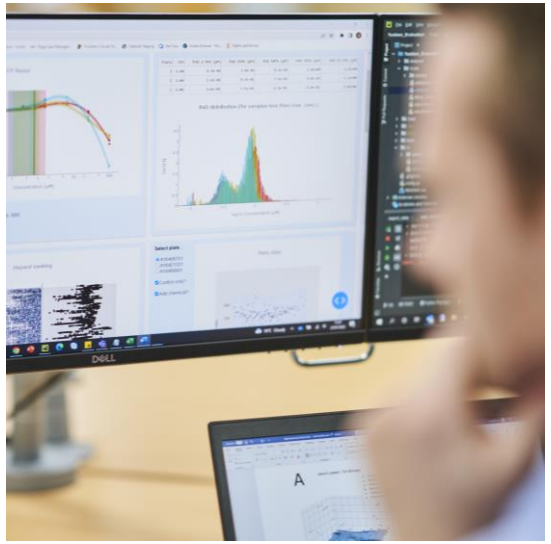
Gaining confidence in NGRA approaches together: A DyNAMic discussion

Sophie Cable
8th April 2024



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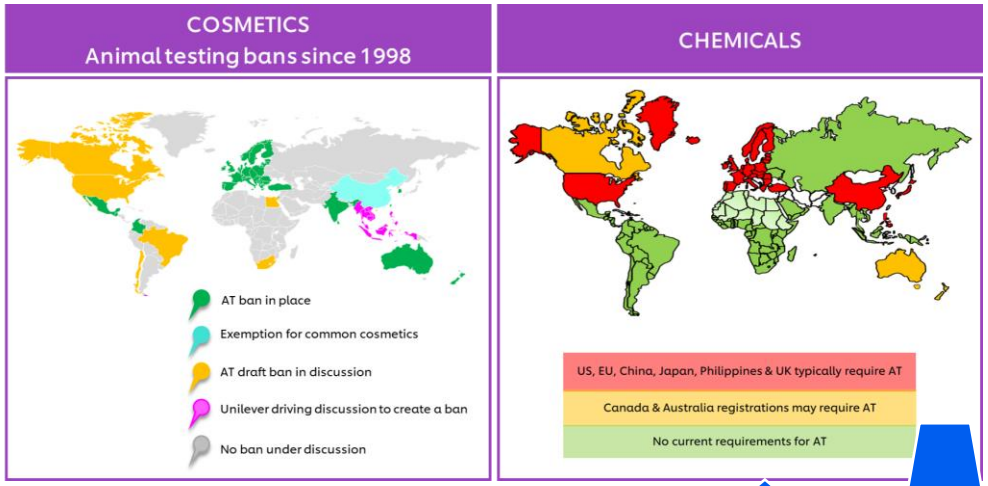
The need for the development and implementation of NAM-based safety assessments

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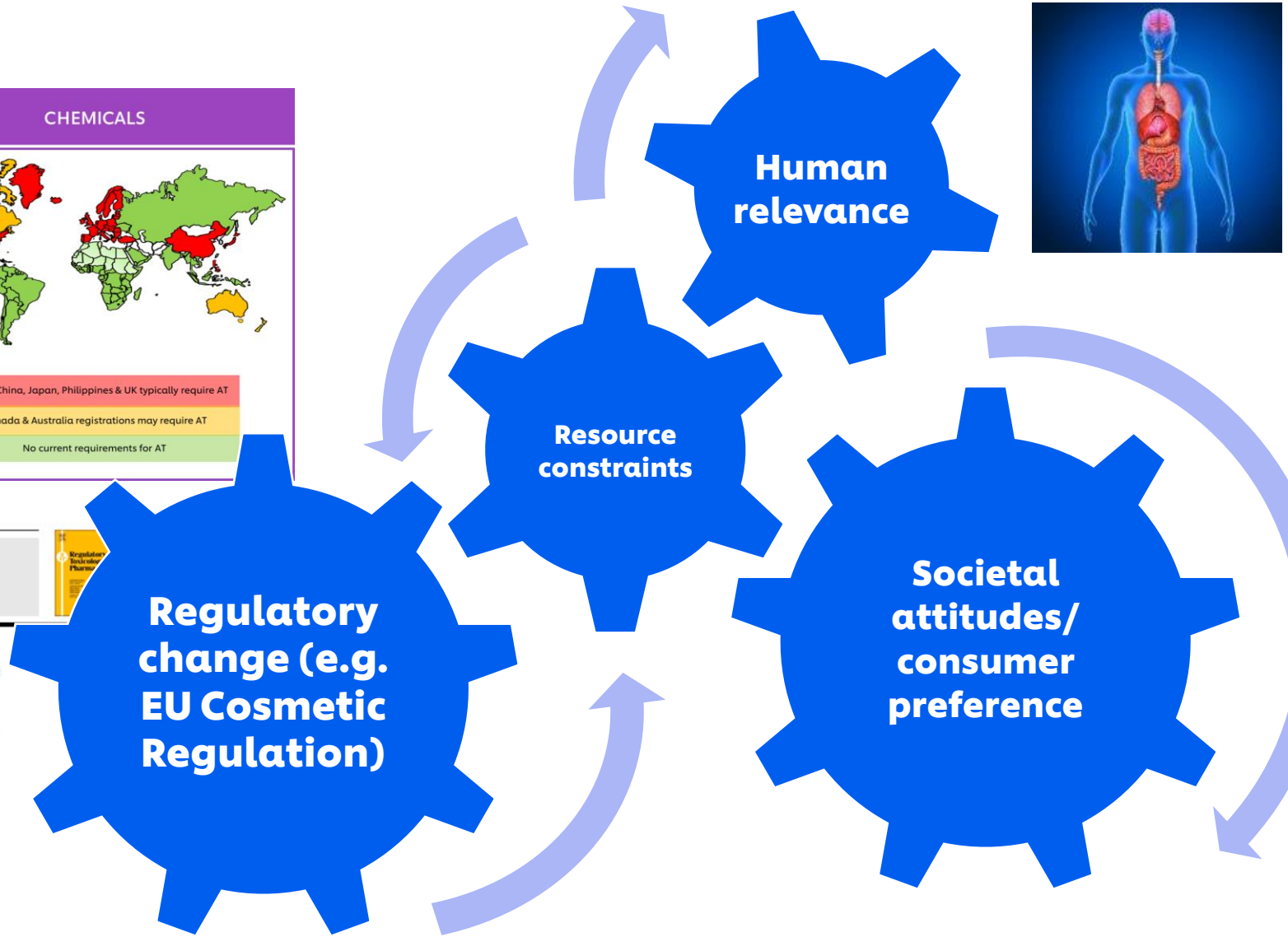
The last resort requirement under REACH: From principle to practice

Donna S. Macmillan [a,*], Anders Bergqvist [b], Eleanor Burgess-Allen [c], Ian Callan [d], James Dawick [d], Benjamin Carrick [e], Graham Ellis [f], Roberto Ferro [g], Katy Goyak [h], Chantal Smulders [i], Ricky A. Stackhouse [j], Espe Troyano [k], Carl Westmoreland [l], Blanca Serrano Ramón [m], Vanessa Rocha [n], Xiaoling Zhang [k]



Cruelty Free INTERNATIONAL

PETA APPROVED Global Animal Test Policy

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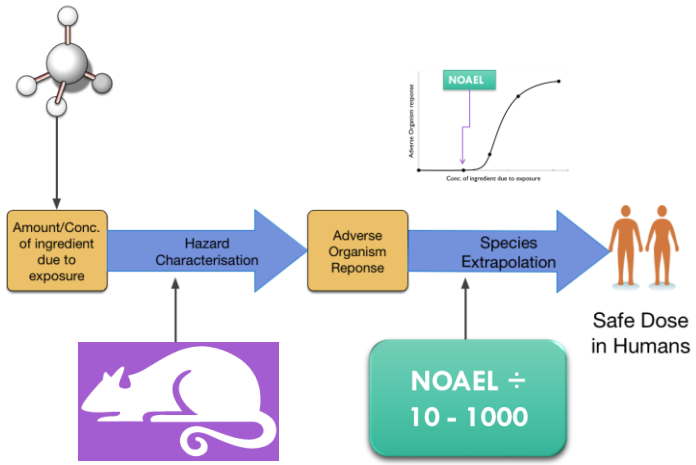
The need for the development and implementation of NAM-based safety assessments

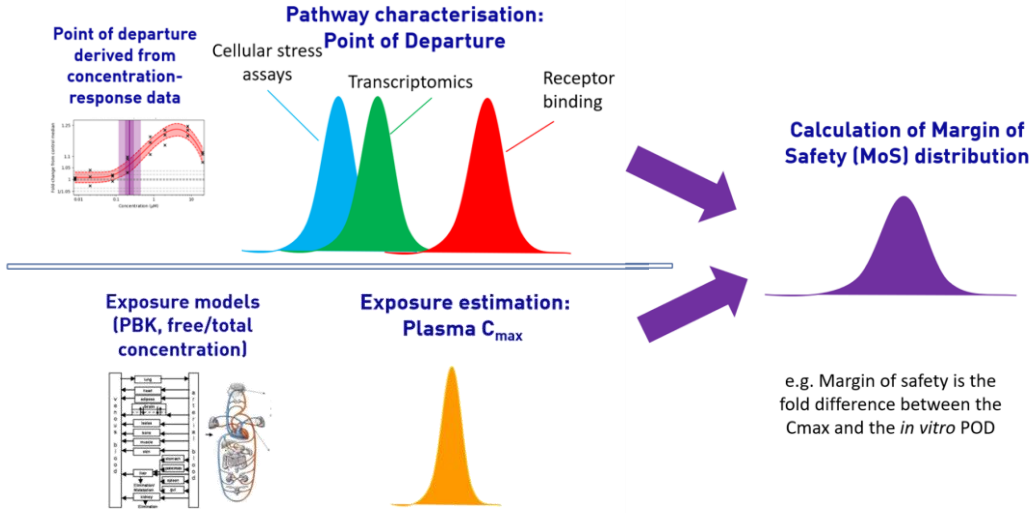
Non-animal safety science is increasingly being used to make decisions on:

1. safety of **consumers** exposed to chemicals in **products**
2. safety of **workers** exposed to chemicals during product **manufacture**
3. safety of **people & non-human species** if exposed to chemicals in the **environment**

‘Traditional’ Risk Assessment



‘Next Generation’ Risk Assessment



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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

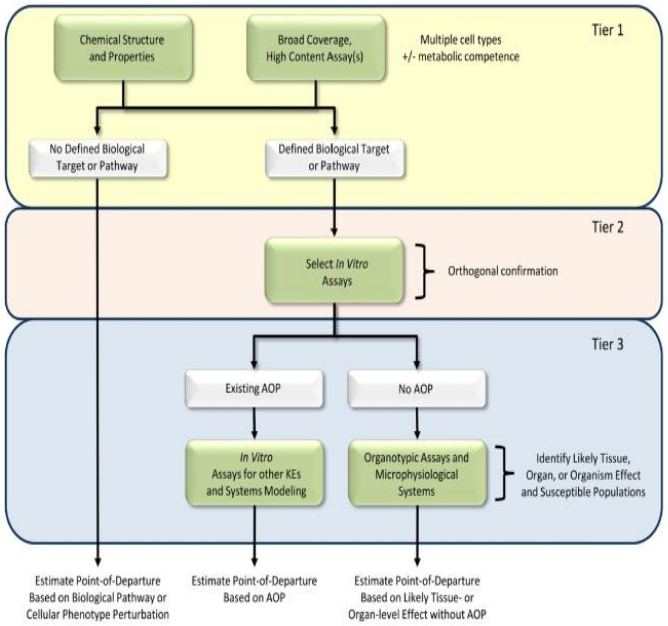
ICCR NINE PRINCIPLES OF NGRA

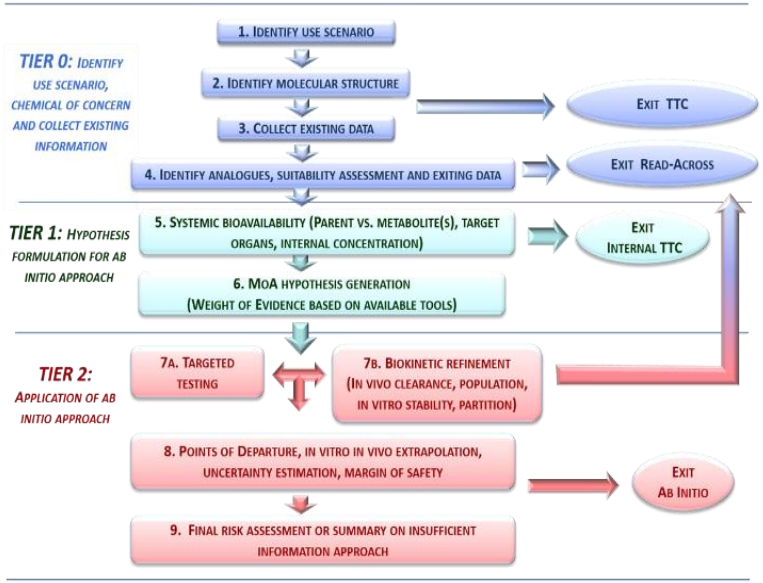
4 Main overriding principles:
- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

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

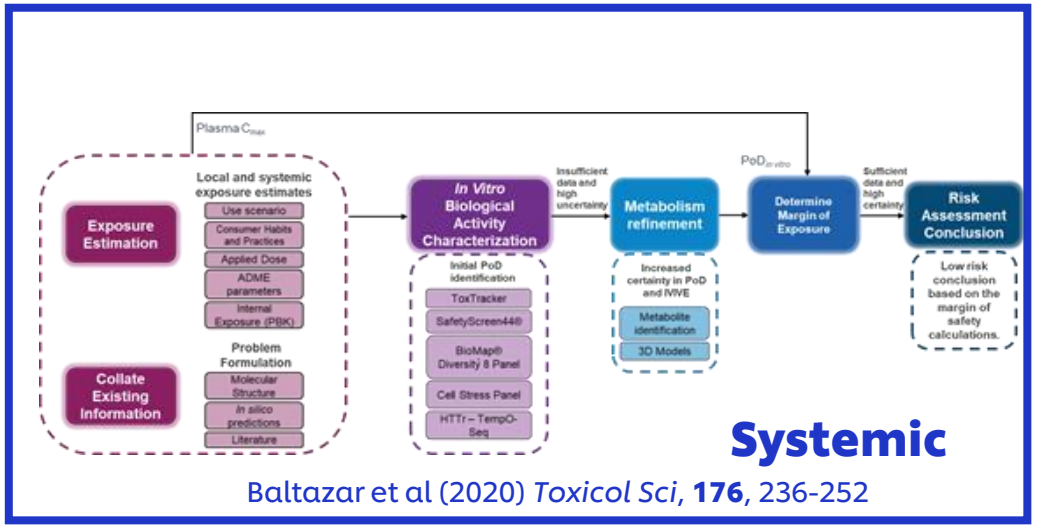
Dent *et al.* 2018 *Computational Toxicology*, 7, 20-26.



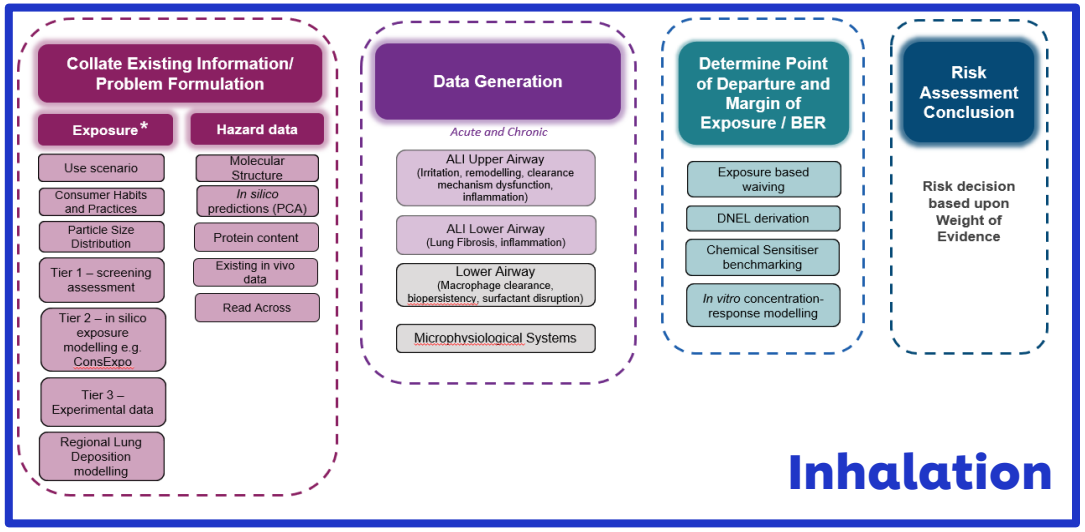


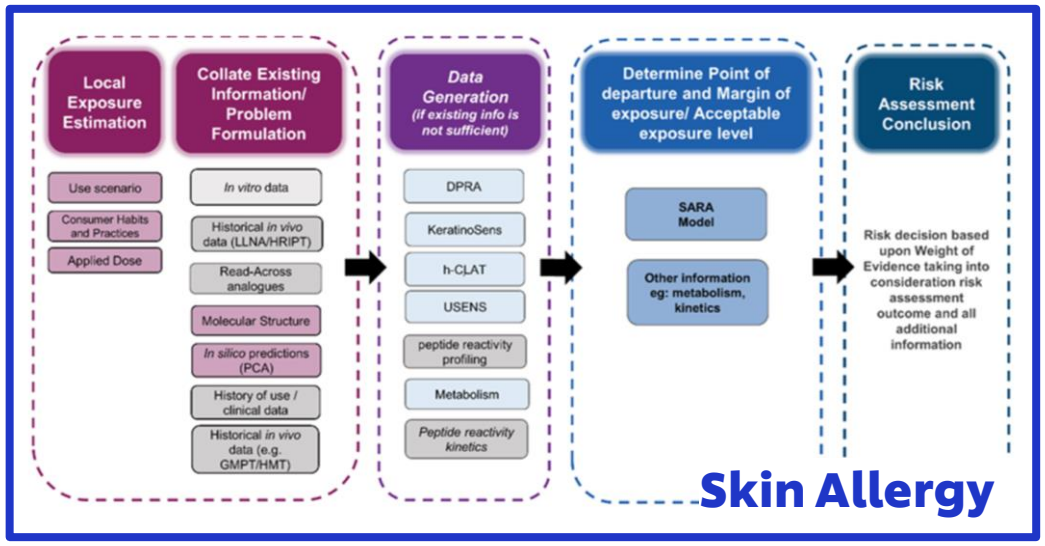
Berggren *et al.*, (2017) *Computational Toxicology* 4: 31-44.

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

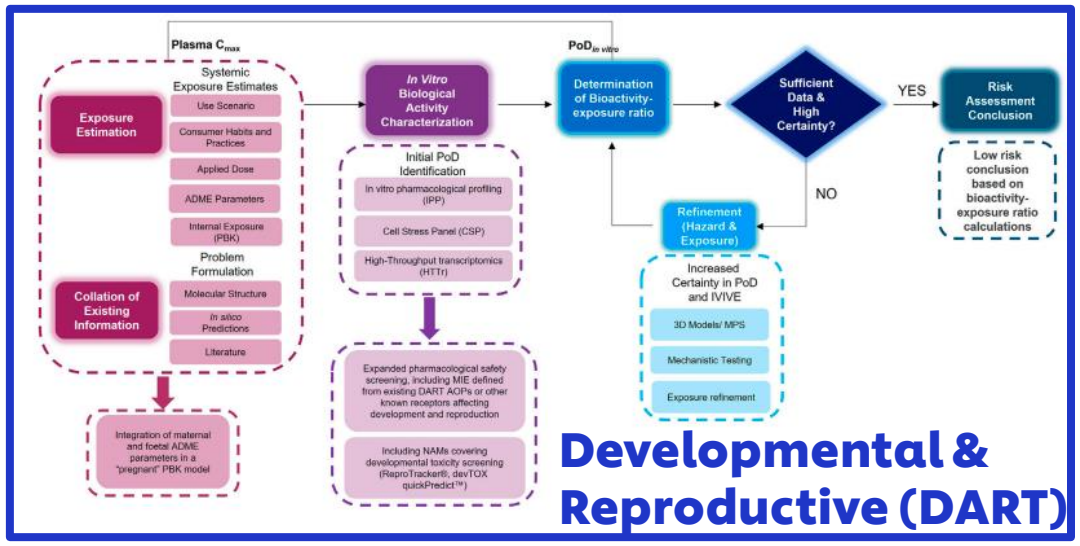


Baltazar et al (2020) *Toxicol Sci*, **176**, 236-252





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



Rajagopal et al (2022) *Frontiers in Toxicology*, **4**, 838466

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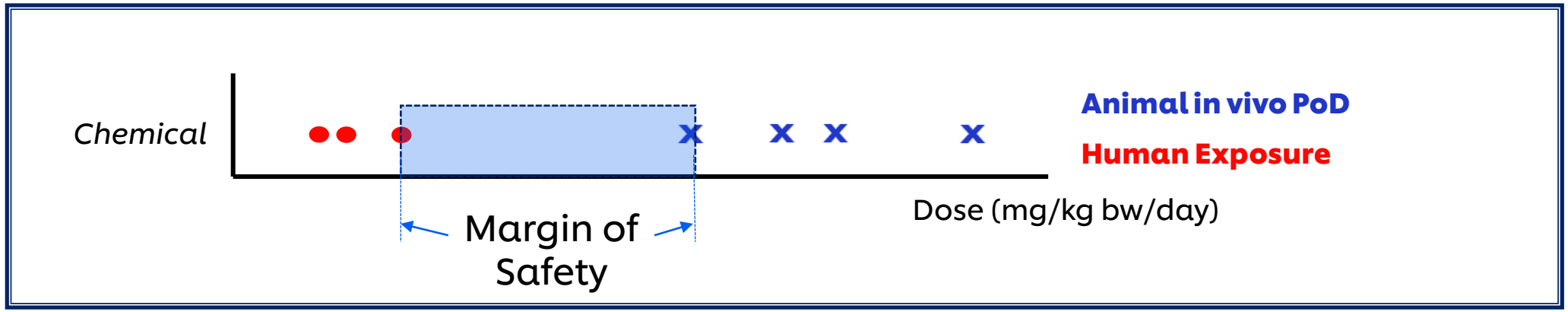
Making safety decisions in systemic toxicity risk assessments using traditional approaches



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

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

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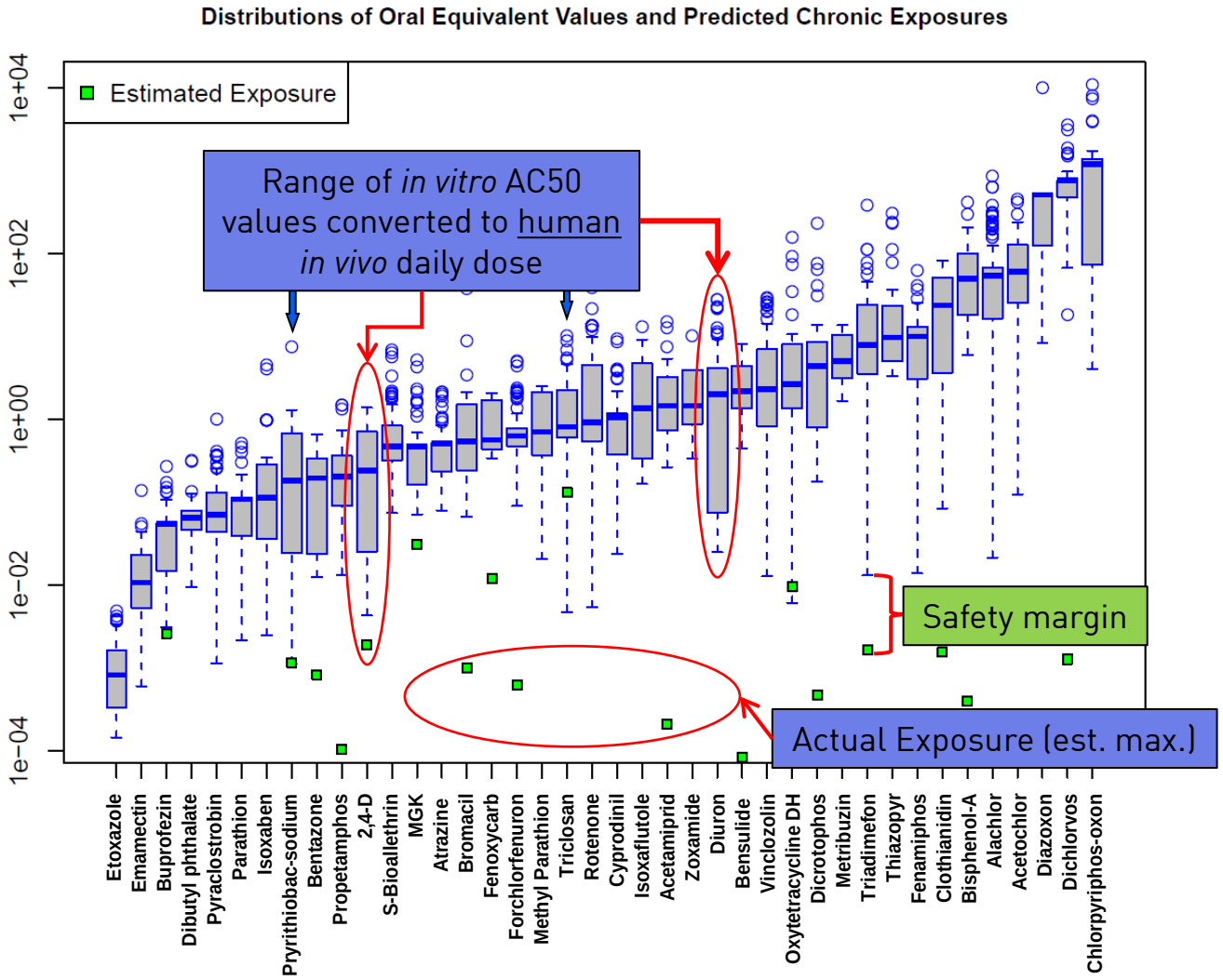
Using NAMs for protective early tier safety decision making



Slide from Dr Rusty Thomas, EPA, with thanks

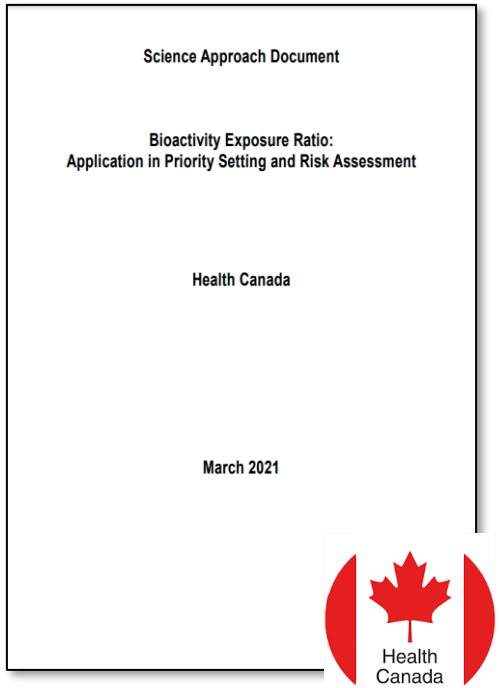
Rotroff, *et al.* Tox.Sci 2010

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.**

Thomas RS et al., 2019. Tox Sci. 1;169(2):317-332.

Examples of ongoing or completed case studies for NAM/NGRA based risk assessment or prioritisation

46 compounds


Science Approach Document

Bioactivity Exposure Ratio:
Application in Priority Setting and Risk Assessment

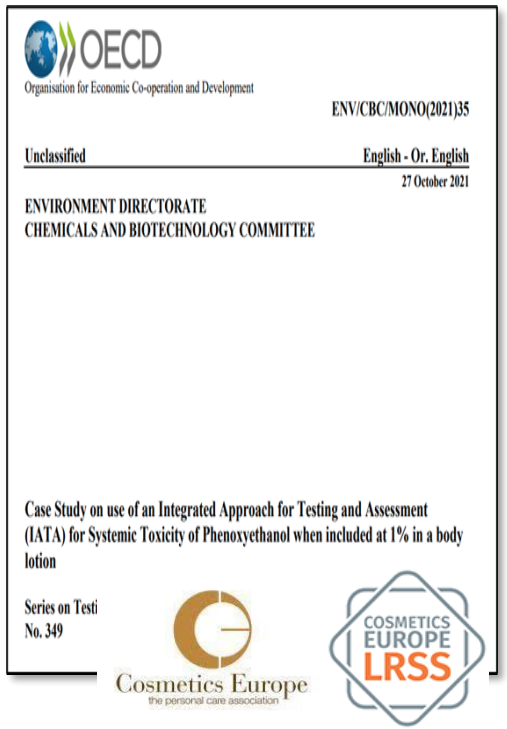
Health Canada

March 2021

Health Canada

https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/science-approach-document-bioactivity-exposure-ratio-application-priority-setting-risk-assessment.html

30 compounds


OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

Unclassified — English - Or. English
27 October 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

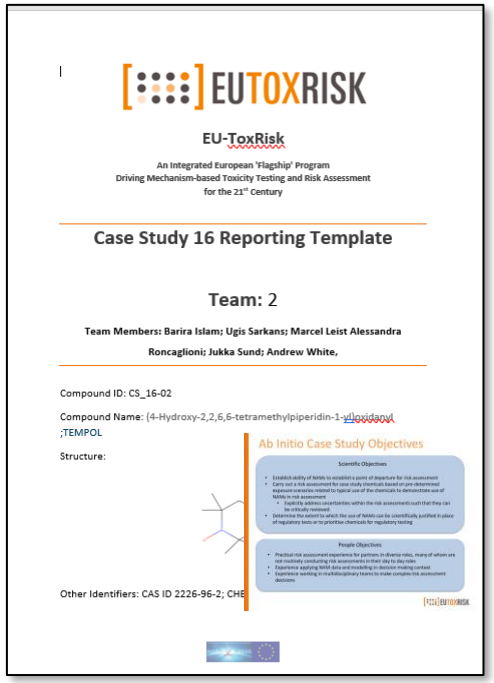
Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

Series on Testi
No. 349

Cosmetics Europe
the personal care association

COSMETICS EUROPE LRSS

>22 compounds


EUTOXRISK

EU-ToxRisk

An Integrated European 'Flagship' Program
Driving Mechanism-based Toxicity Testing and Risk Assessment
for the 21st Century

Case Study 16 Reporting Template

Team: 2

Team Members: Barira Islam; Ugis Sarkans; Marcel Leist Alessandra Roncaglioni; Jukka Sund; Andrew White,

Compound ID: CS_16-02

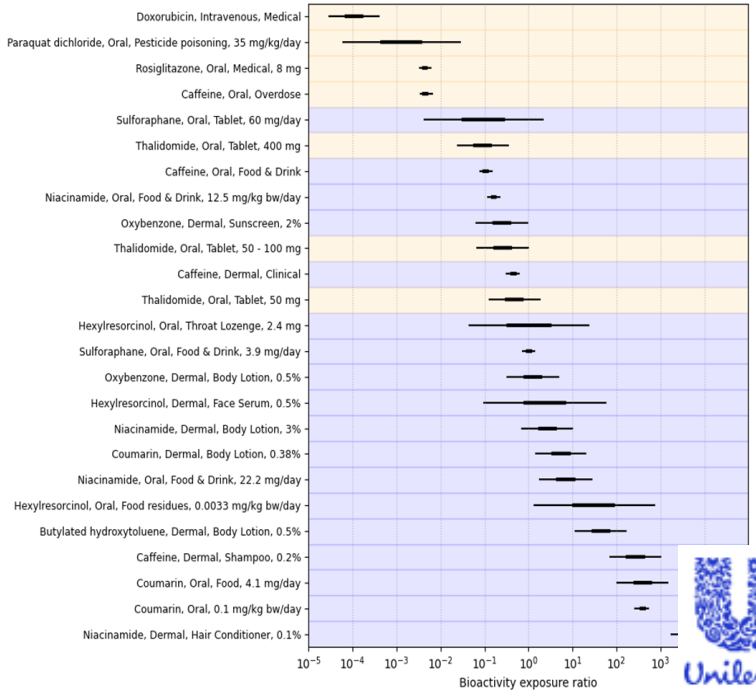
Compound Name: (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl ;TEMPOL

Structure:

Ab Initio Case Study Objectives

Other Identifiers: CAS ID 2226-96-2; CHE

>85 scenarios
Pilot + Full study



Benchmark BER against risk category for each exposure scenario

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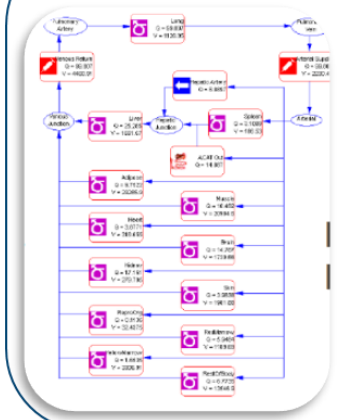
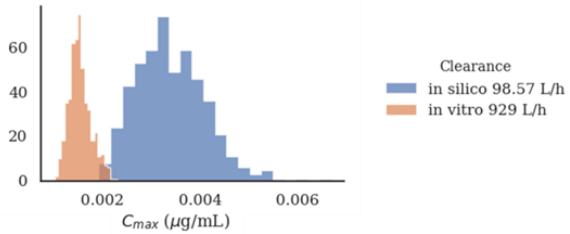
A early-tier toolbox-based approach to evaluating the performance of NAMs in the systemic toxicity risk assessment of chemicals

- Choose set of NAMs that represents coverage of exposure modelling and in vitro bioactivity
- Choose set of test chemicals to cover a broad range of chemistry and biological effects/toxicity.
- Define a ‘truth’ to evaluate the performance of the NAM toolbox when making safety decisions for the test chemicals and their exposure scenarios.

NAMs comprising the early-tier systemic toolbox

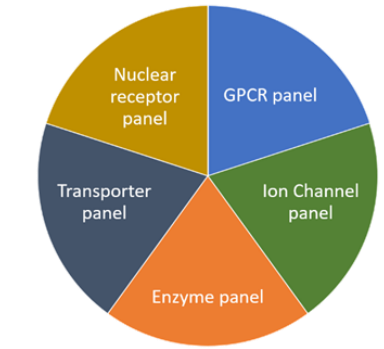
PBK Modelling





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

In vitro pharmacological profiling

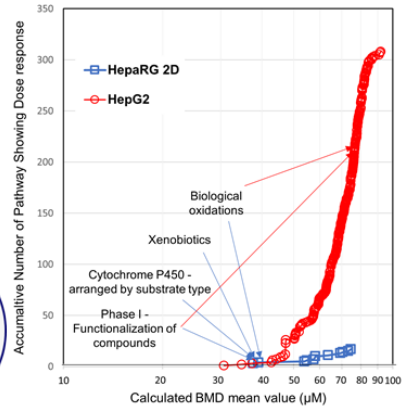


eurofins | Cerep

Transcriptomics

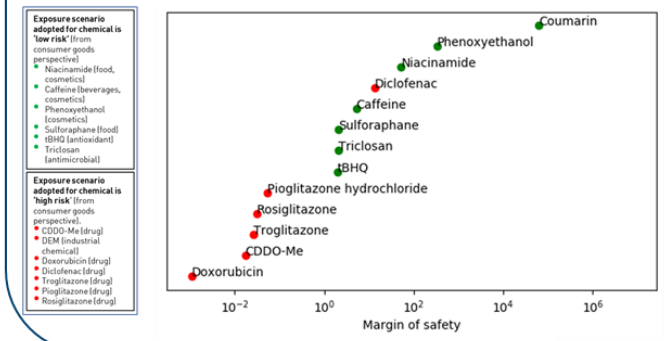
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7

BMDExpress 2

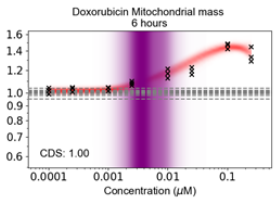


Cellular Stress Pathways

36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways



cyprotex AN EVOTEC COMPANY



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

https://www.thepsci.eu/nam-webinars/
https://youtu.be/FCQ5kM-Thuk?si=RDLLY-X-Ikt-krQx

Middleton et al (2022), *Tox Sci,* Volume 189, Issue 1, Pages 124-147

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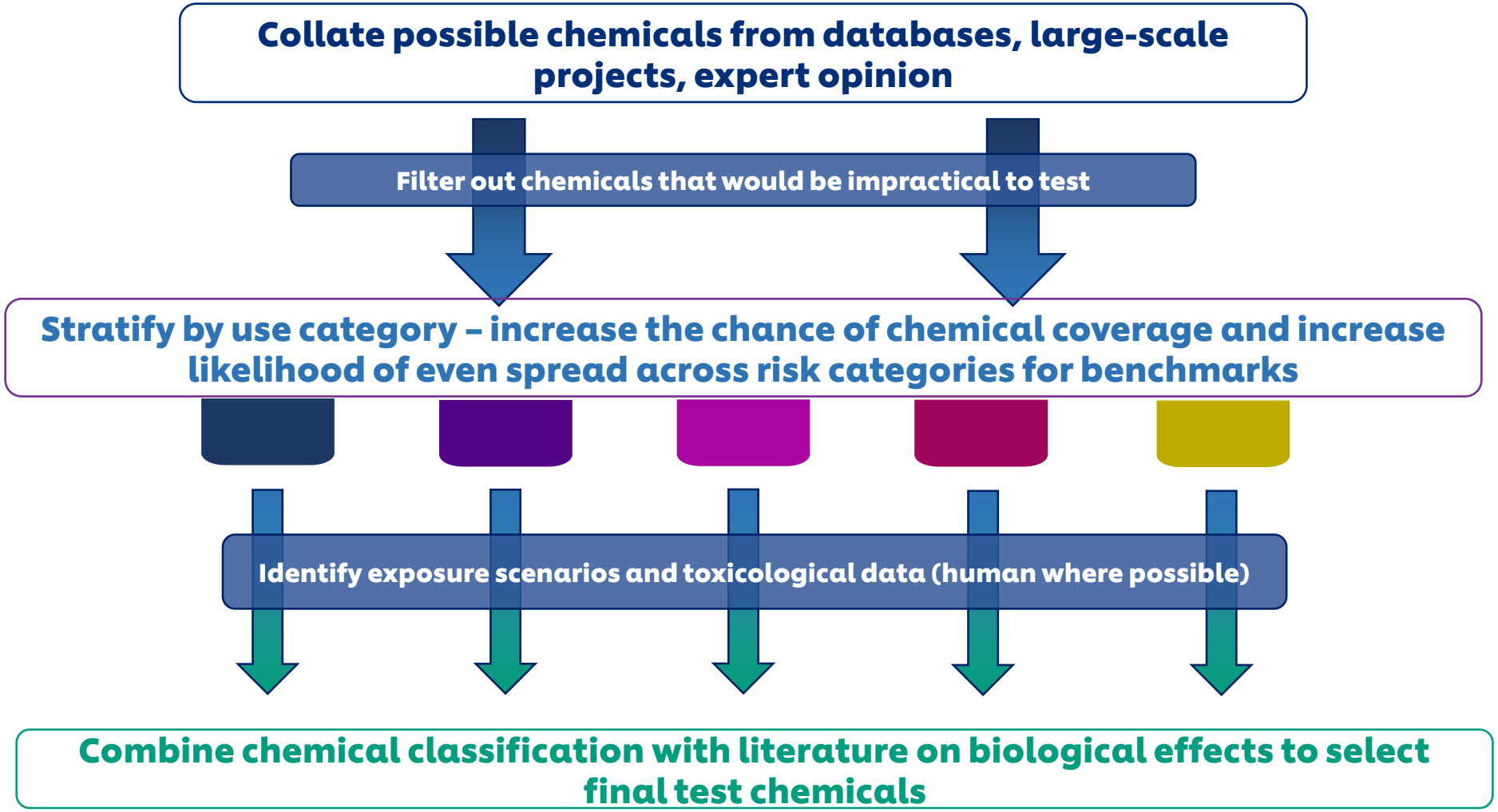
Selection of test chemicals



Selection of test chemicals

Collate possible chemicals from databases, large-scale

38 test chemicals

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

- Oral, dermal IV and inhalation exposure scenarios

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

final test chemicals

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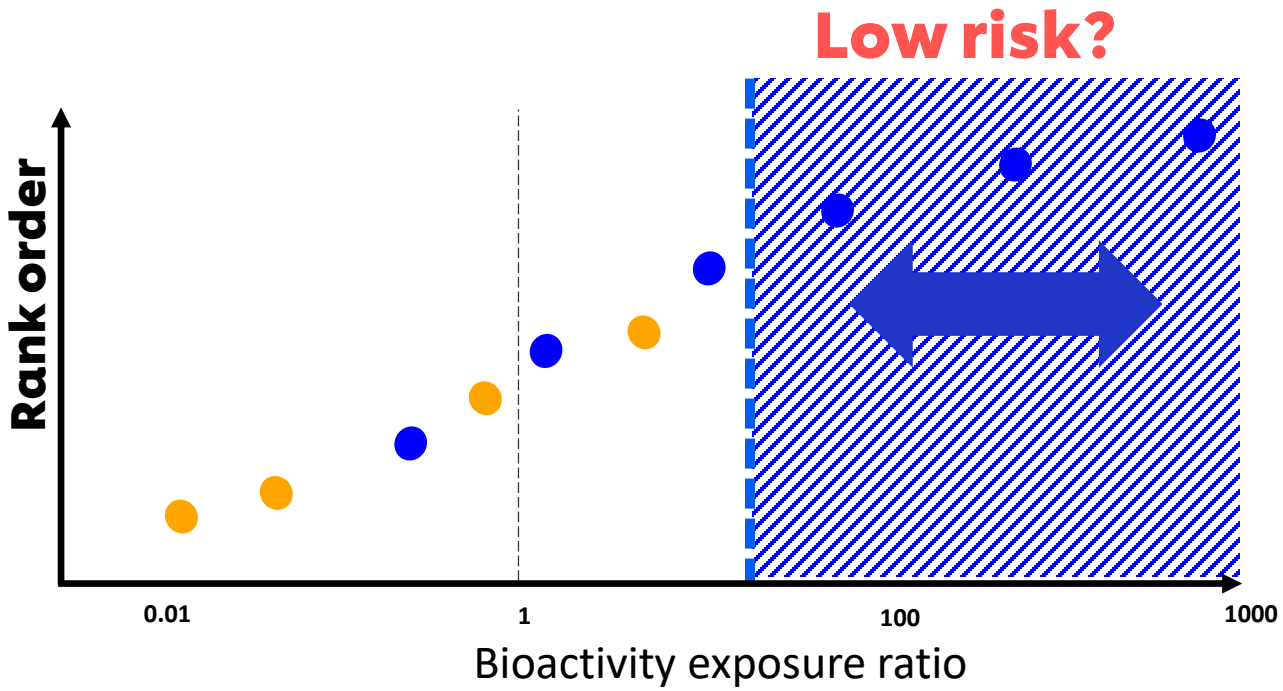
Defining a 'truth' to evaluate the outcome and performance of safety decisions made using the NAM-based toolbox

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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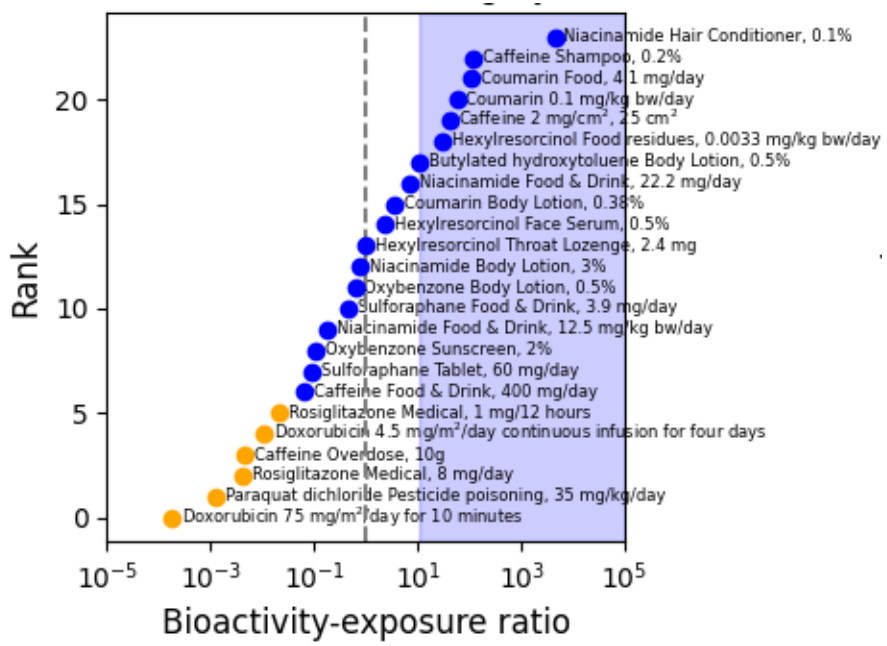
'Low' risk for consumers from systemic perspective

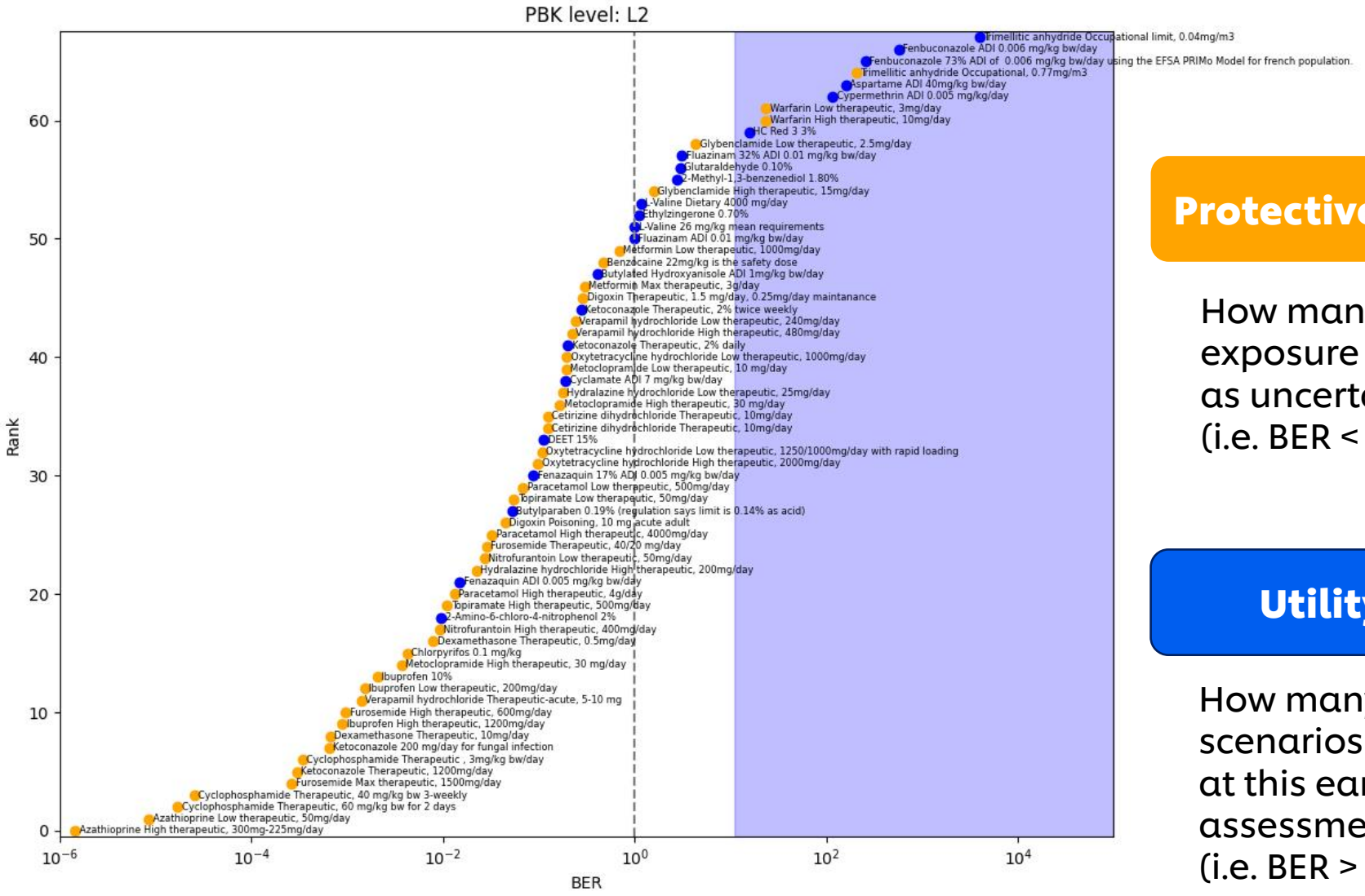
'High' risk for consumers from systemic perspective



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

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)

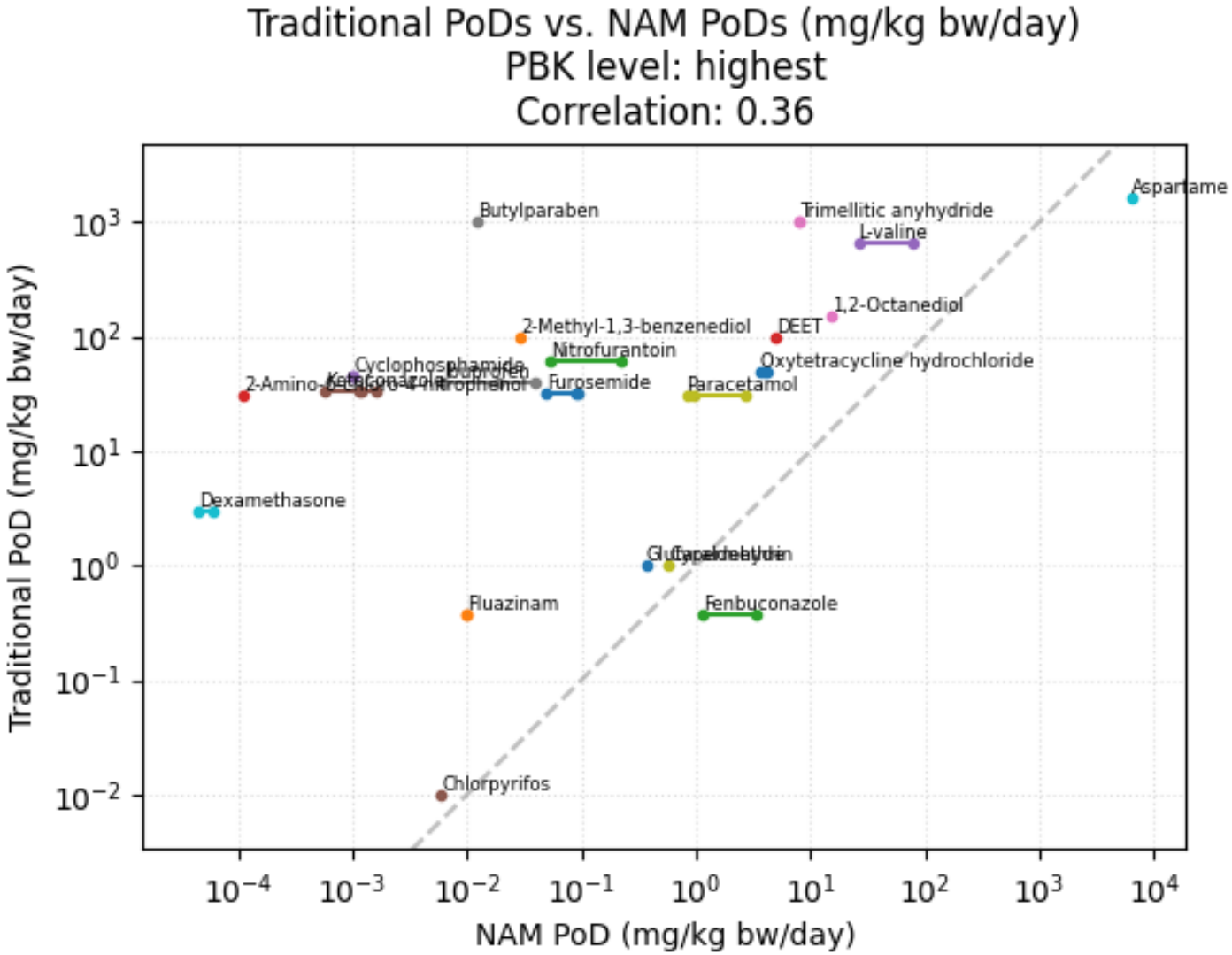
Utility — **27% (6 out of 22)**

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)

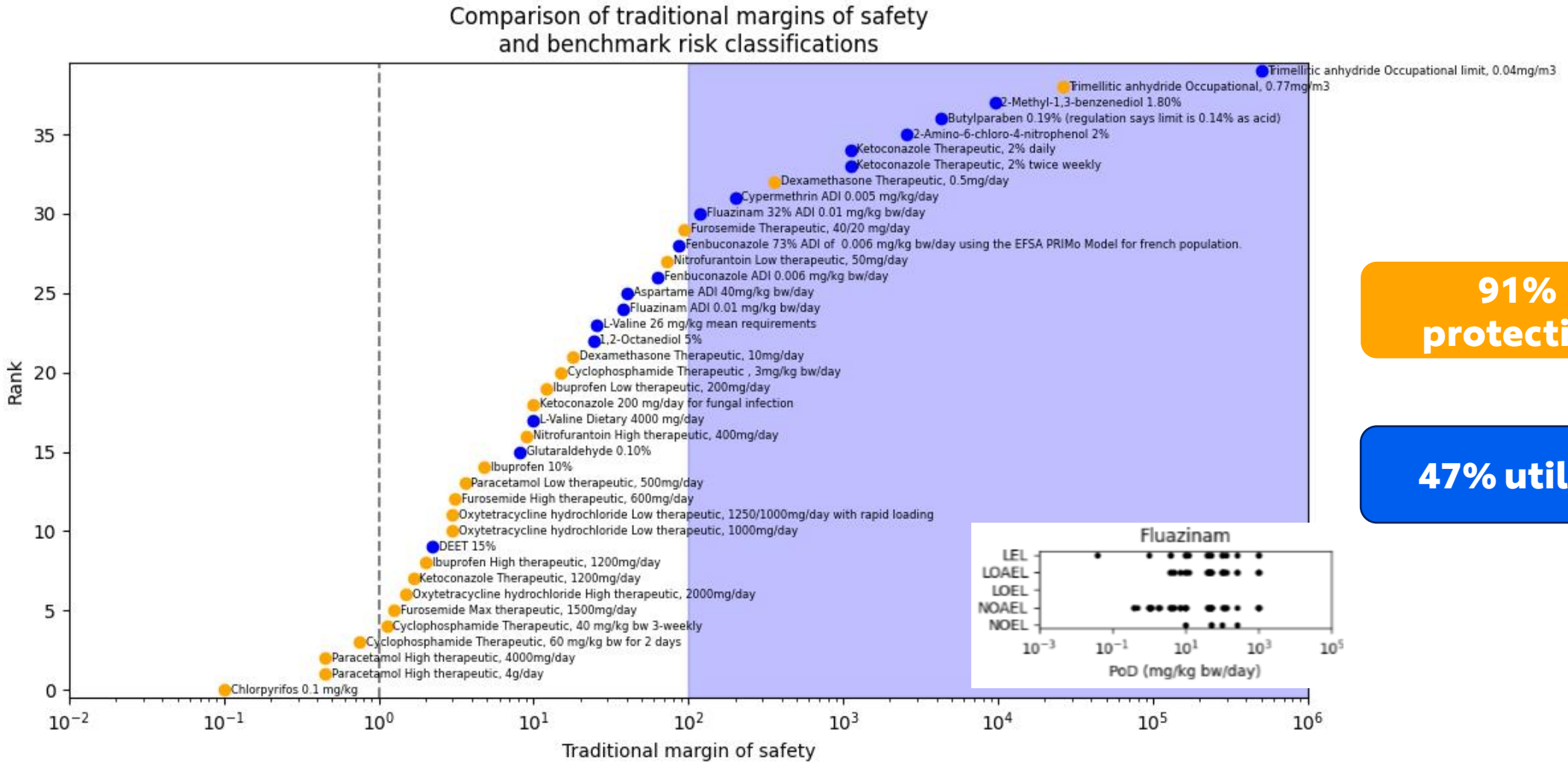
Comparison of a NAM-based early tier toolbox with early-tier decision making using in vivo data

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

But how can we build confidence in this approach by addressing remaining uncertainties?

- Currently the toolbox HTTr component uses 3 cell lines, how does cell line diversity impact the results?
- The metabolic competency of the bioactivity assays has not been addressed, how can we investigate this better to see if protective decisions are made for both parent and metabolites?
- How does the use of additional bioactivity assays impact the results? Is there an optimum combination of inputs to maximise protectiveness and utility?
- What if we want to use these approaches for environmental safety assessment as well as human safety assessment?

Thank You

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