Integrating in vitro bioactivity data, computational modelling and exposure science in animal-free cosmetic safety assessments

Maria Baltazar, Safety Science Leader

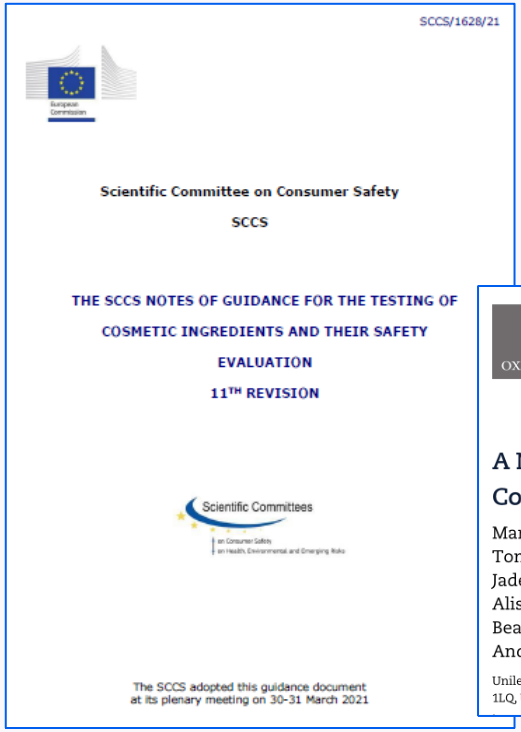
Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ;

Unilever

Non-animal Safety Science → Next Generation Risk Assessment

2007

2021


SCCS/1628/21

Scientific Committee on Consumer Safety

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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


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SOT Society of Toxicology

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TOXICOLOGICAL SCIENCES, 2020, 1–17

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Research article

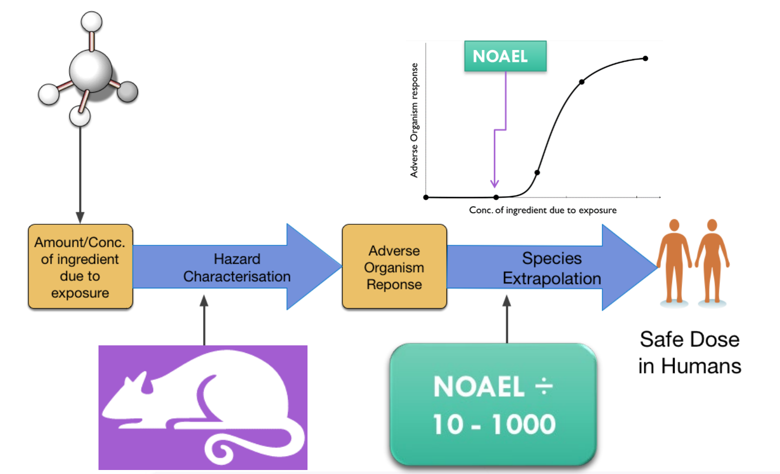
A Next-Generation Risk Assessment Case Study for Coumarin in Cosmetic Products

Maria T. Baltazar,[1] Sophie Cable, Paul L. Carmichael, Richard Cubberley, Tom Cull, Mona Delagrange, Matthew P. Dent, Sarah Hatherell, Jade Houghton, Predrag Kukic, Hequn Li, Mi-Young Lee, Sophie Malcomber, Alistair M. Middleton, Thomas E. Moxon, Alexis V. Nathanail, Beate Nicol, Ruth Pendlington, Georgia Reynolds, Joe Reynolds, Andrew White, and Carl Westmoreland

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

2021

'Traditional' Risk Assessment

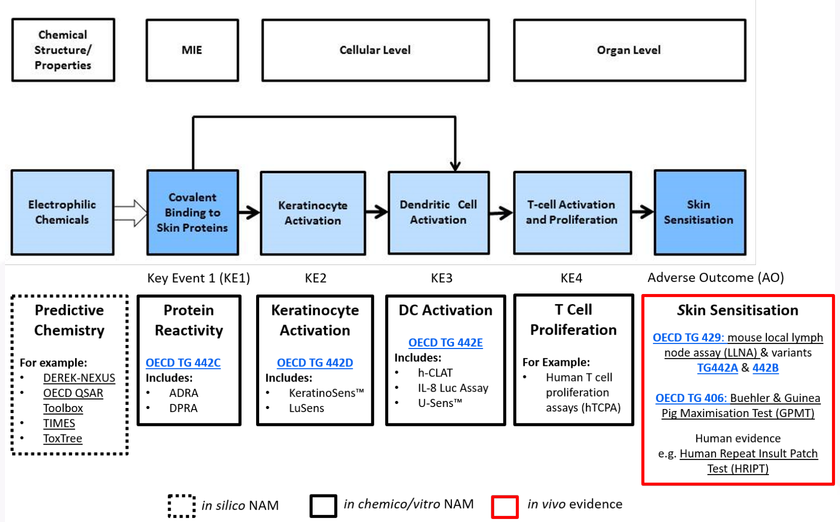


'Next Generation' Risk Assessment

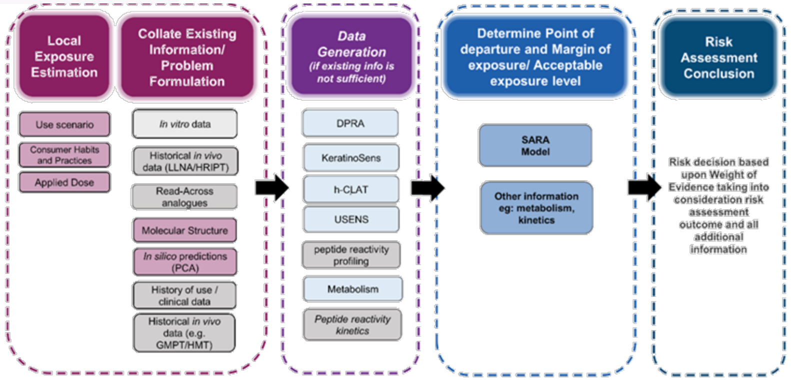
based on advances in human biology and in vitro/computational modelling

Success in skin allergy NGRA- Unilever SARA Model

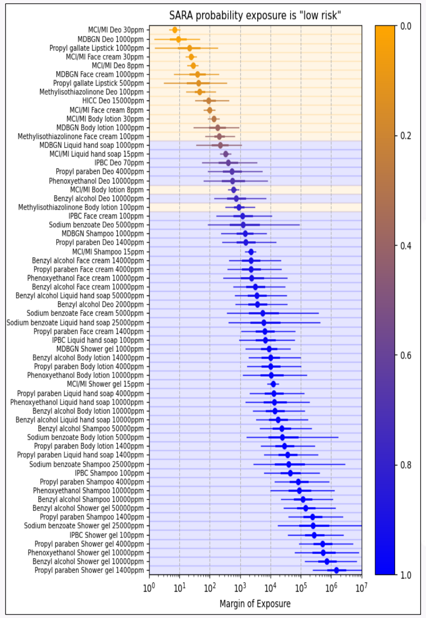
NAMs mapped into the AOP

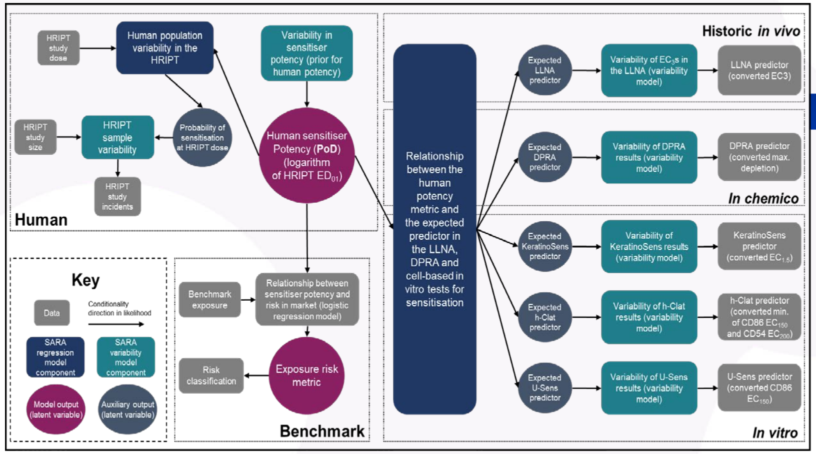


Developing a risk assessment framework…



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.

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

ELSEVIER

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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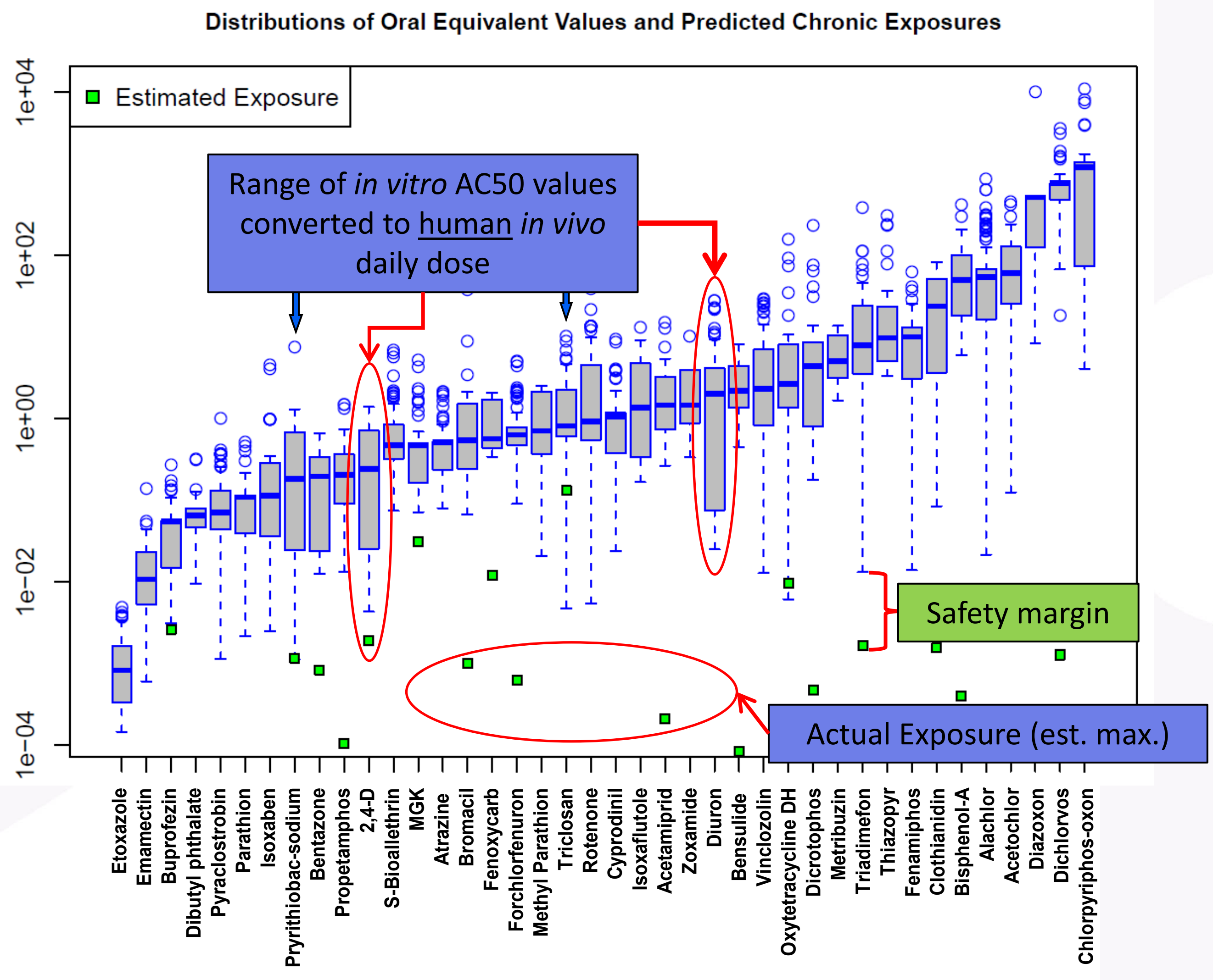
Paradigm shift for systemic safety - Protection not Prediction



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.

Progress in the application of NAMs in NGRA for systemic safety

NAMs applied in an *ab initio* hypothetical NGRA case study (e.g. coumarin and phenoxyethanol)

OXFORD SOT Society of Toxicology academic.oup.com/toxsci

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Advance Access Publication Date: April 10, 2020
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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 Testing and Assessment, No. 349

NAMs applied in real-life chemical safety assessments

APPLIED IN VITRO TOXICOLOGY
Volume 7, Number 2, 2021
© Mary Ann Liebert, Inc.
DOI: 10.1089/aivt.2021.0005

Use of the MucilAir Airway Assay, a New Approach Methodology, for Evaluating the Safety and Inhalation Risk of Agrochemicals

Marie McGee Hargrove,[1,i] Bob Parr-Dobrzanski,[2] Lei Li,[3] Samuel Constant,[4] Joanne Wallace,[5] Paul Hinderliter,[1,*] Douglas C. Wolf,[1] and Alex Charlton[2]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

https://www.regulations.gov/document/EPA-HQ-OPP-2011-0840-0080

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Progress in the application of NAMs in NGRA for systemic safety

NAMs applied in an *ab initio* hypothetical NGRA case study (e.g. coumarin and phenoxyethanol)

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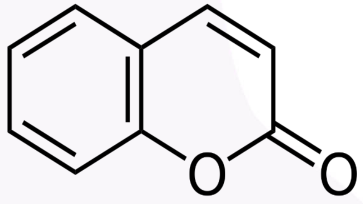
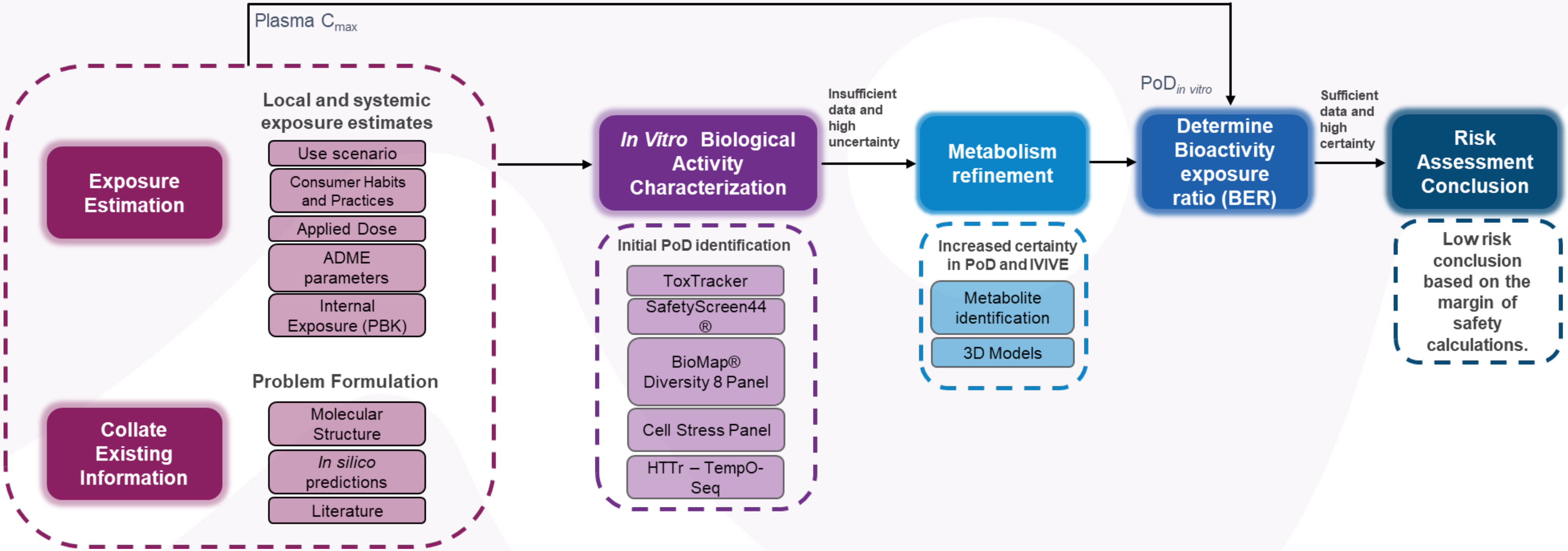
Exposure-led and hypothesis driven NGRA

0.1% COUMARIN IN COSMETIC PRODUCTS

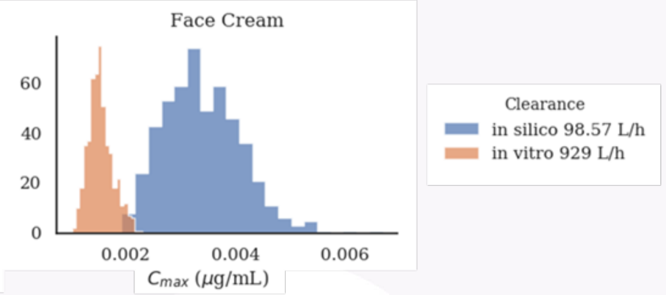




Baltazar *et al.*, (2020) *Tox Sci* Volume 176, Issue 1, 236–252

The key NAMs in our NGRA approach

PBK Modelling



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

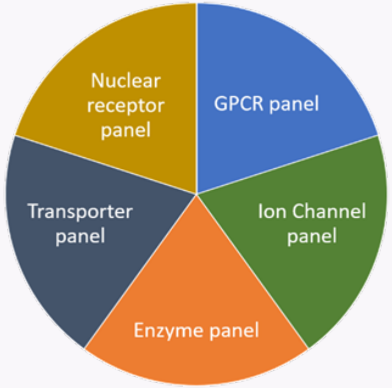
In vitro pharmacological profiling

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

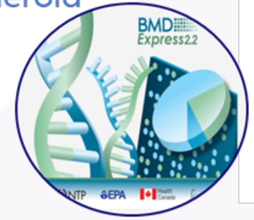


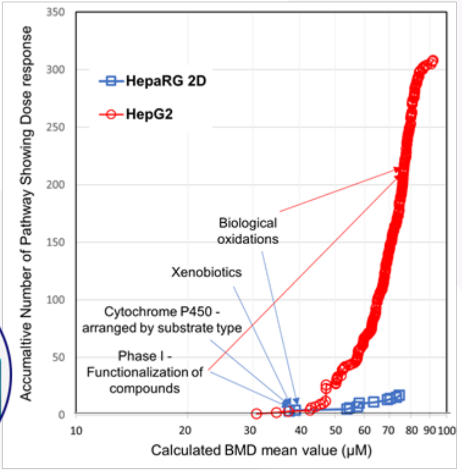
eurofins Cerep

Transcriptomics

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

BMDexpress 2





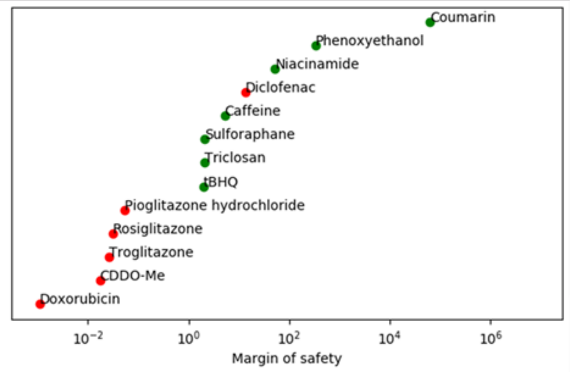
Cellular Stress Pathways

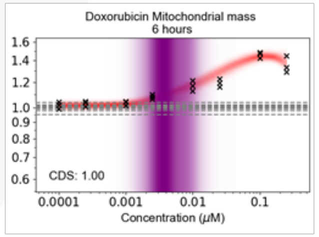
13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways

cyprotex AN EVOTEC COMPANY

Exposure scenario adopted for chemical is 'low risk' (from consumer goods perspective)
- Niacinamide (food, cosmetics)
- Caffeine (beverages, cosmetics)
- Phenoxyethanol (cosmetics)
- Sulforaphane (food)
- tBHQ (antioxidant)
- Triclosan (antimicrobial)

Exposure scenario adopted for chemical is 'high risk' (from consumer goods perspective).
- CDDO-Me (drug)
- DEM (industrial chemical)
- Doxorubicin (drug)
- Diclofenac (drug)
- Troglitazone (drug)
- Pioglitazone (drug)
- Rosiglitazone (drug)





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

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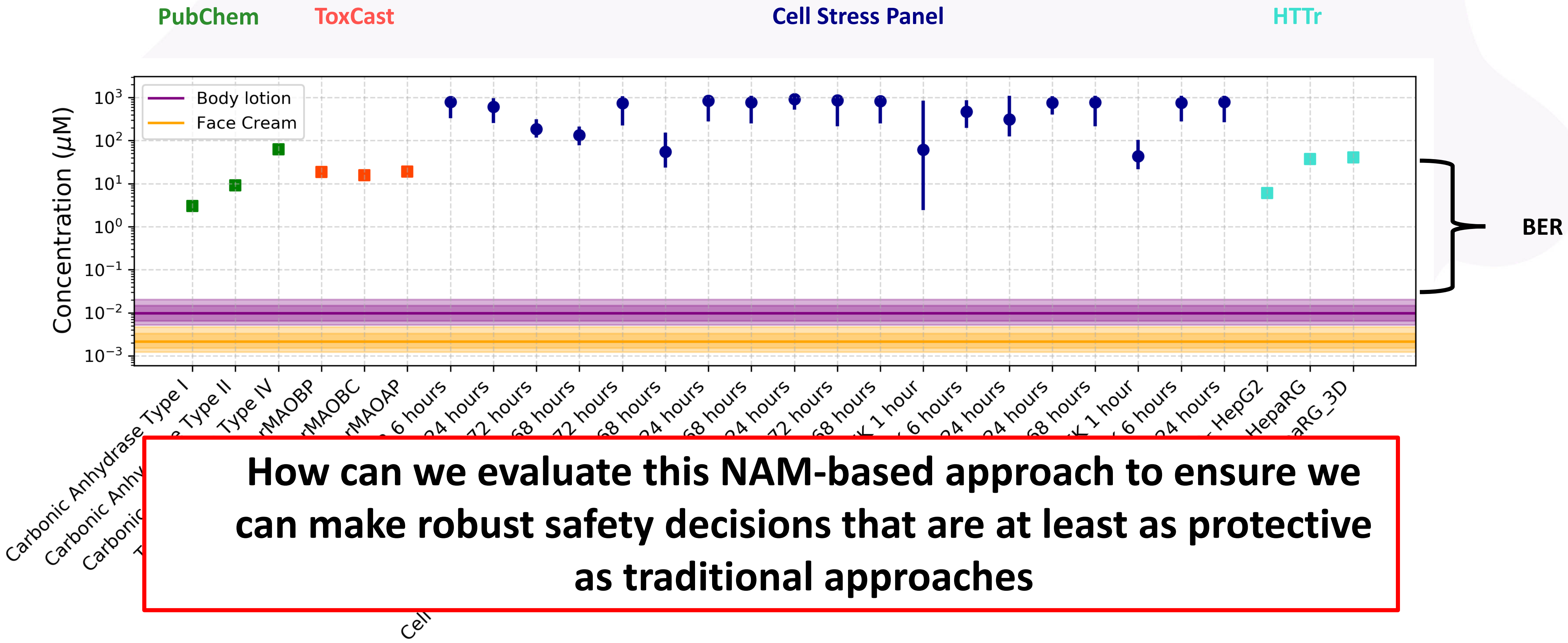
Exposure and PoD are plotted and used to derive a Bioactivity-Exposure Ratio (BER)



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

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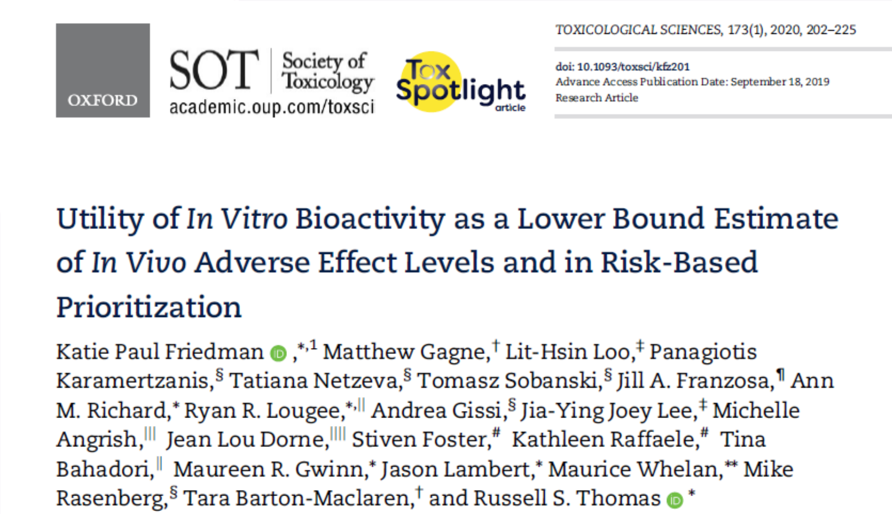
APRCA approach to evaluate the integration of exposure and bioactivity



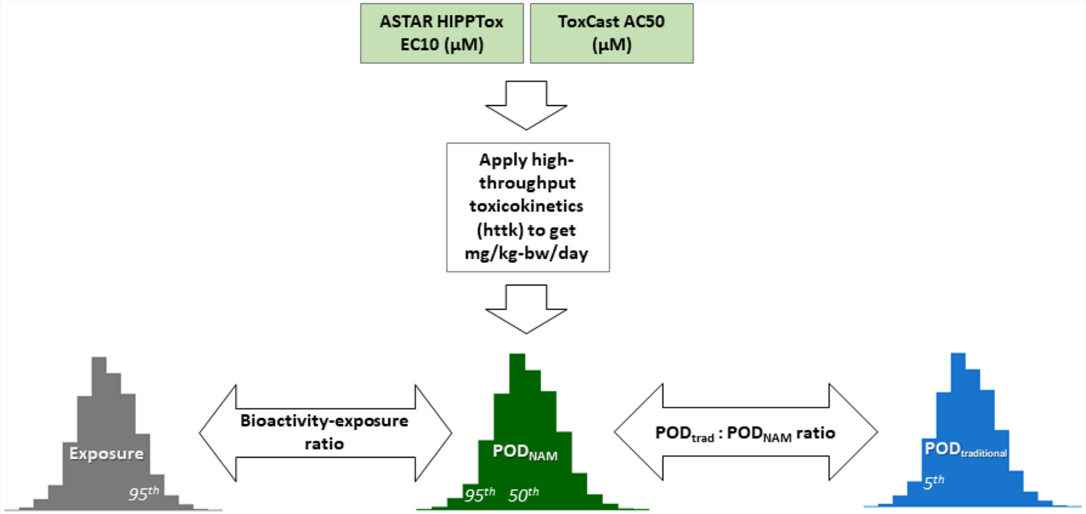
OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

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.

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

Approach to evaluate our in vitro NAMs and computational models for risk assessment- **benchmarking BERs generated using the toolbox against existent safety decisions**

1. Establish **a core toolbox of NAMs (in vitro and computational)** that can be used to provide BERs which enable protective systemic safety decisions to be made without using any animal data.
2. Present a proof-of-concept study **on how to evaluate the performance of the core** toolbox against historical safety decisions.
3. **Establish the decision model** upon which to conduct the full evaluation.

The core toolbox

- HTTr – 3 cell lines
- Cell stress panel
- IPP
- PKB models
- Dose-response models

Middleton et al 2022. Manuscript in preparation

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 Cmax 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?

Stage 1- Define benchmark chemical-exposure scenarios

- 11 different chemicals
- 25 benchmark exposure scenarios
- Mixture of ‘high risk’ and ‘low risk’ exposure scenarios

Example of the evidence gathered for each benchmark

Caffeine	Oral Dietary intake – 400 mg/day	Low risk	No evidence for concern with respect to systemic toxicity from the available toxicological data, as concluded by EFSA, Health Canada and the US Food and Drug Administration (FDA).	(Blanchard and Sawers 1983, Nawrot, Jordan et al. 2003, EFSA Panel on Dietetic Products and Allergies 2015)
	Dermal 0.2% shampoo	Low risk		
	Oral Tablets/overdose >10g	High risk	Evidence of serious adverse systemic effects which can result in death.	(Jabbar and Hanly 2013)
Rosiglitazone	Oral 8mg/day	High risk	The maximum recommended daily dose for the treatment of diabetes is 8 mg per day. Rosiglitazone leads to adverse effects such as weight gain, anaemia, fluid retention, and adverse effects on lipids. Importantly, fluid retention may exacerbate or lead to heart failure and other effects.	https://www.fda.gov/media/75754/download (Yki-Järvinen 2004)

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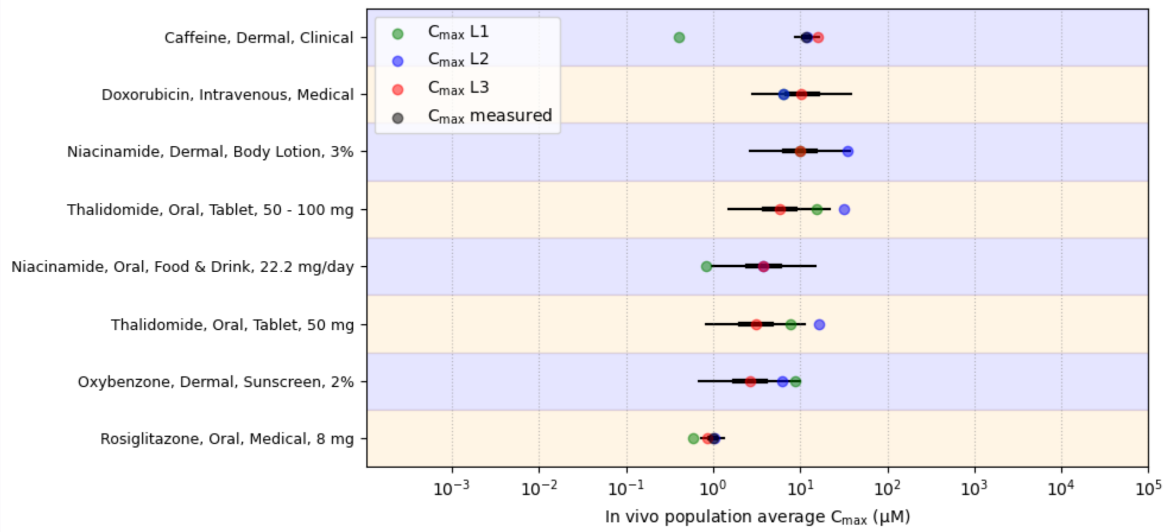
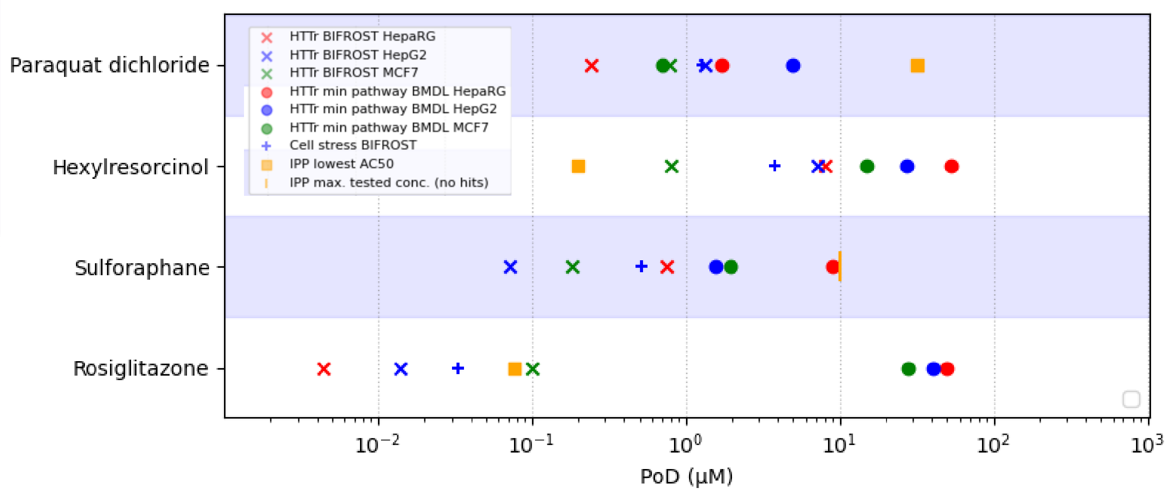
Stage 2 & 3 – Estimation Of Population average Cmax and PoD

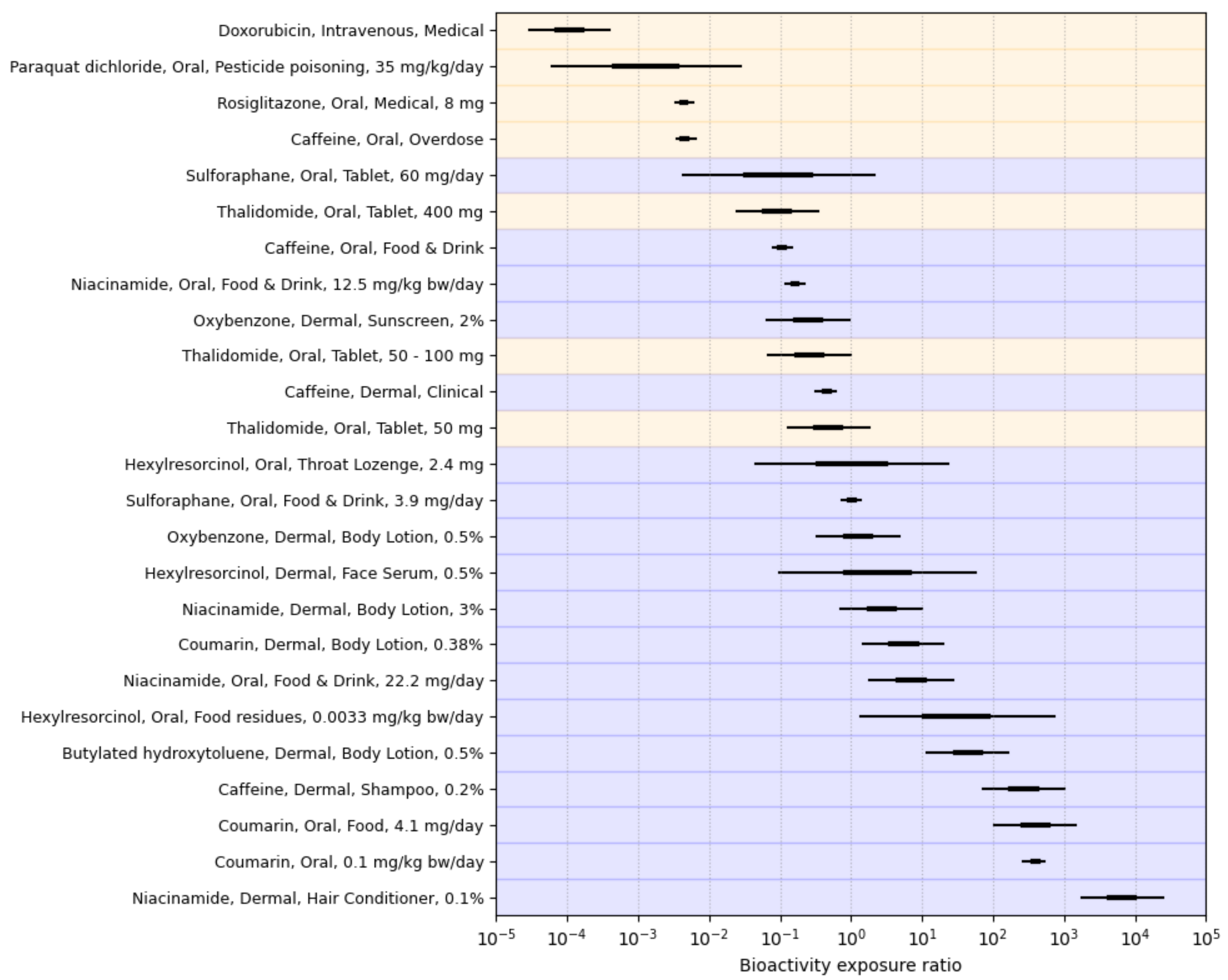
- For most cosmetics exposure, human clinical data is not available.
- There is a need to characterise the uncertainty in Plasma Cmax predictions from PBK models
- We developed a model that predicts a probabilistic estimate of what the 'true' population average Cmax is, based on all the training data .



- For most chemicals (8 out of 11), the lowest PoDs tended to come from the HTTr when analysed using the Bayesian concentration-response approach



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



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

Conclusion & Next steps

- A core toolbox of NAMs (in vitro and computational) was developed that can be used to provide **BERs which appeared to enable protective systemic safety decisions** to be made without using any animal data.

- This work will enable **a full evaluation of the performance of the toolbox** to ensure it is protective and useful across a broader range of chemical exposures

Testing 40+ chemicals using the exact same approach

Addition of DART tools and DART chemicals in a separate evaluation

REPROTRACKER®

Animal-free developmental toxicity predictions

devTOX qP™ quickPREDICT

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Rajagopal et al 2022. Frontiers in Toxicology. Accepted for publication

Recognition of NGRA in cosmetic safety assessment…

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[j], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

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[n] Cosmetics Europe, Avenue Herrmann-Debroux 40, 1160 Auderghem, Belgium
[o] Health Canada (HC), Consumer Product Safety Directorate, Healthy Environments and Consumer Safety Branch, 269 Laurier Ave. W., Ottawa, ON K1A 0K9, Canada
[p] Independent Cosmetic Manufacturing and Distributors (ICMAD), 21925 Field Parkway, Suite 2015, Deer Park, IL 60010, USA

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New approach methodologies
Cosmetics risk assessment

ABSTRACT

Consumer safety is a p
bring safe products to n
Generation Risk Assess
that integrates *in silico*,
of each NGRA means t
appropriate. The Intern
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corporating these new
the overall goals of NG
harm); how an NGRA
literature search and ev
how the assessment sho
of uncertainty). Those w
the application of novel

International Cooperation on Cosmetics Regulation

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

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

European Commission: Scientific Committee on Consumer Safety (2021)

… Could we apply similar approaches to chemical registration?

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]

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