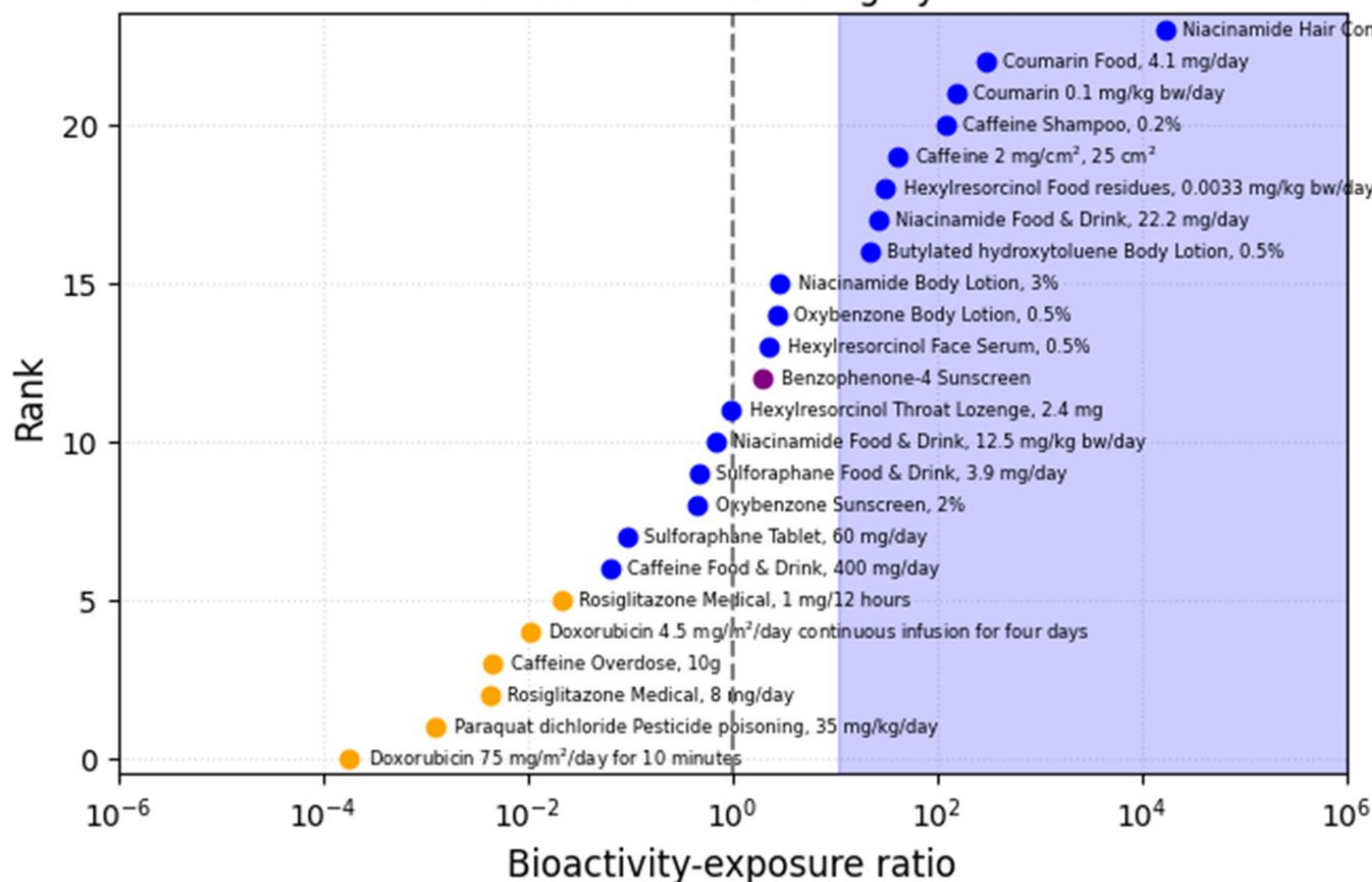
AR CALUX

BDS BioDetection Systems

"It's easy to say that models are wrong. The hard part is figuring out which models are useful and how wrong they are."
 (George Box)

Practical utility of BERs can only be determined by benchmarking safety decisions

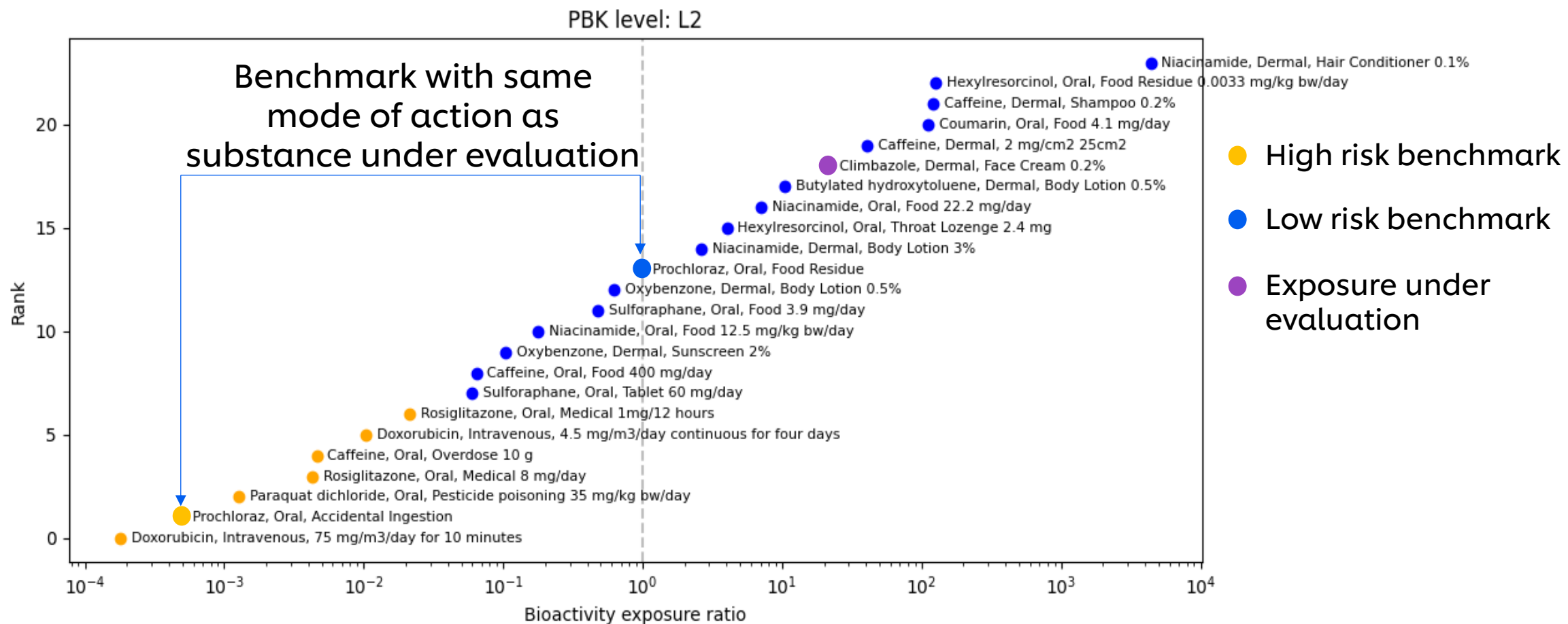
PBK Level 2
Correlation with risk category: -0.77



- High risk benchmark
- Low risk benchmark
- Exposure under evaluation

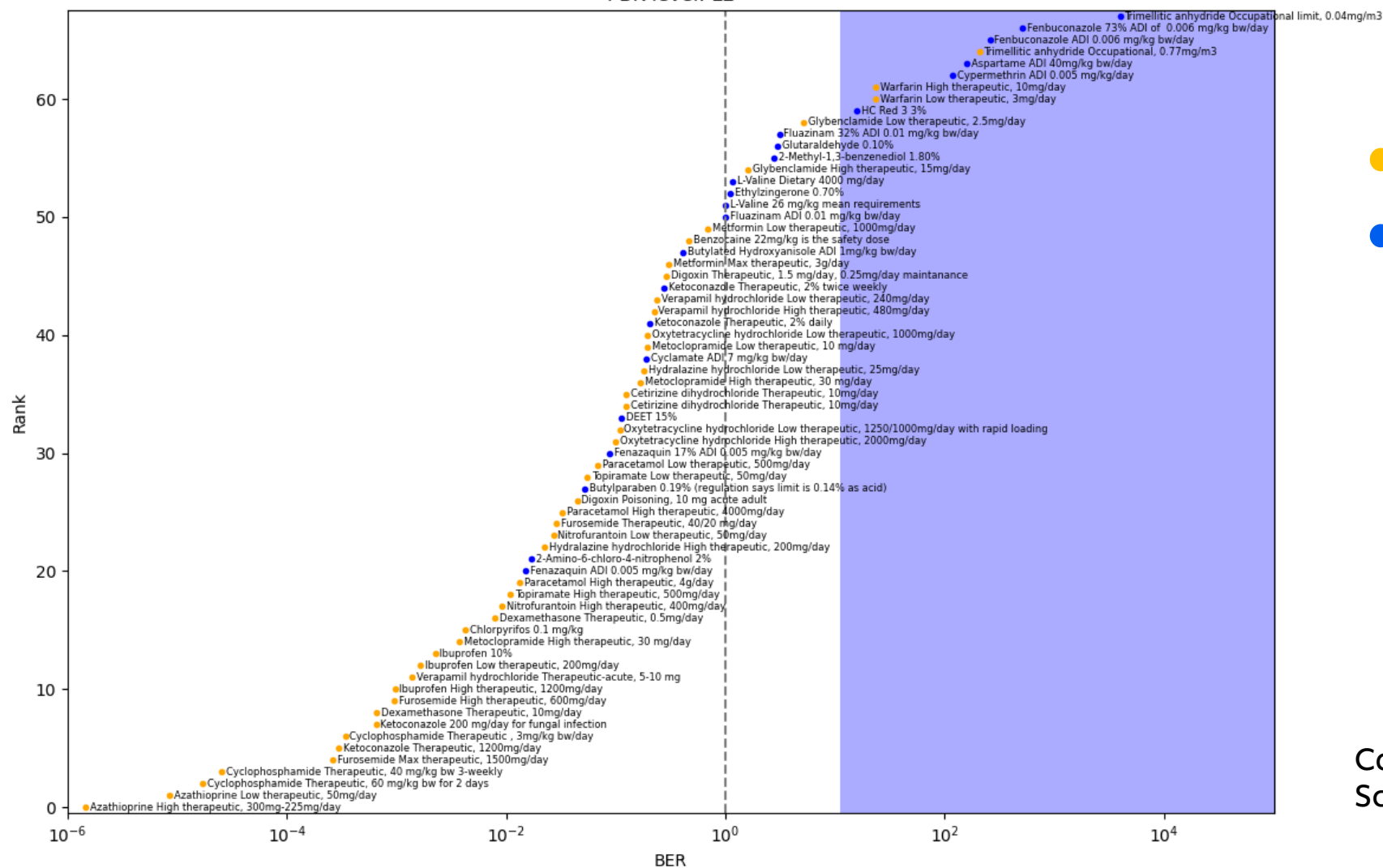
PBK Level	BER threshold	Empirical Protectiveness	Empirical Utility
1	110	6/6 (100%)	3/18 (17%)
2	11	6/6 (100%)	6/18 (33%)
3	2.5	5/5 (100%)	9/13 (69%)

Including relevant benchmarks



Lessons from testing broader chemical space

Comparison of BERs and benchmark risk classifications
PBK level: L2



- High risk benchmark (46)
- Low risk benchmark (24)

Cable et al., 2024 (Toxicological Sciences, Accepted)

Which NAMs contribute to the protection?

Pharmacological profiling	Cell Stress Panel	HTTr – Gene	HTTr – BMD minimum pathway	Protectiveness	Utility
Y	Y	Y		96% (44 out of 46)	29% (7 out of 24)
Y	Y		Y	83% (38 out of 46)	54% (13 out of 24)
		Y		89% (41 out of 46)	33% (8 out of 24)
			Y	48% (22 out of 46)	62% (15 out of 24)
Y		Y		96% (44 out of 46)	29% (7 out of 24)
Y			Y	74% (34 out of 46)	54% (13 out of 24)

For this toolbox and benchmarks, the cell stress panel does not add to the level of protection if the gene-level HTTr PoD is used

The level of protection depends on the tools used and the analysis methods

As a low-tier approach, it is designed to be conservative, and where BER is insufficient, this allow you to identify areas for refinement

Lessons from practical application of BERs

- BERs provide a robust basis for safety decisions
- An acceptable (low risk) BER is dependent on the toolbox and analysis techniques used
Hence the need to define for the combination of tools used
- “uncertain risk” isn’t the same as “high risk”: the risk assessment is tiered
- BERs need to be integrated with other lines of evidence (existing data, in silico predictions)
- Suitability of benchmarks needs to be considered (are relevant benchmarks included?)

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The International Collaboration on Cosmetic Safety

Thank You



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