

Making sure that NAM-based safety assessments are protective

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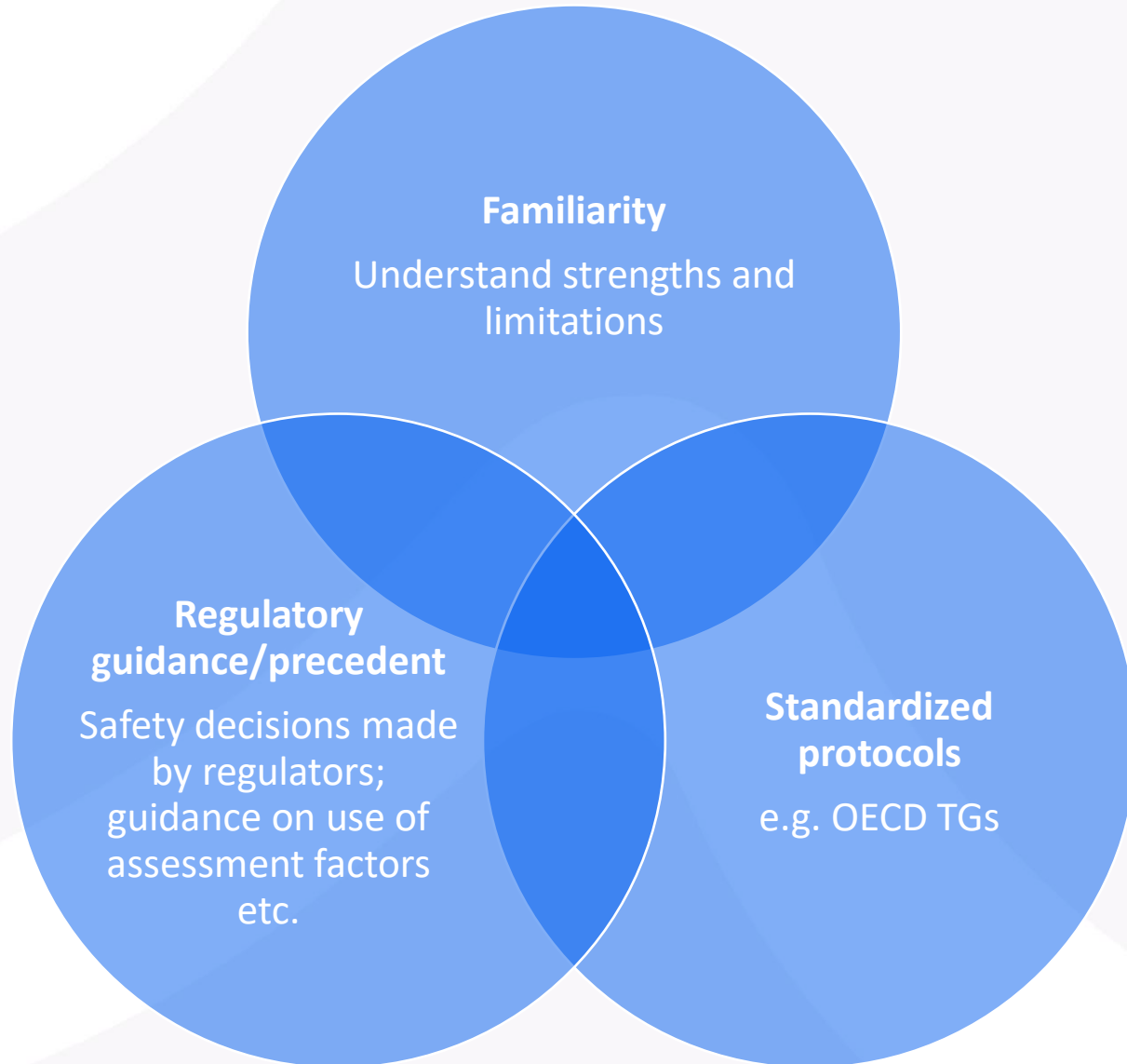


Unilever

Outline

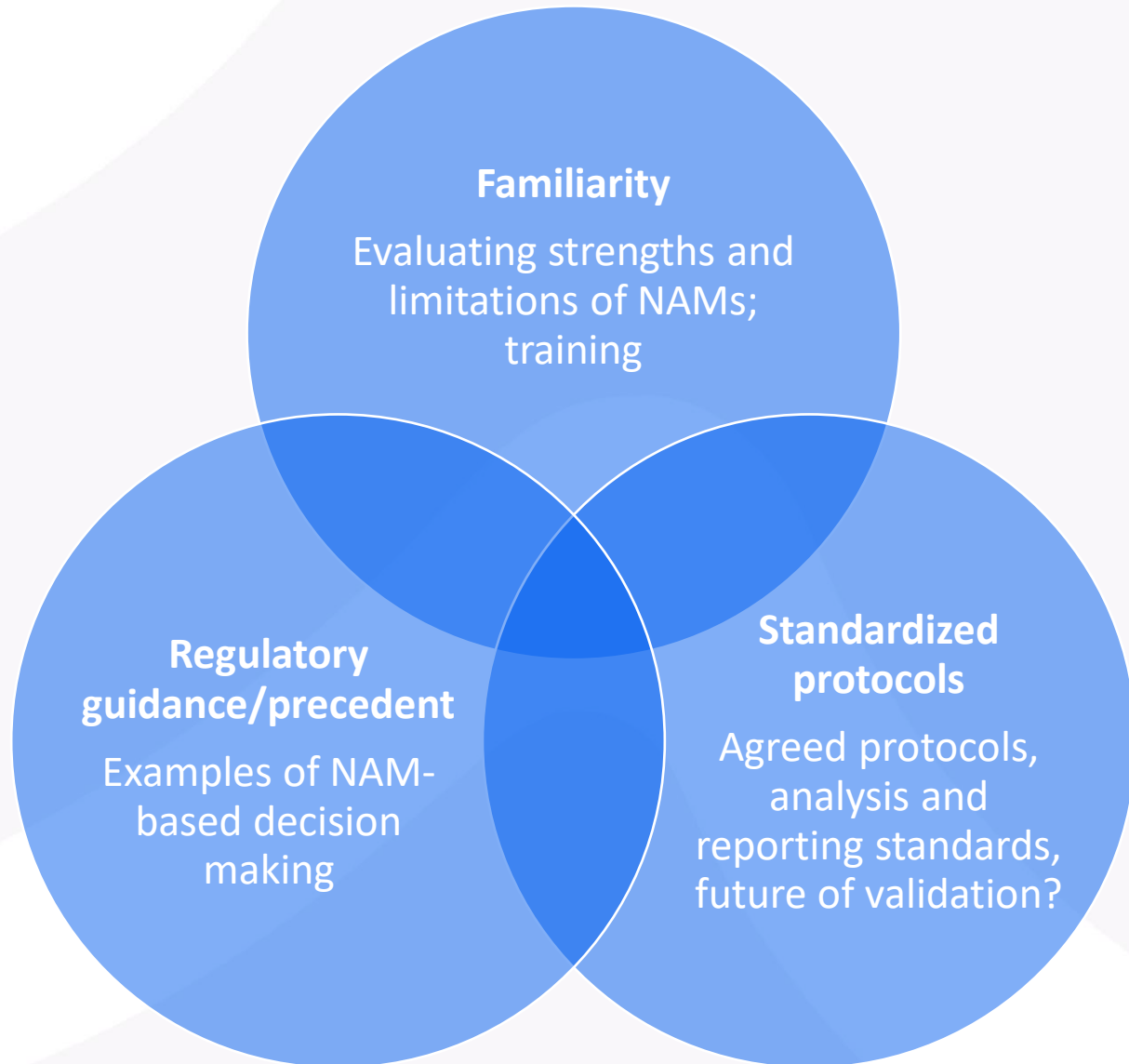
1. Why do we have confidence that *in vivo*-based risk assessments are protective?
2. Can this inform our approach to NAM-based assessments?

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



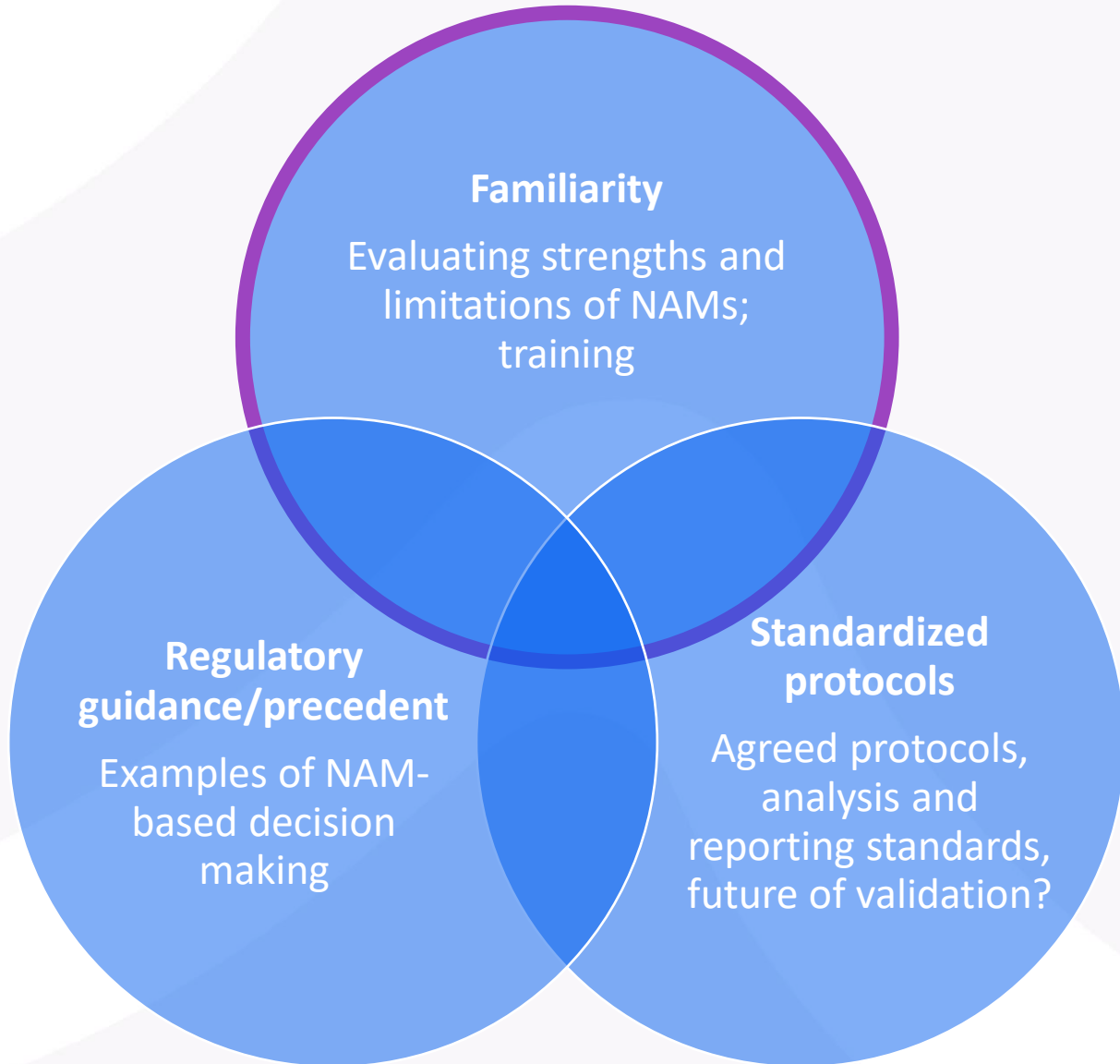
Important to remember that animal tests are not necessarily predictive of adverse health effects in people – but *used in a certain way* they are useful for making safety decisions

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



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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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**

APRCA approach to evaluate the integration of exposure and bioactivity



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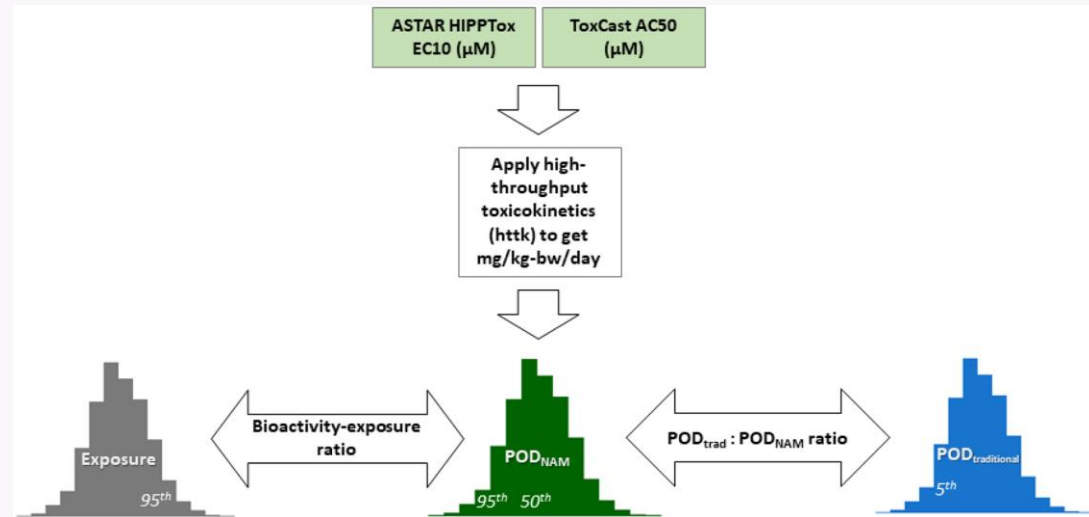


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Research Article

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

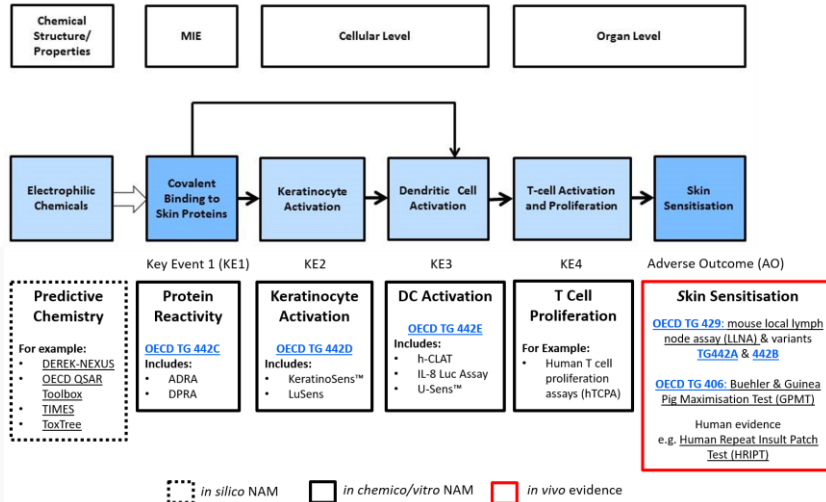
Katie Paul Friedman ,^{*,1} Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,^{*} Ryan R. Lougee,^{*,||} Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,^{||l} Jean Lou Dome,^{||lll} Stiven Foster,[#] Kathleen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



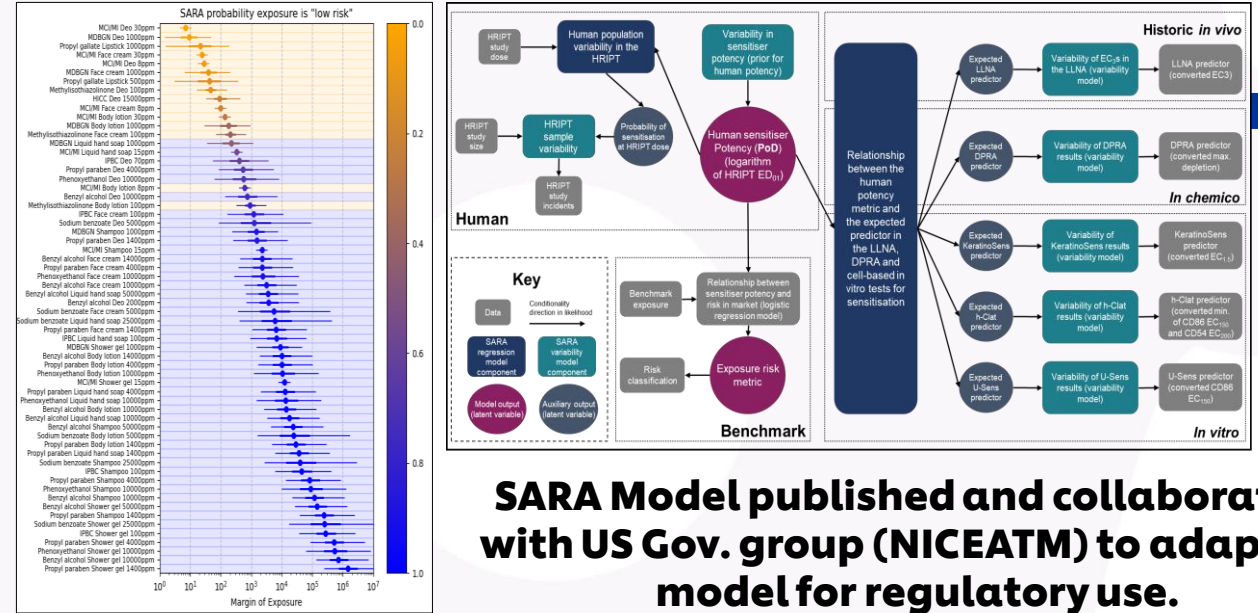
- Evaluation of *in vitro* NAMs, exposure modelling and dose-response models.
- For 89% of the chemicals NAM PoD was more conservative than the traditional POD.
- Bioactivity:exposure ratios (BERs) approach useful for accelerate screening and assessment using NAMs for hazard and exposure.

Confidence in skin allergy NGRA - Unilever SARA Model

NAMs mapped into the AOP

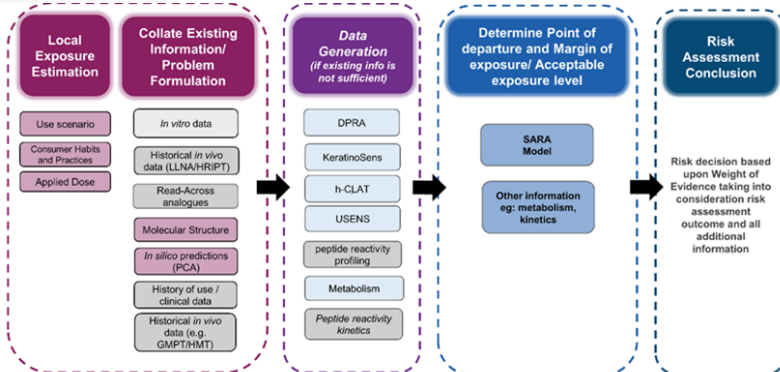


Bayesian computational model that integrates information from the historical data and NAMs



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

Developing a risk assessment framework...



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

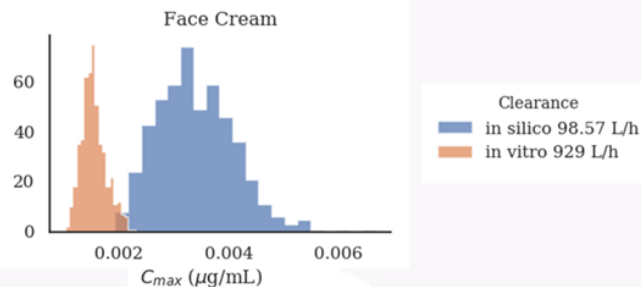
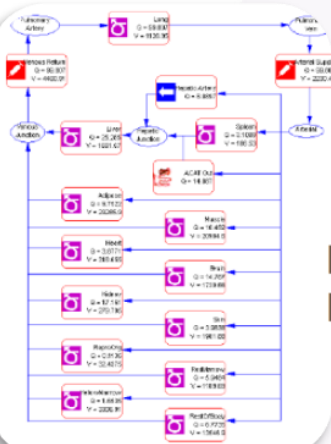
G. Reynolds*, J. Reynolds, N. Gilmour, R. Cubberley, S. Spriggs, A. Aptula, K. Przybylak, S. Windebank, G. Maxwell, M.T. Baltazar**

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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 Brown, Andrew J. Brown, Jacques Héman, Wolfgang Jorntink, Arun Sridhar, Gareth Waldron and Steven Whitbread

Abstract In vitro pharmacological profiling is increasingly being used earlier in the drug discovery process to identify undesirable off-target activity profiles that could hinder or halt the development of candidate drugs or even lead to market withdrawal after a drug is approved. Here, for the first time, the rationale, strategies and methodologies for *in vitro* pharmacological profiling at four major pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Novartis and Pfizer) are presented and illustrated with examples of their impact on the drug discovery process. We hope that this will enable other companies and academic institutions to benefit from this knowledge and consider joining us in our collaborative knowledge sharing.

Decreasing the high attrition rate in the drug discovery and development process is a primary goal of the pharmaceutical industry. One of the main challenges in achieving this goal is striking an appropriate balance between drug efficacy and potential adverse effects as early as possible in order to reduce safety-related attrition, particularly in the more expensive late stages of clinical development. Gaining better understanding of the safety profile of drug candidates early in the process is also crucial for reducing the likelihood of safety issues limiting the use of approved drugs, or even leading to their market withdrawal, having to incur the associated financial and regulatory costs.

target (or targets), whose secondary effects are due to interactions with targets other than the primary target (or targets) that is off-target interactions. Off-target interactions are often the cause of ADRs in animal models or clinical studies, and so careful characterization and identification of secondary pharmacology profiles of drug candidates early in the drug discovery process might help to reduce the incidence of type A ADRs.

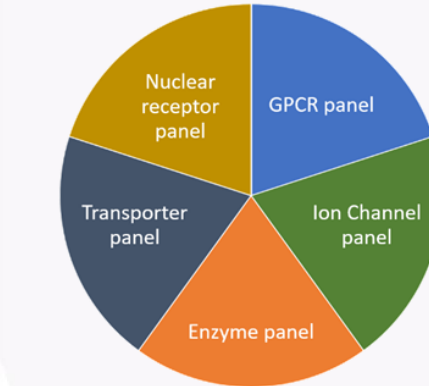
In vitro pharmacological profiling involves the screening of compounds against a broad range of targets (receptors, ion channels, enzymes and transporters) that are distinct from the intended

safety testing of drug candidates and are designed to prevent serious ADRs from occurring in clinical studies.

The *in vitro* pharmacology assay that is absolutely required by regulatory authorities is one that measures the effects of new chemical entities on the ionotropic current of hK₁ or heterologously expressed human voltage-gated potassium channels (shaded yellow) H₂ member 2 (hKCNH2), also known as hERG. The mechanism by which blockade of hERG can elicit primarily fatal cardiac arrhythmias (torsades de pointes) following a prolongation of the QT interval is well characterized^{1,2}, and the seriousness of this ADR is one reason why this assay is a mandatory regulatory requirement. Receptor binding studies are also recommended as the first tier approach for the assessment of the dependence potential of novel chemical entities³.

However, current regulatory guidance does not describe which targets should constitute an *in vitro* pharmacological profiling panel and does not indicate the stage of the discovery process at which *in vitro* pharmacological profiling should occur. Nevertheless, this general need for more pharmaceutical companies to perform this testing early in drug discovery to reduce attrition and to facilitate better prediction of ADRs in the later stages of drug discovery and development.

Here, for the first time, four major pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Novartis and Pfizer) share their knowledge and experience of the innovative application of existing screening technologies to detect off-target interactions of compounds. The objective of this article is to describe the rationale and main advantages for the use of *in vitro* pharmacological profiling to reduce both production and

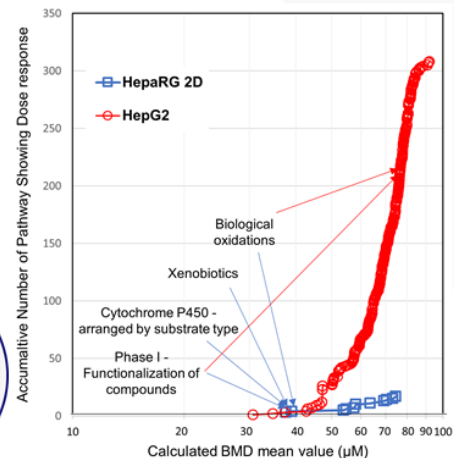
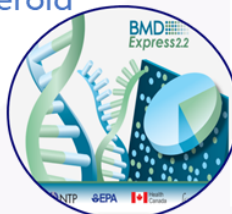


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Transcriptomics

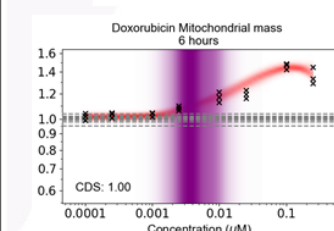
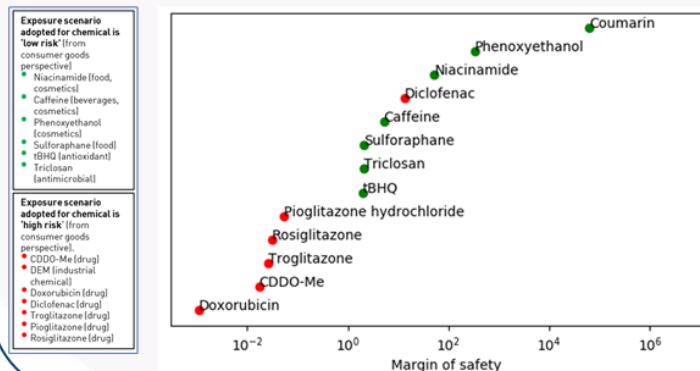
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDexpress 2



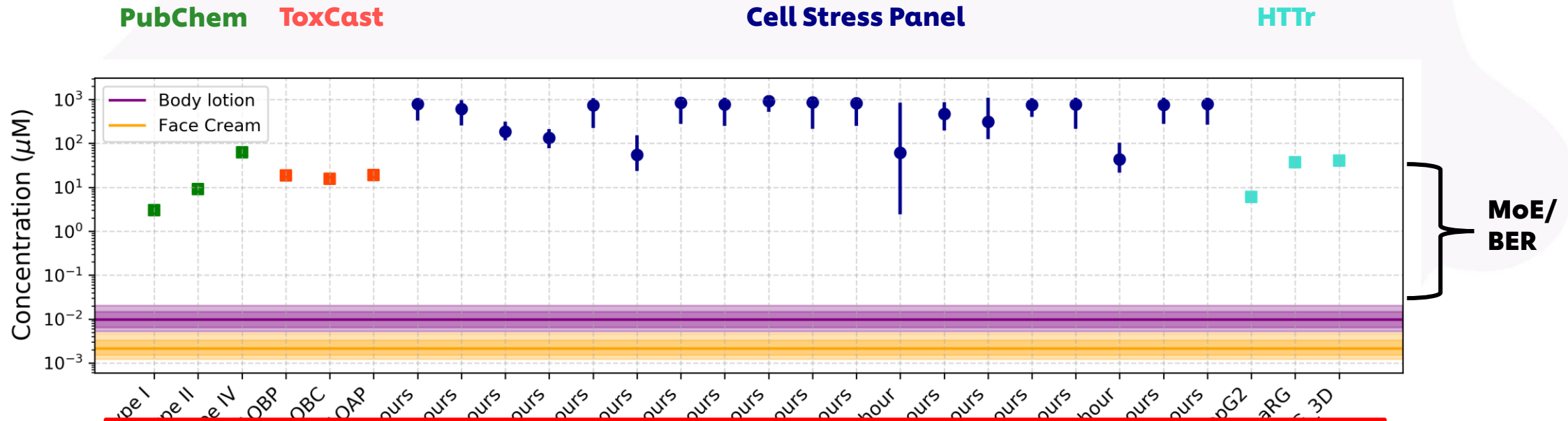
Cellular Stress Pathways

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



Toxicol Sci (2020), 176, 11-33

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



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 C_{max} to calculate the BER

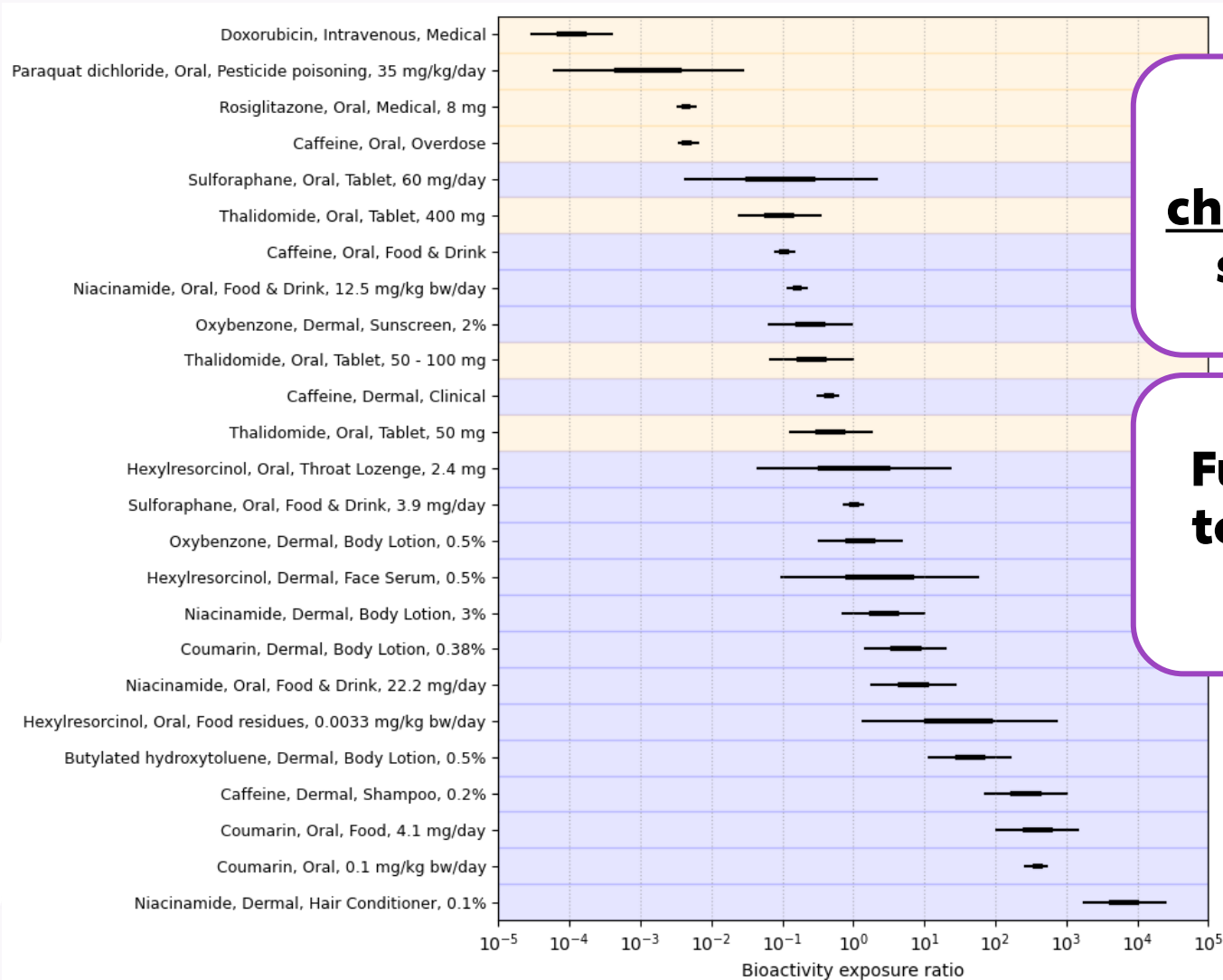


Stage 4

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

Can the toolbox correctly identify the risk classification?

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



Testing 40+ chemicals using the same approach

Further iterations to ensure toolbox protective

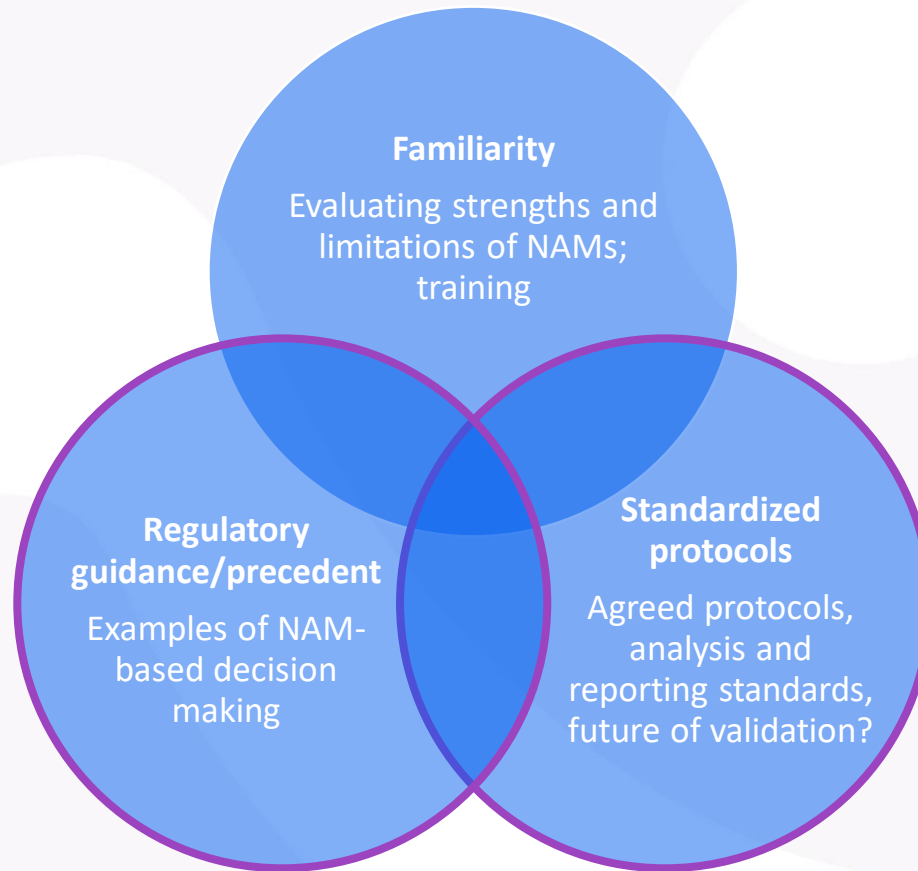


Centred 50% and 95% credible intervals summarising the distribution of the BER when using all available predicted C_{max} estimates. Background colours indicate the assigned risk category for each benchmark exposure (blue – low, orange – high).



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?

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

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ARTICLE INFO ABSTRACT

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 Cosmetics risk assessment

Consumer safety is a primary goal of the European Commission. The Commission is committed to ensuring that products placed on the market are safe for consumers. The Commission is currently reviewing the regulatory framework for consumer safety products to ensure that it is fit for purpose and that it integrates in silico, in vitro and in vivo data. The Commission is also reviewing the regulatory framework for consumer safety products to ensure that it is fit for purpose and that it integrates in silico, in vitro and in vivo data. The Commission is also reviewing the regulatory framework for consumer safety products to ensure that it is fit for purpose and that it integrates in silico, in vitro and in vivo data.

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REGULATORY TOXICOLOGY

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

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International Cooperation on Cosmetics Regulation (2018)

European Commission

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
 for Consumer Safety
 in Health, Environmental and Emerging Risks

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

European Commission: Scientific Committee on Consumer Safety (2021)



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