Making sure that NAM-based safety assessments are protective

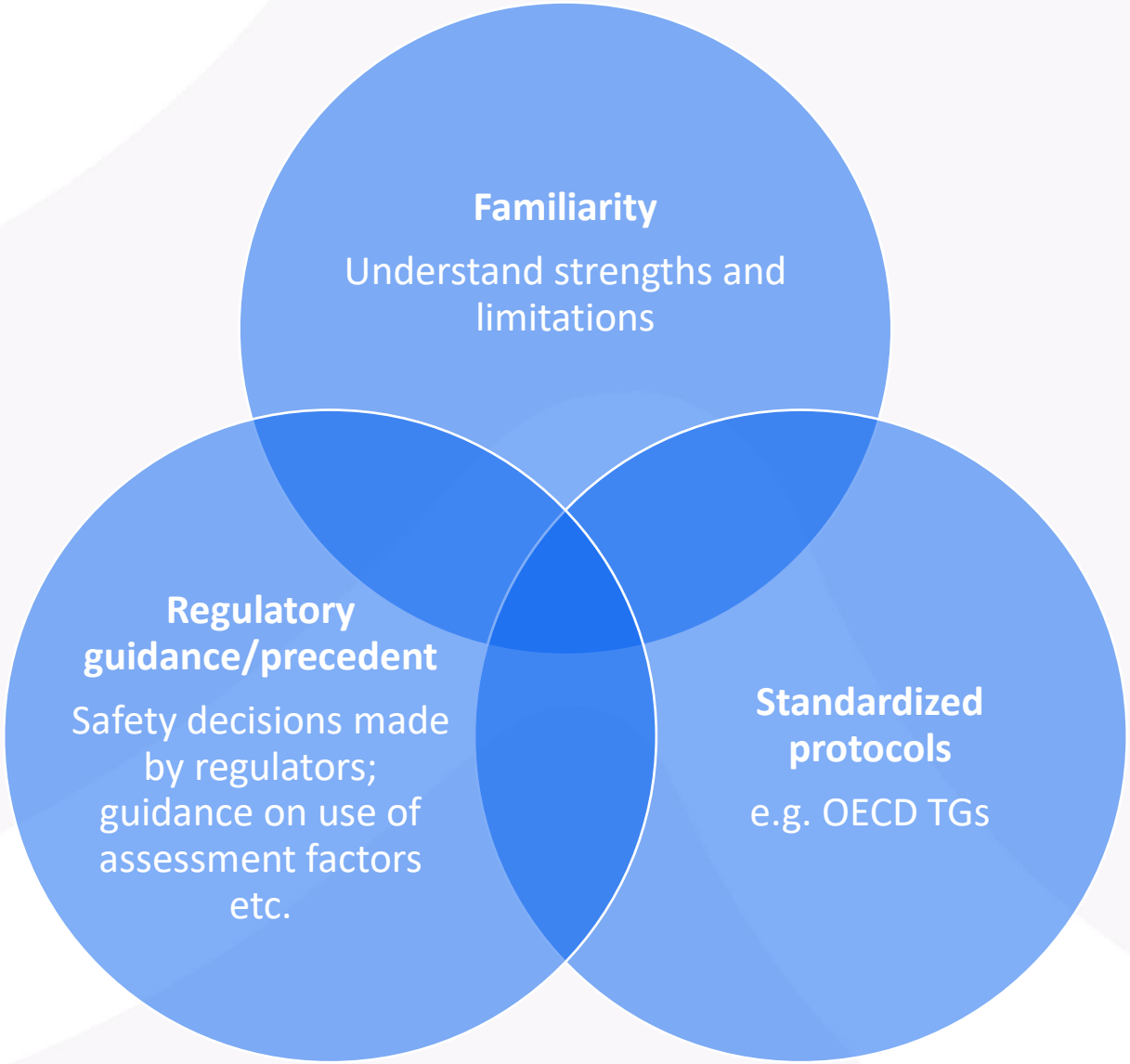
Matt Dent

Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ;

Outline

1. Why do we have confidence that *in vivo*-based risk assessments are protective?
2. Can this inform our approach to NAM-based assessments?

Why are we confident that animal-based assessments are protective?



Important to remember that animal tests are not necessarily predictive of adverse health effects in people – but *used in a certain way* they are useful for making safety decisions

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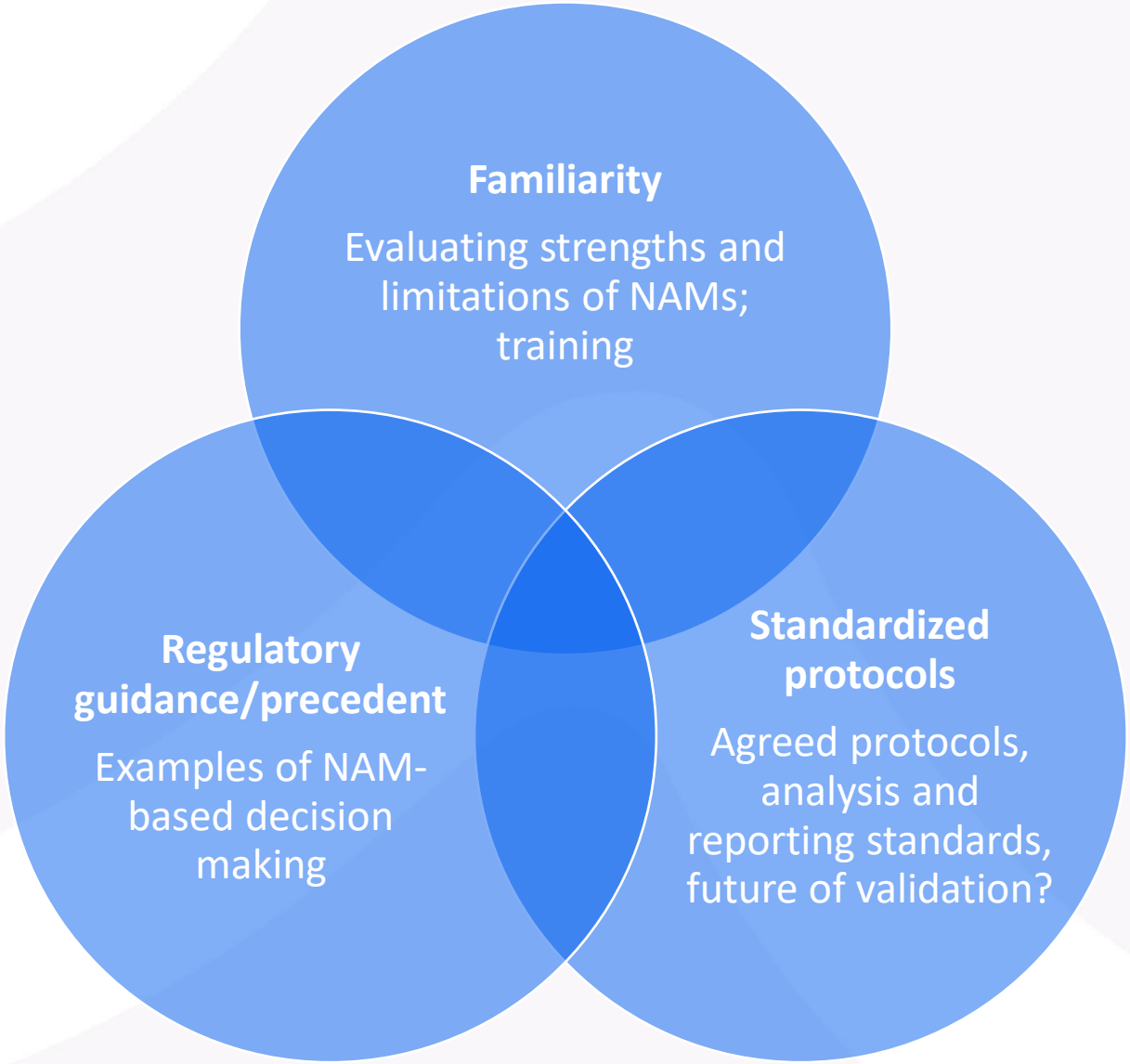
So how do we build confidence that NAM-based assessments are protective?



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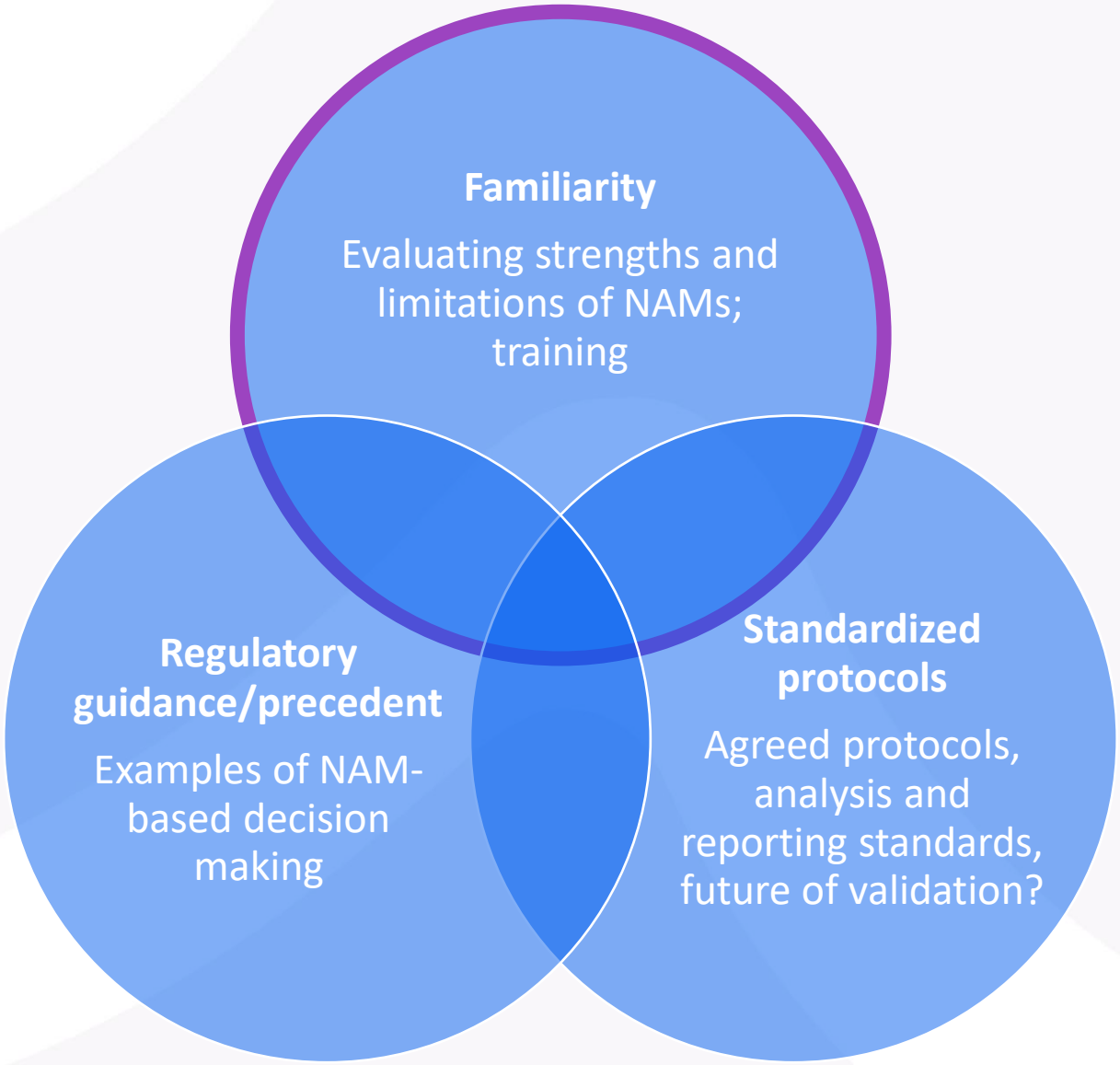

Important to remember that *in vitro* tests are not necessarily predictive of adverse health effects in people – but *used in a certain way* they are useful for making safety decisions

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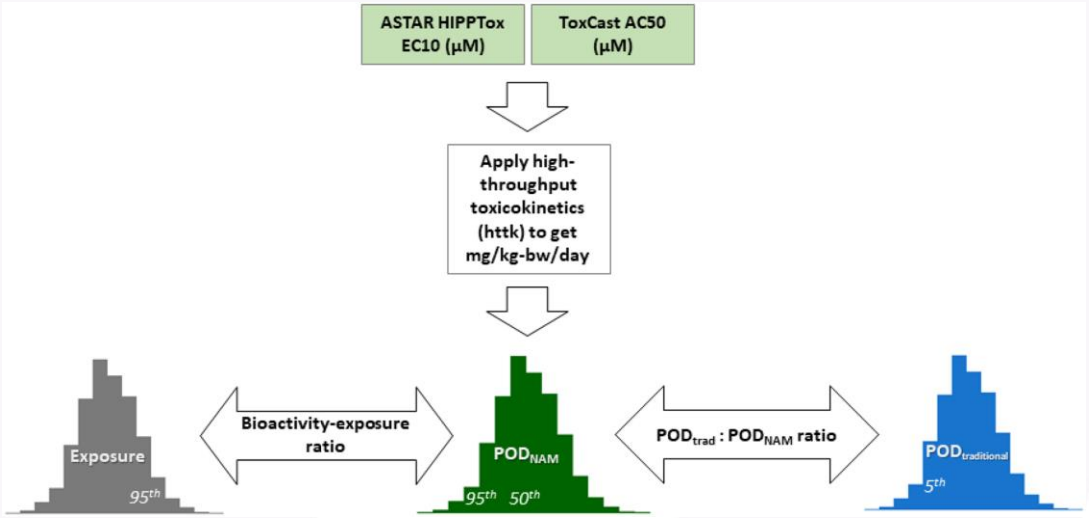
APRCA approach to evaluate the integration of exposure and bioactivity

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman ,*,[1] Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,* Ryan R. Lougee,*,[||] Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,[|||] Jean Lou Dorne,[||||] Stiven Foster,[#] Kathleen Raffaele,[#] Tina Bahadori,[||] Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,[§] Tara Barton-Maclaren,[†] and Russell S. Thomas *

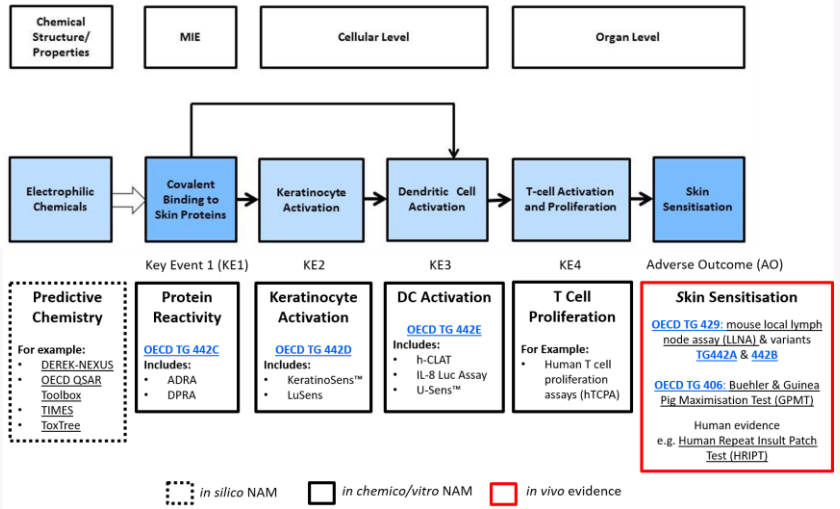


- Evaluation of in vitro NAMs, exposure modelling and dose-response models.
- For 89% of the chemicals NAM PoD was more conservative than the traditional POD.
- Bioactivity:exposure ratios (BERs) approach useful for accelerate screening and assessment using NAMs for hazard and exposure.

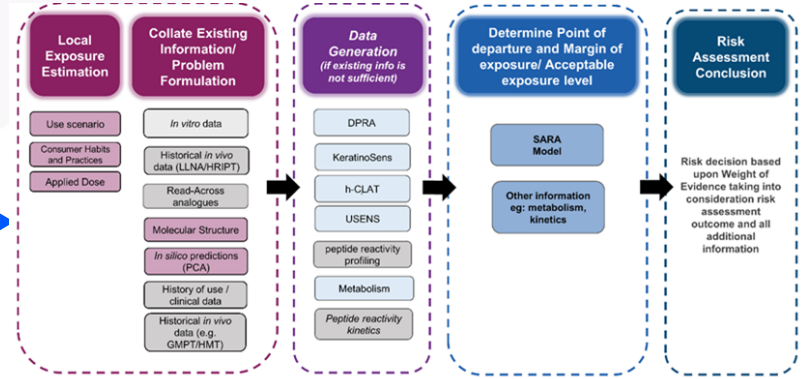
https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/science-approach-document-bioactivity-exposure-ratio-application-priority-setting-risk-assessment.html

Confidence in skin allergy NGRA- Unilever SARA Model

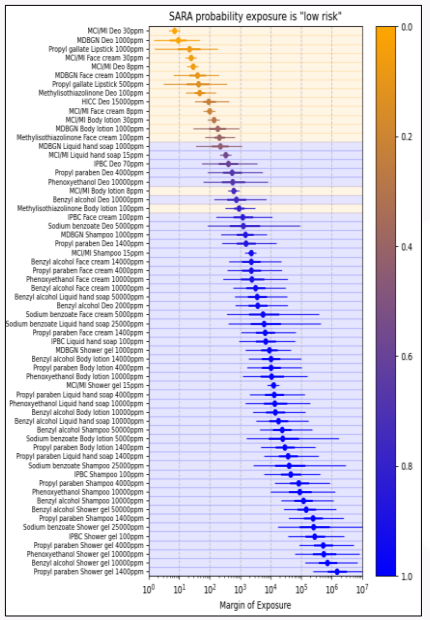
NAMs mapped into the AOP

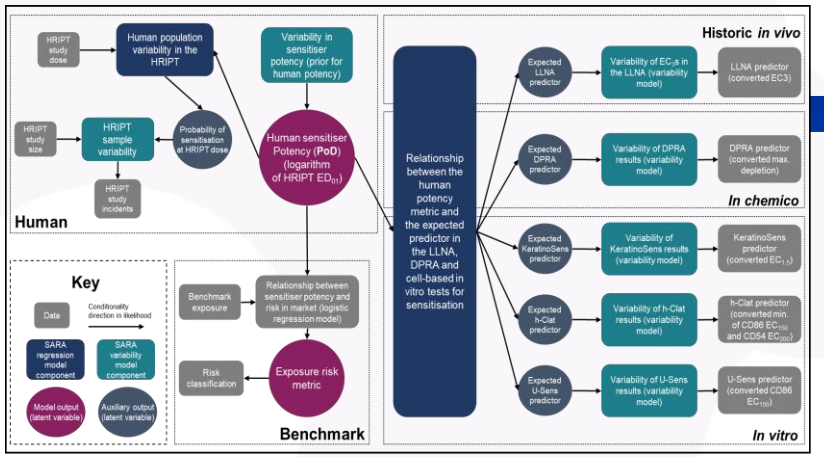


Developing a risk assessment framework...



Bayesian computational model that integrates information from the historical data and NAMs





SARA Model published and collaboration with US Gov. group (NICEATM) to adapt the model for regulatory use.

A hypothetical skin sensitisation next generation risk assessment for coumarin in cosmetic products

G. Reynolds *, J. Reynolds, N. Gilmour, R. Cubberley, S. Spriggs, A. Aptula, K. Przybylak, S. Windebank, G. Maxwell, M.T. Baltazar **

Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK

National Toxicology Program
U.S. Department of Health and Human Services

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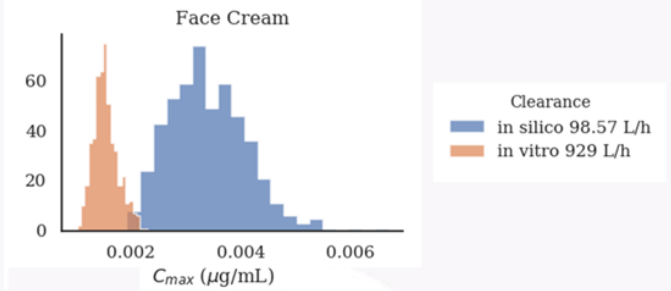
The key NAMs in our Systemic NGRA approach

PBK Modelling



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

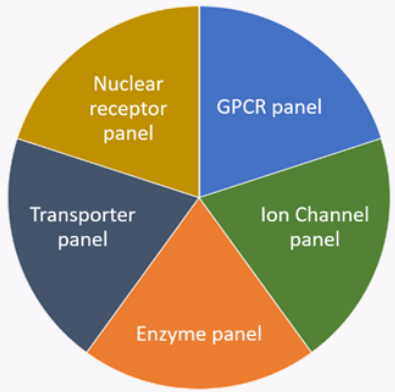
In vitro pharmacological profiling


PERSPECTIVES

A GUIDE TO DRUG DISCOVERY — OPINION

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling

Joanne Bowes, Andrew J. Brown, Jacques Hamon, Wolfgang Jarolimek, Arun Sridhar, Gareth Waldron and Steven Whitebread

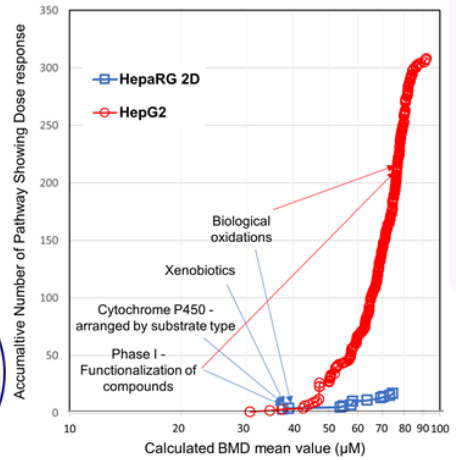


eurofins | Cerep

Transcriptomics

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

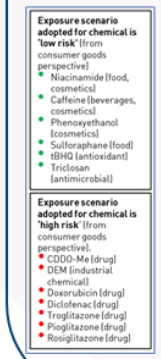
BMDExpress 2

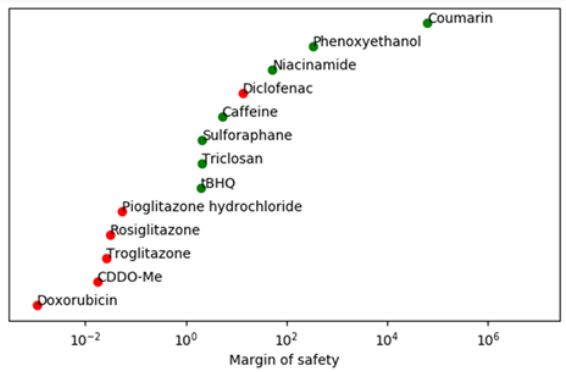


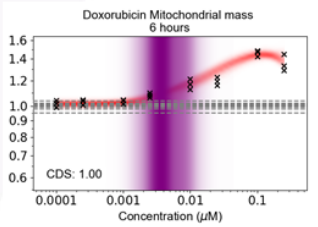
Cellular Stress Pathways

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

cyprotex AN EVOTEC COMPANY







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

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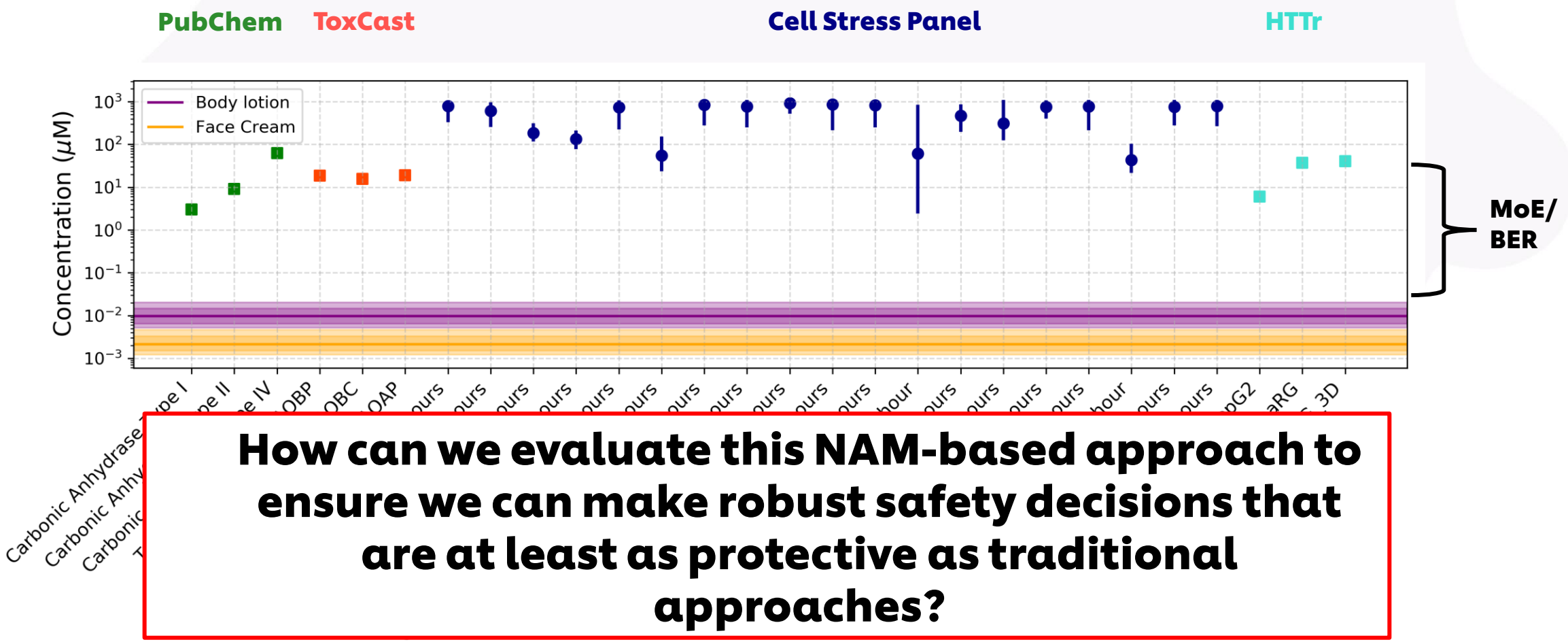
Exposure and PoD are plotted and used to derive a Bioactivity-Exposure Ratio (MoE/BER)



How can we evaluate this NAM-based approach to ensure we can make robust safety decisions that are at least as protective as traditional approaches?

Overview of the toolbox evaluation strategy

Stage 1 — **Define benchmark chemical-exposure scenarios**

Chemical	Exposure scenario	Risk category
Chem X1	Scenario Y1	High
Chem X2	Scenario Y2	Low

Stage 2 — **Apply NAM tools to generate bioactivity and exposure data for POD and C_{max} estimates**

Stage 3 — **Estimate minimum platform POD and population average Cmax to calculate the BER**

Stage 4 — **Benchmark BER against risk category for each exposure scenario in Step 1**

Can the toolbox correctly identify the risk classification?

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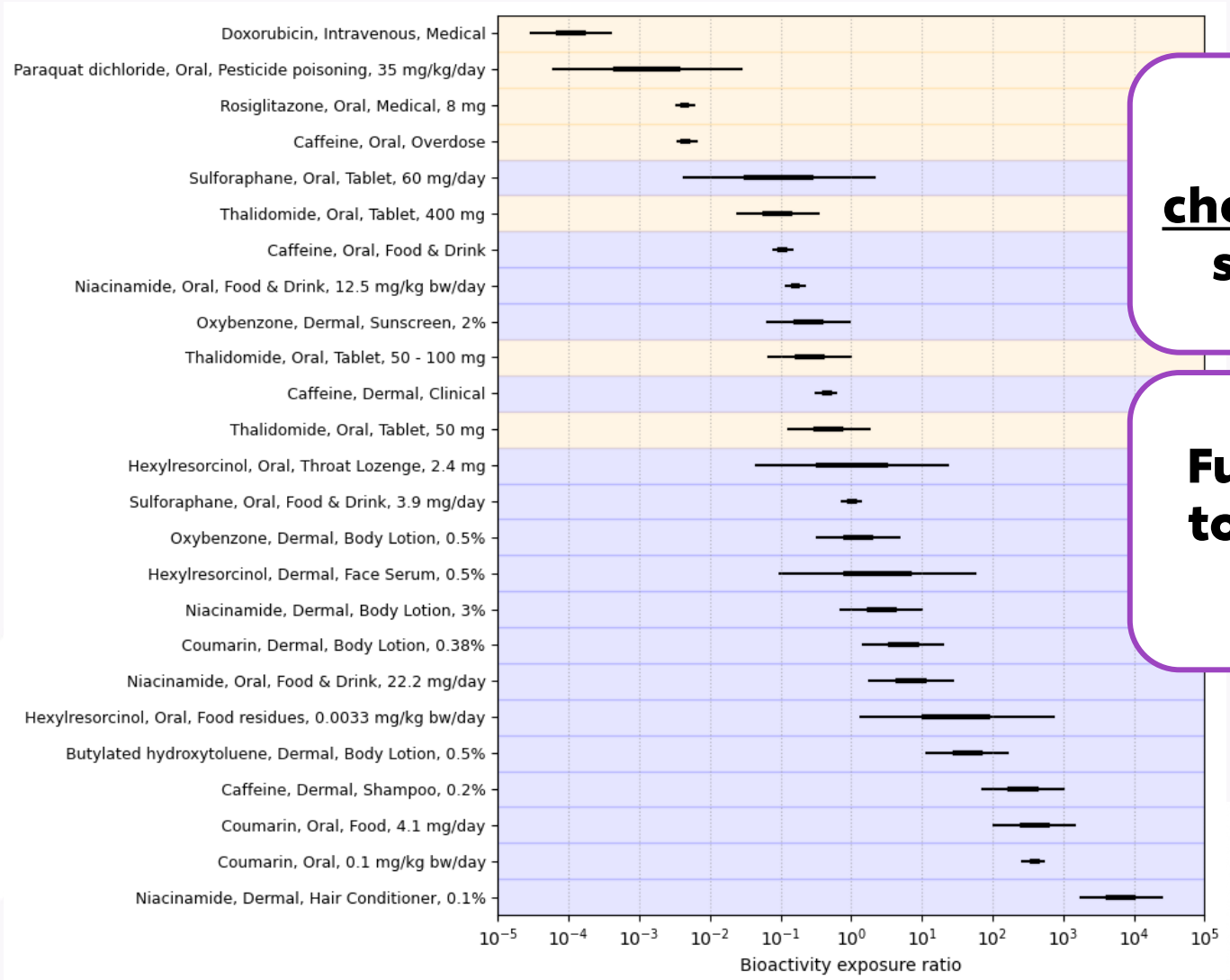
Stage 4- Benchmark BER against risk category for each exposure scenario in Step 1



<u>Testing 40+ chemicals</u> using the same approach

Further iterations to ensure toolbox protective

devTOX qP™ quickPREDICT

REPROTRACKER®

Centred 50% and 95% credible intervals summarising the distribution of the BER when using all available predicted C_{max} estimates. Background colours indicate the assigned risk category for each benchmark exposure (blue – low, orange – high).

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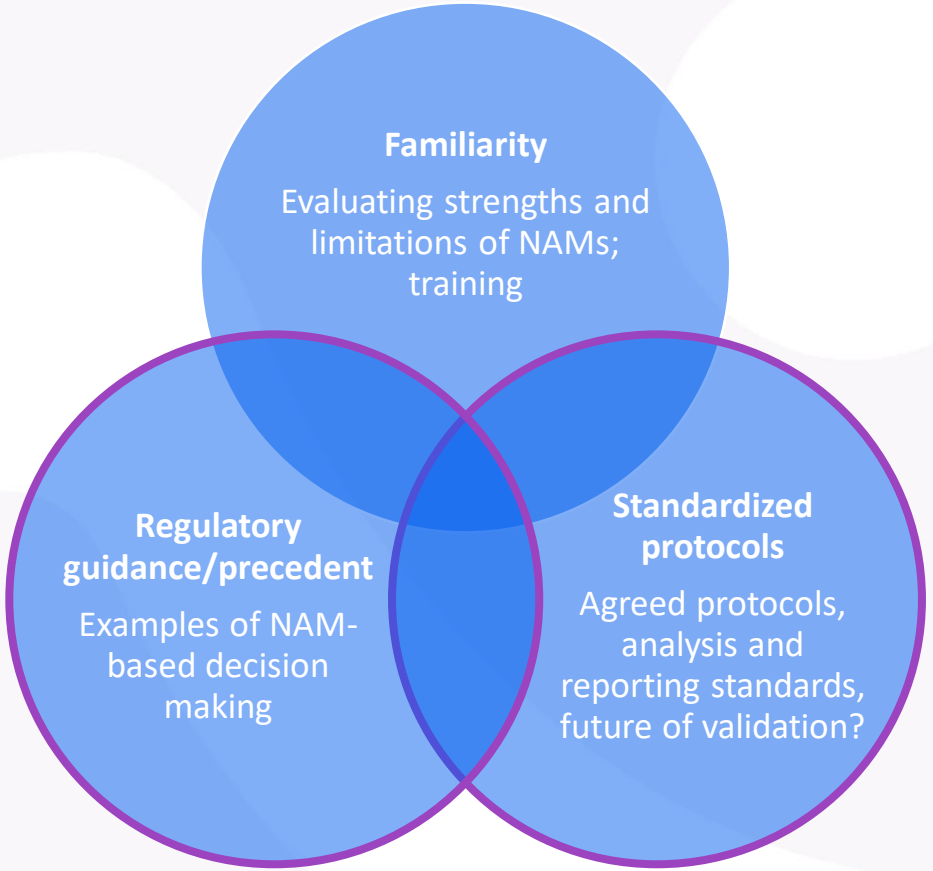
Conclusion & Next steps

- The first step in building confidence that NAM-based assessments can be protective is to build familiarity – understanding the strengths and weaknesses of the technology

- Without evaluations like this NAM-based assessments will always be viewed with suspicion



Recognition of NGRA in cosmetic safety assessment…

… Could we apply similar approaches to chemical registration?

Computational Toxicology 7 (2018) 20–26

Contents lists available at ScienceDirect

Computational Toxicology

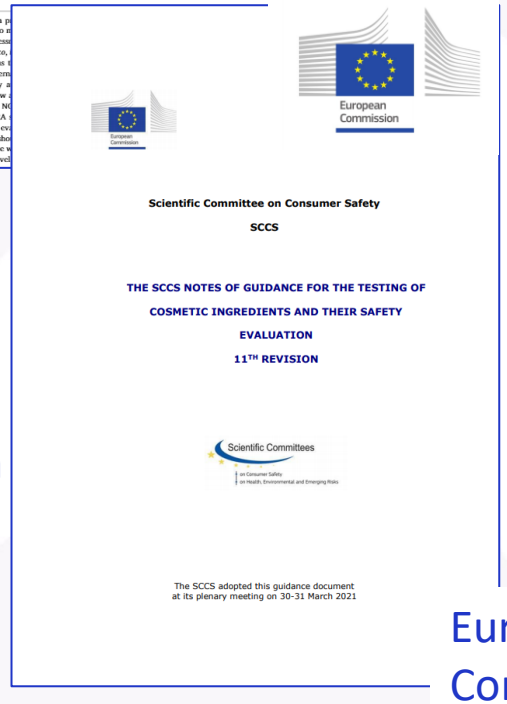
journal homepage: www.elsevier.com/locate/comtox

Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Matthew Dent[a,*], Renata Teixeira Amaral[b], Pedro Amores Da Silva[b], Jay Ansell[c], Fanny Boisleve[d], Masato Hatao[e], Akihiko Hirose[f], Yutaka Kasai[g], Petra Kern[h], Reinhard Kreiling[i], Stanley Milstein[j], Beta Montemayor[k], Julcemara Oliveira[l], Andrea Richarz[m], Rob Taalman[n], Eric Vaillancourt[o], Rajeshwar Verma[l], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

ARTICLE INFO

ABSTRACT



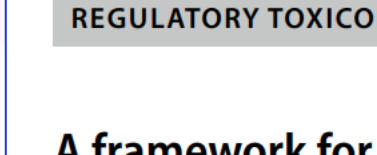
Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 11TH REVISION

Scientific Committees

The SCCS adopted this guidance document at its plenary meeting on 30-31 March 2021



Archives of Toxicology (2022) 96:743–766
https://doi.org/10.1007/s00204-021-03215-9

REGULATORY TOXICOLOGY

A framework for chemical safety assessment incorporating new approach methodologies within REACH

Nicholas Ball[1] · Remi Bars[2] · Philip A. Botham[3] · Andreea Cuciureanu[4] · Mark T. D. Cronin[5] · John E. Doe[5] · Tatsiana Dudzina[6] · Timothy W. Gant[7] · Marcel Leist[8] · Bennard van Ravenzwaay[9]

International Cooperation on Cosmetics Regulation (2018)

European Commission: Scientific Committee on Consumer Safety (2021)

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