Assessing the protectiveness and utility of a NAM-based approach to safety decision making

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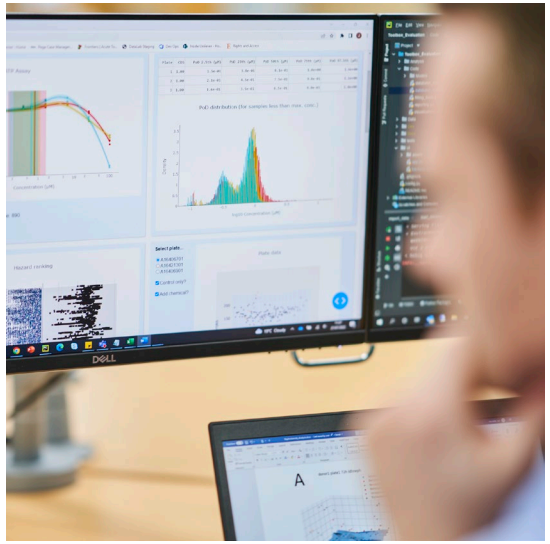

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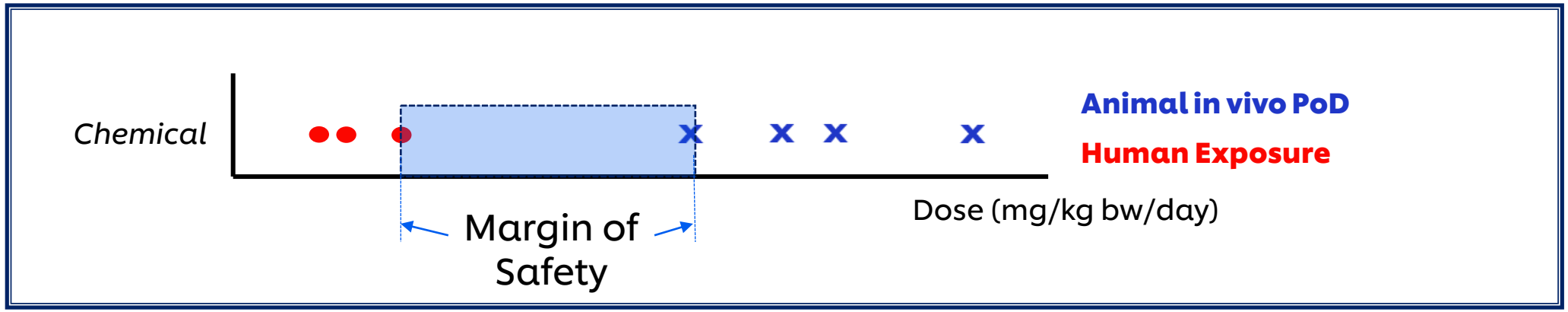
Making safety decisions in systemic toxicity risk assessments using traditional approaches



'All models are wrong but some are useful' – George Box

'The proper study of mankind is man' – Alexander Pope

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Framework Approach: The overall goal is a human safety risk assessment

*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***

Dent et al 2018. Computational Toxicology Volume 7, August 2018, Pages 20-26

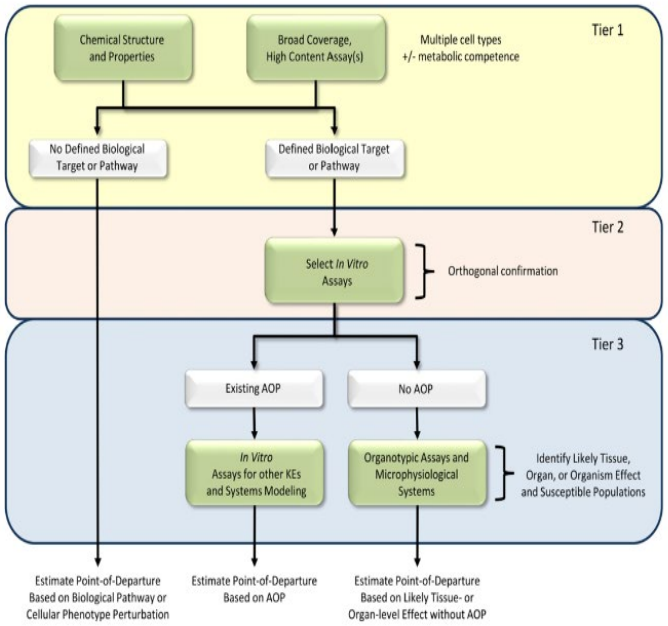
ICCR NINE PRINCIPLES OF NGRA

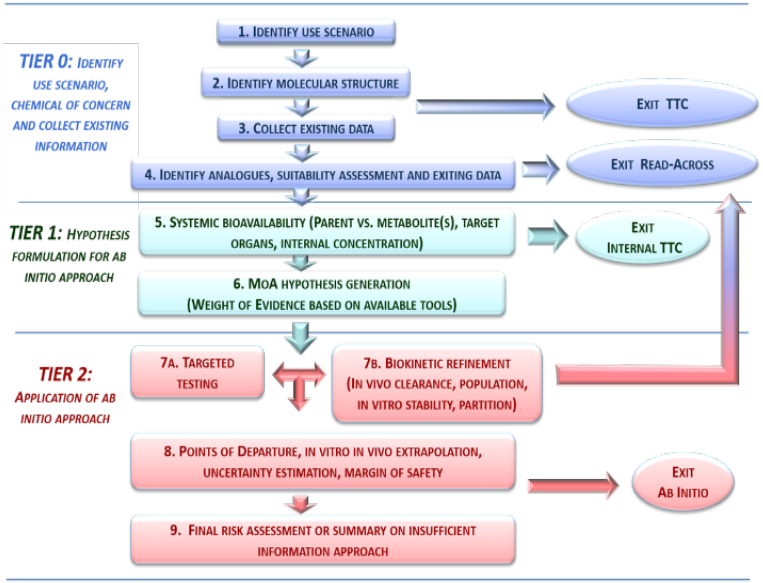
4 Main overriding principles:
- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:
- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:
- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented

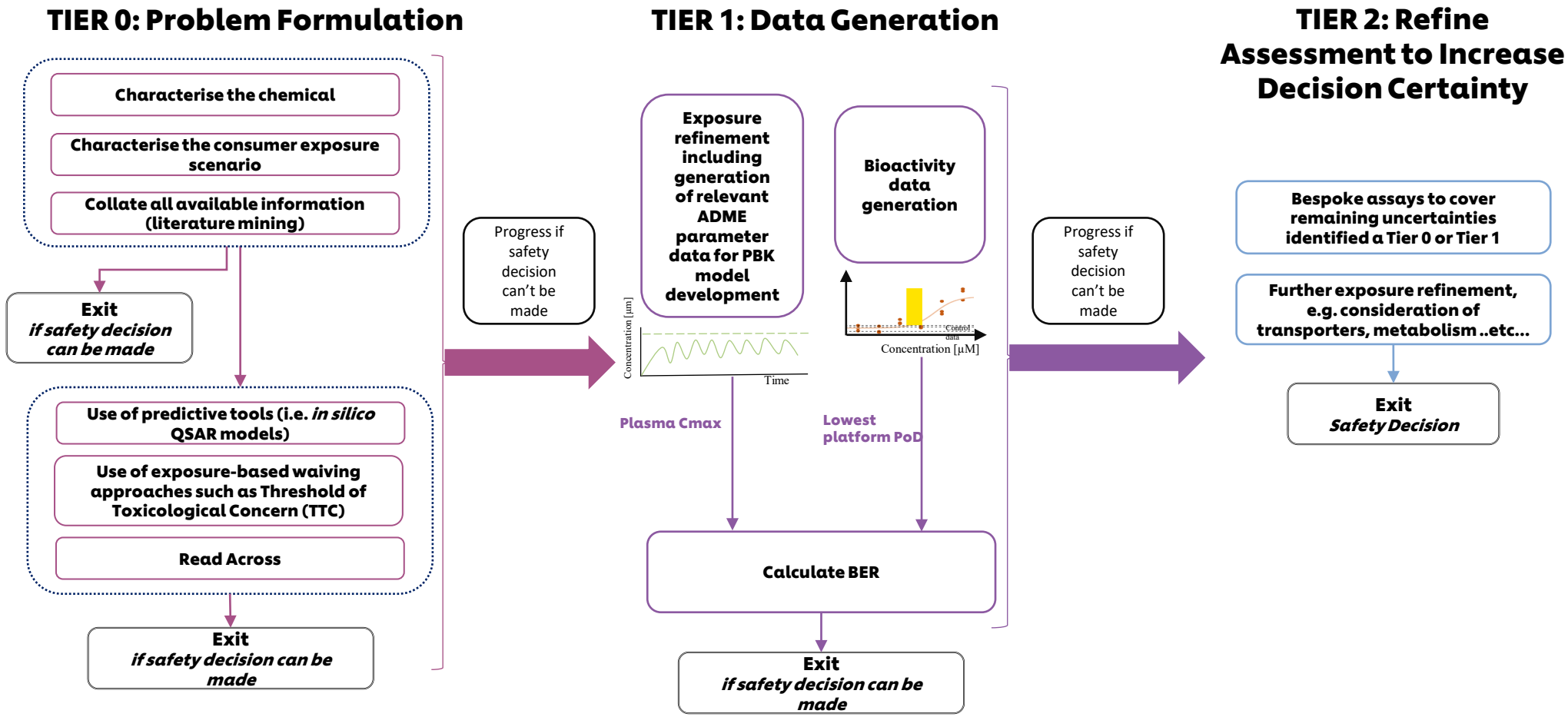
Dent *et al.* 2018 *Computational Toxicology*, 7, 20-26.





Berggren *et al.*, (2017) *Computational Toxicology* 4: 31-44.

Framework Approach: The overall goal is a human safety risk assessment



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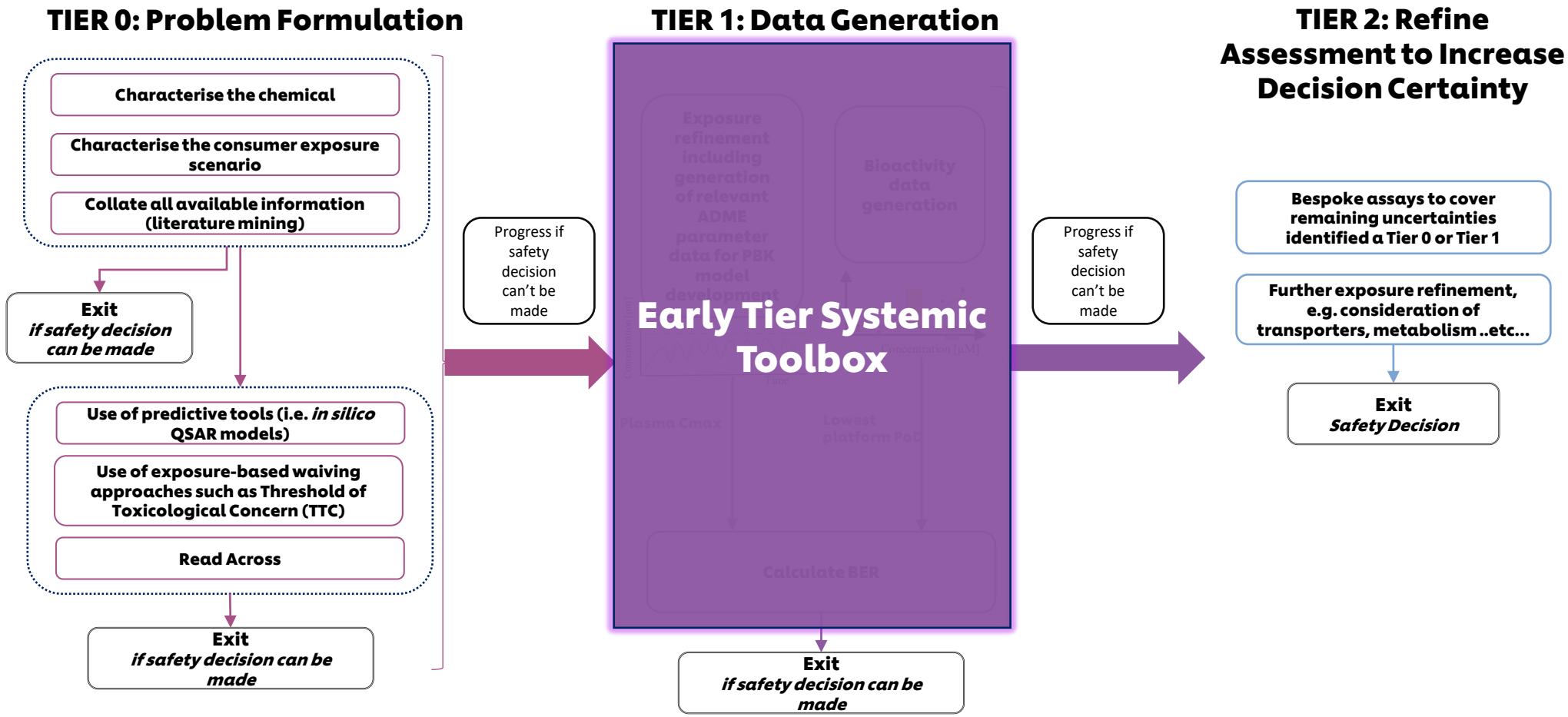

Evaluation of an early tier systemic toolbox for safety decision making

AIM: Use NAMs to ensure the protection of consumers: can the approach be used to confidently identify low risk chemical exposure scenarios?

- **Define the toolbox components** Choose a set of NAMs covering exposure modelling and bioactivity investigations to evaluate
- **Select test chemicals** Choose as many as possible to maximise coverage of different chemistries and biological effects/toxicity
- **Set performance criteria** Define the 'truth' that the performance of the toolbox will be compared to

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Evaluation of an early tier systemic toolbox for safety decision making: Defining the toolbox components

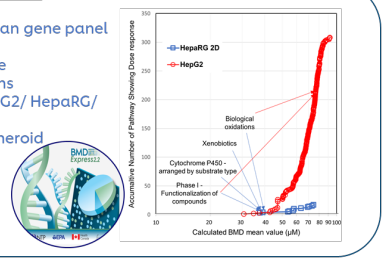
Point of Departure determination

Non-specific effects

Transcriptomics

- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

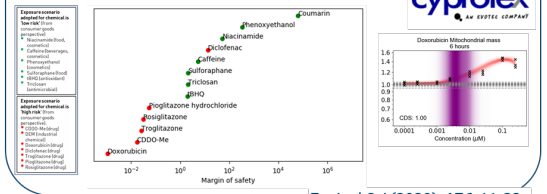
BMDexpress 2



Cellular Stress Pathways

13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways

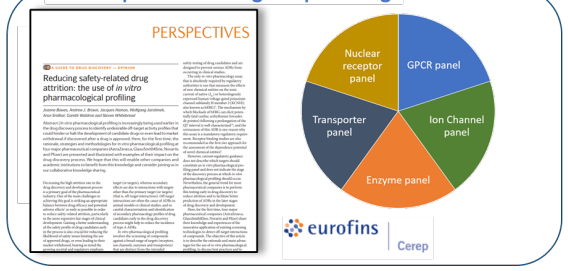
cyprotex



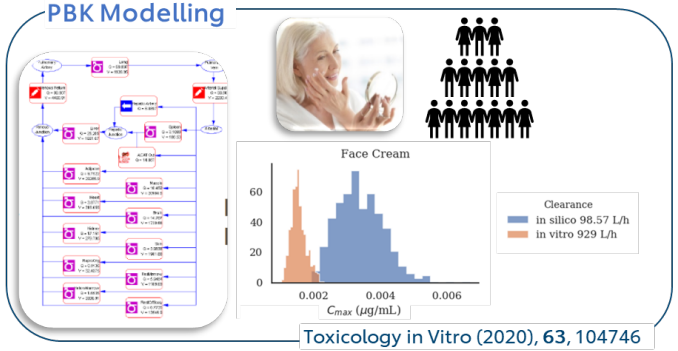
Toxicol Sci (2020), **176**, 11-33

Specific effects

In vitro pharmacological profiling



PBK Modelling

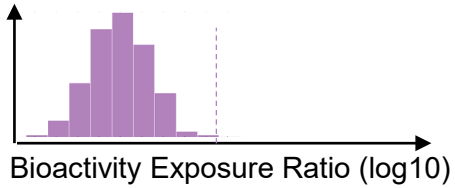


Toxicology in Vitro (2020), **63**, 104746

Plasma C_{max} estimate → **C_{max} Error Distribution model (CMED)**

(Bayesian model)

Bioactivity Exposure Ratio Distribution



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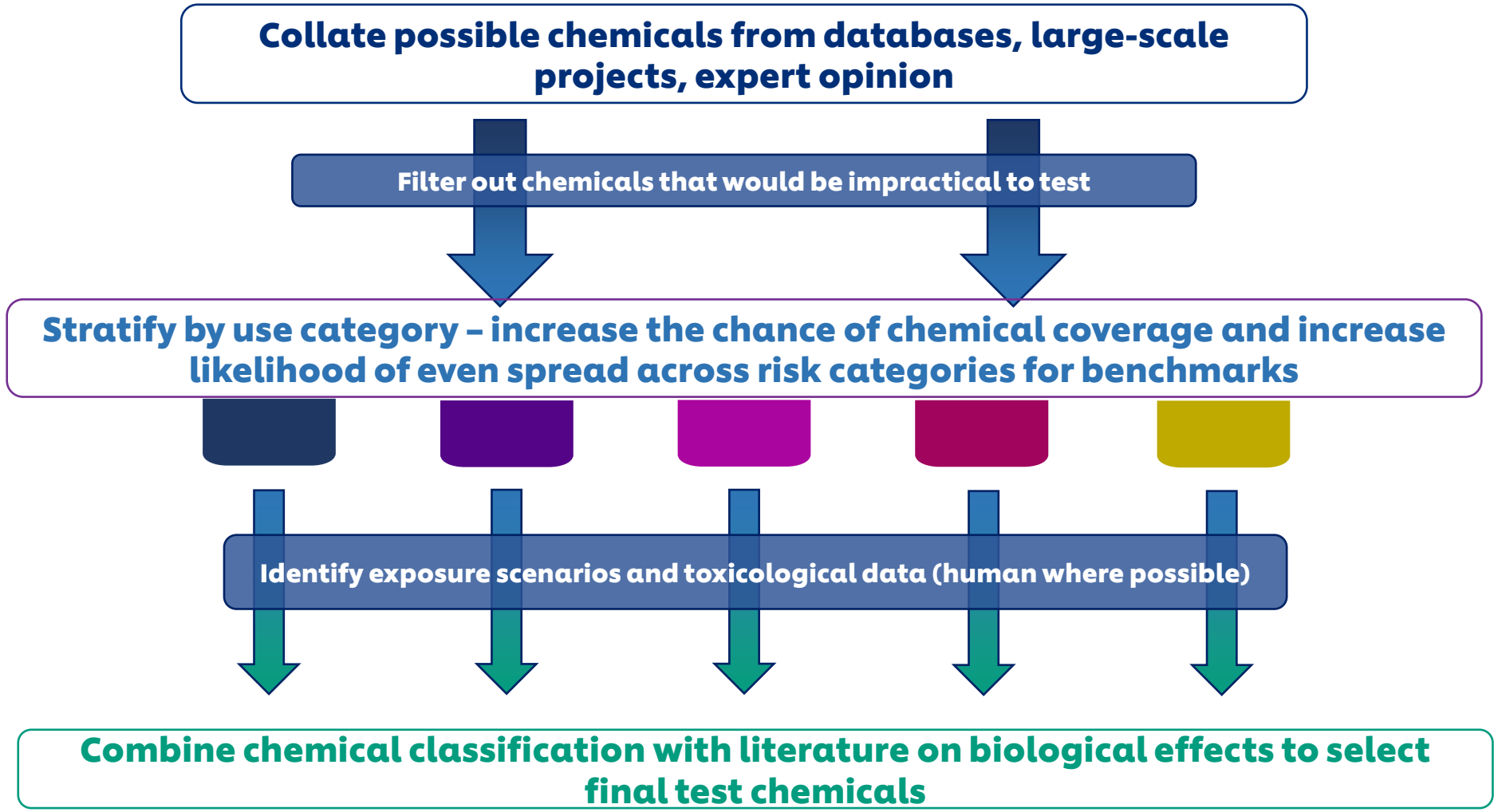
Evaluation of an early tier systemic toolbox for safety decision making: Select test chemicals



Evaluation of an early tier systemic toolbox for safety decision making: Select test chemicals

38 test chemicals

- 9 cosmetics, 21 drugs, 3 food additives, 5 agricultural chemicals, 1 industrial chemical

- Oral, dermal, IV and inhalation exposure scenarios

- Organ toxicities, CNS disruptions, immune system dysregulation, non-specific effects, blood-based disorders etc…

Combine chemical classification with literature on biological effects to select final test chemicals

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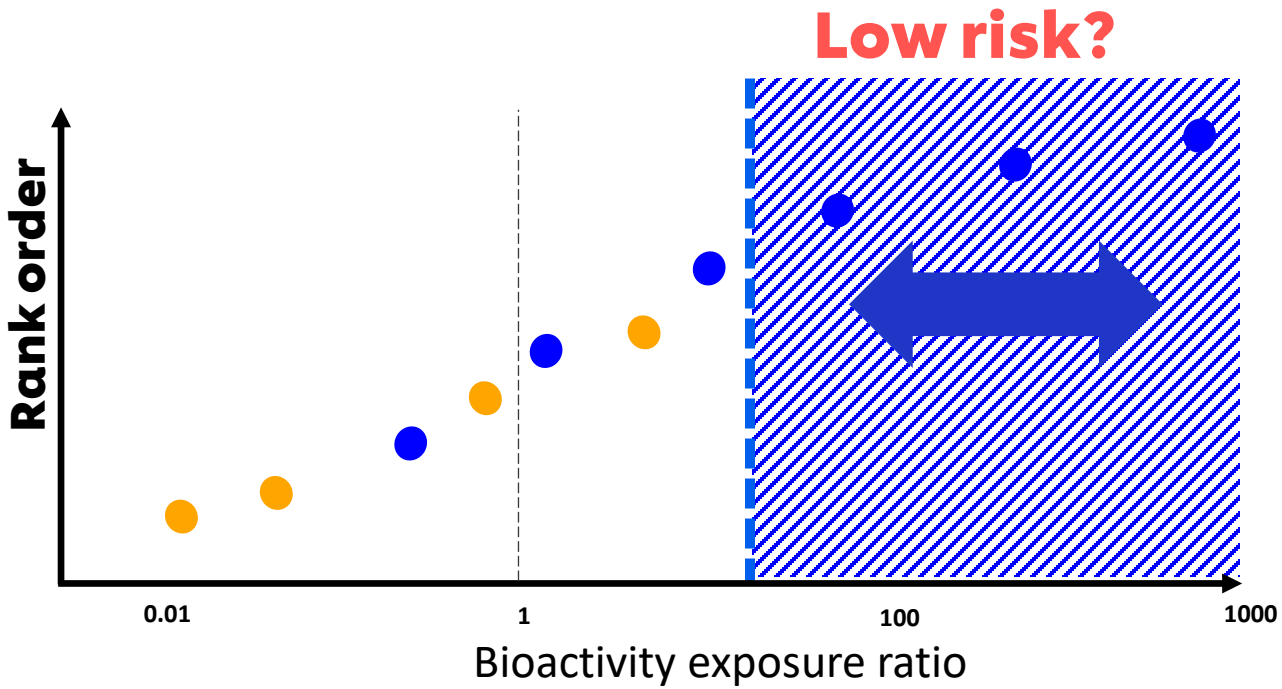
Evaluation of an early tier systemic toolbox for safety decision making: Set performance criteria

Benchmarking using chemical-exposure scenarios

- Chemicals with well-defined human exposures
- Traditional safety assessment available
- High certainty in the risk classification for each chemical-exposure scenario from a consumer goods perspective
- Risk class is relative to consumer health



‘Low’ risk for consumers from systemic perspective

‘High’ risk for consumers from systemic perspective

Protectiveness

How many of the high risk exposure scenarios are identified as uncertain/high risk
(i.e. BER < threshold)

Utility

How many of the low risk scenarios are identified as low risk at this early tier stage in a risk assessment framework
(i.e. BER > threshold)

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Evaluation of an early tier systemic toolbox for safety decision making: Set performance criteria

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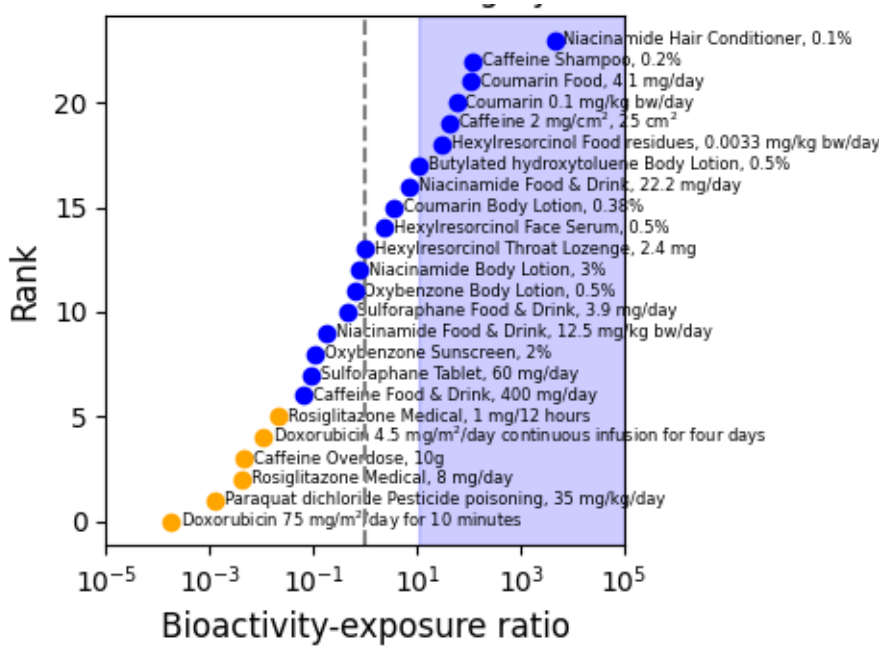


Threshold values of the BER point estimates for determining whether an exposure is low risk

PBK Level	Threshold BER Required for Exposure to Be Identified as Low Risk	Confidence Threshold ($p_{threshold}$) Required for Exposure Scenario to Be Identified as Low Risk
1	110	.98
2	11	.97
3	2.5	.95

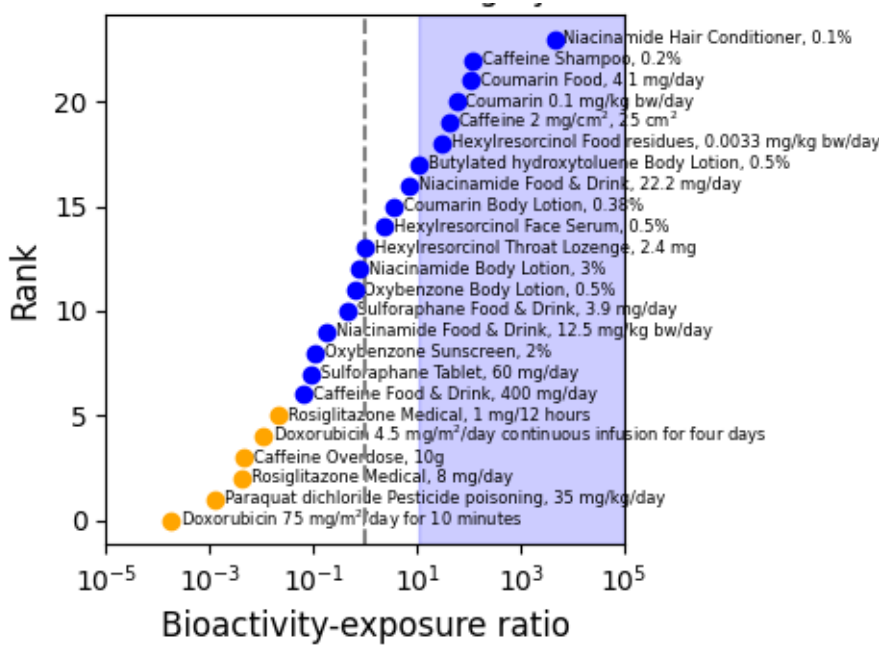
Defining a 'truth' to evaluate the outcome and performance of safety decisions made using the NAM-based toolbox

Select appropriate benchmarks

- Chemicals with well-defined human exposures
- Traditional safety assessment available
- High certainty in the risk classification for each chemical-exposure scenario from a consumer goods perspective
- Risk class is relative to consumer health

'Low' risk for consumers from systemic perspective

'High' risk for consumers from systemic perspective



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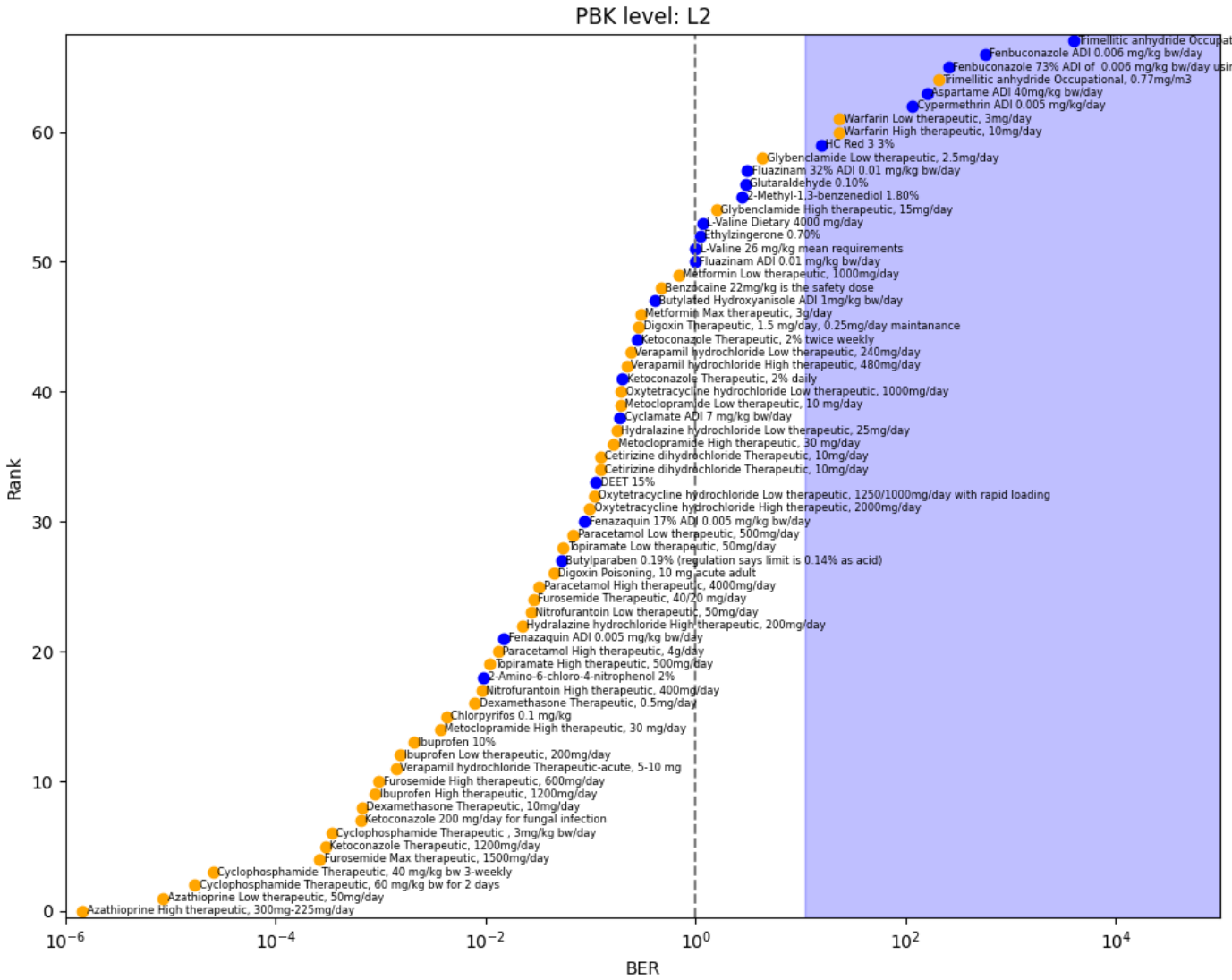
Results for a set of 38 test chemicals and 70 exposure scenarios



Protectiveness **93% (43 out of 46)**

How many of the high risk exposure scenarios are identified as uncertain/high risk
(i.e. BER < threshold)

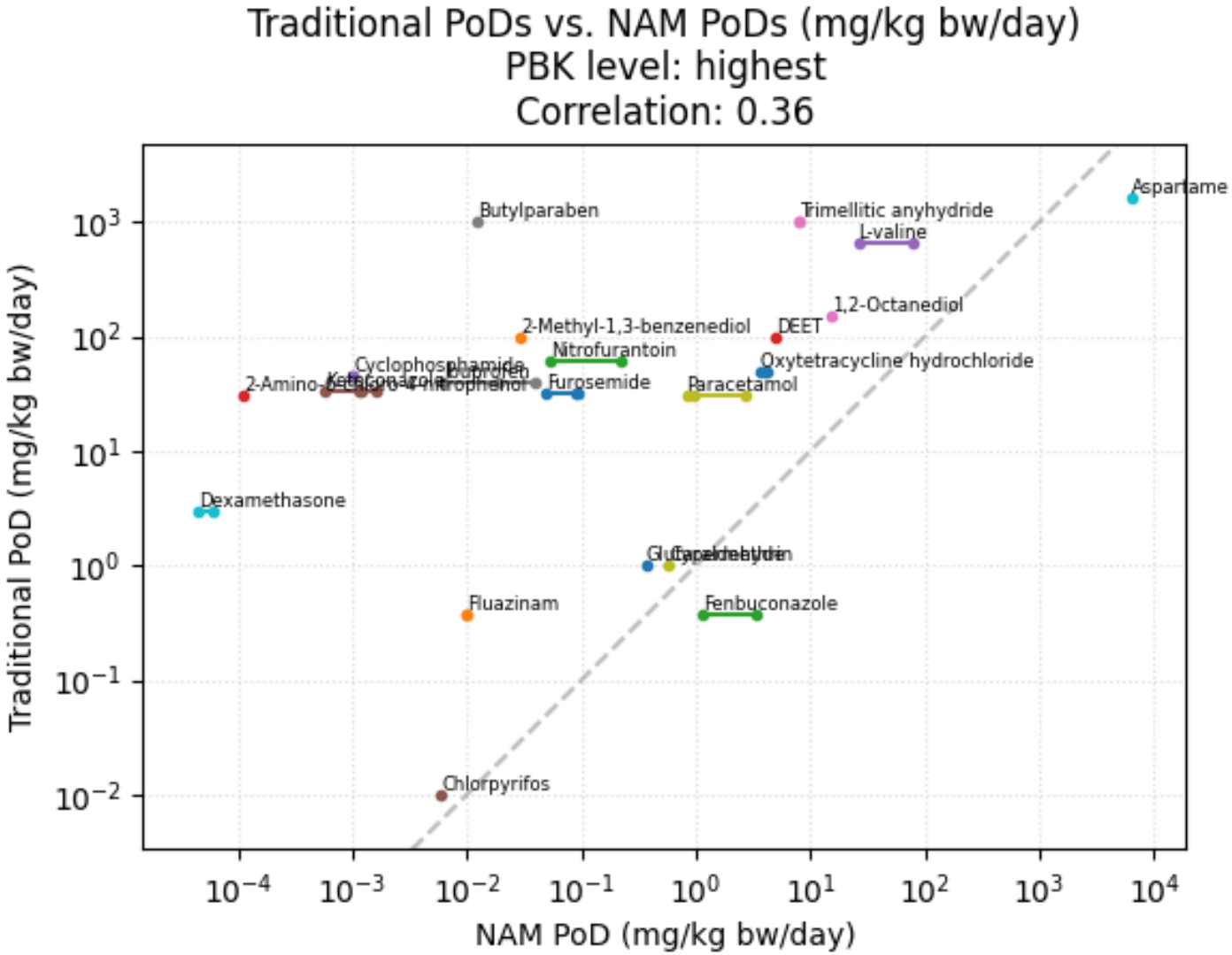
Utility **27% (6 out of 22)**

How many of the low risk scenarios are identified as low risk at this early tier stage in a risk assessment framework
(i.e. BER > threshold)

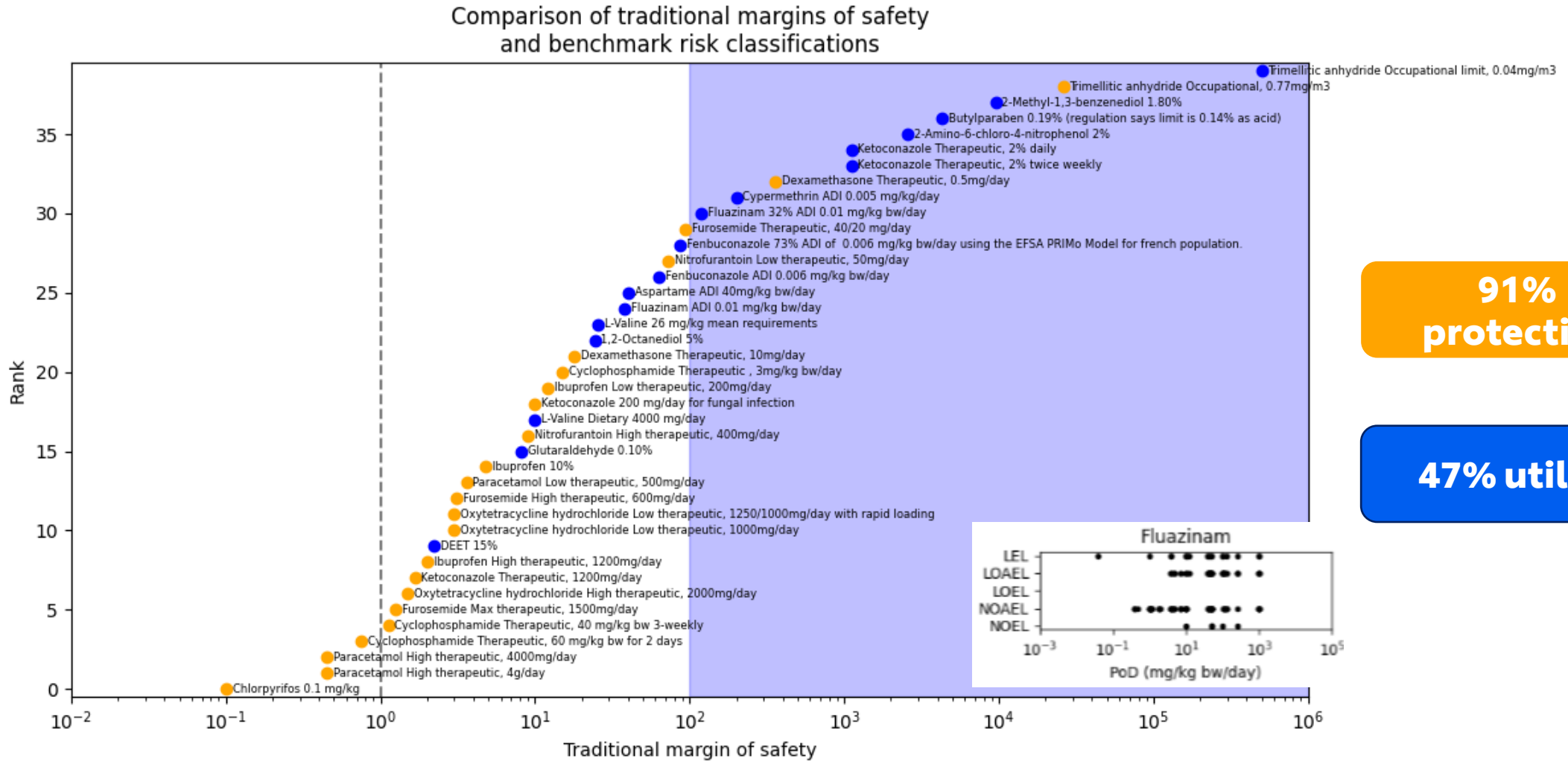
Comparison of a NAM-based early tier toolbox with early-tier decision making using in vivo data

What if we took the same approach with *in vivo* data.

- Repeat dose in vivo data identified for 27 chemicals of the 38 tested.
- In most cases NAM PoDs are more conservative than traditional PoDs



- Using the minimum of NOAELs/LOAELs identified, margins of safety plotted and threshold at MoS = 100



91% protective

47% utility

Conclusions and next steps

- For the test chemicals in this evaluation, an early tier systemic toolbox is **93% protective.**
- A NAM-based toolbox for systemic toxicity has comparable performance to safety decision making using traditional in vivo data.
- What is the applicability domain of this toolbox?
- How would the toolbox perform with a wider set of chemicals?
- What would the performance be like with a different set of assays? Is there an optimum combination of inputs to maximise both protectiveness and utility?

Acknowledgements

Alistair Middleton
Maria Baltazar
Sharon Scott
Sophie Malcomber
Predrag Kukic
Beate Nicol
Gopal Pawar
Dawei Tang
Joe Reynolds
Andrew White
Paul Carmichael
Matt Dent
Georgia Reynolds

Thank You

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