Next Generation Risk Assessment (NGRA) – Accelerating the Paradigm Shift

Dr Gavin Maxwell

Safety Science Advocacy Lead

Unilever Safety & Environmental Assurance Centre (SEAC)

Unilever Policy & Approach
Safe & Sustainable Products without Animal Testing

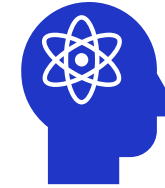**We say use science. Not animals.**

What we believe

- **Every Unilever product must be safe for people and our environment**

- **Animal testing is not needed to assess ingredient & product safety** – there are a wide range of non-animal alternatives grounded in modern science and new technology
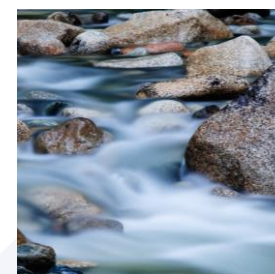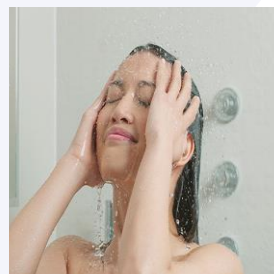
How we do it

40+ years of developing non-animal safety science

70+ collaborations

600+ publications

A **paradigm shift is underway** as use of non-animal safety science increases & safety assessment frameworks evolve to embed NGRA
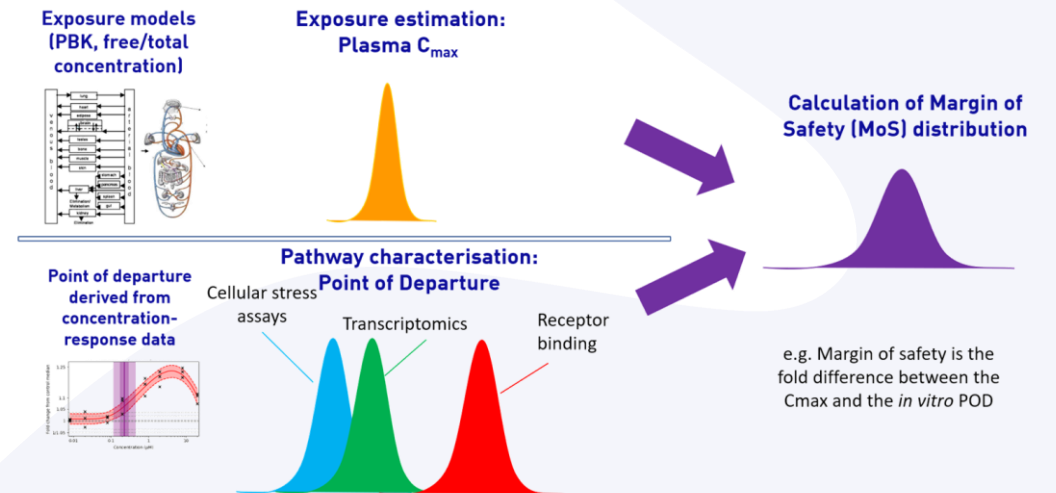
Non-animal safety science is increasingly being used to make decisions on:

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
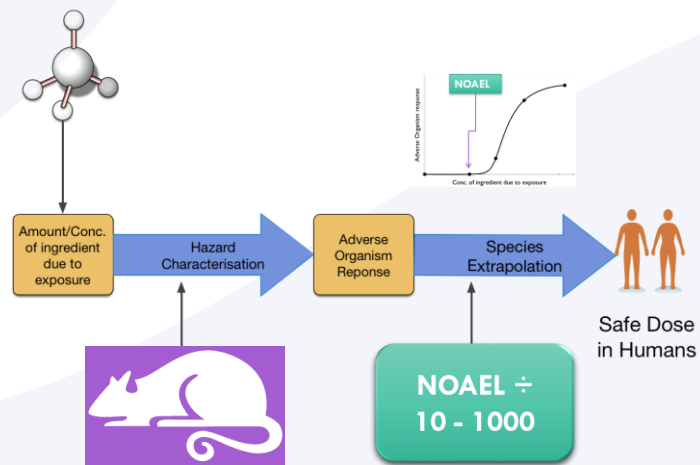
'Next Generation' Risk Assessment
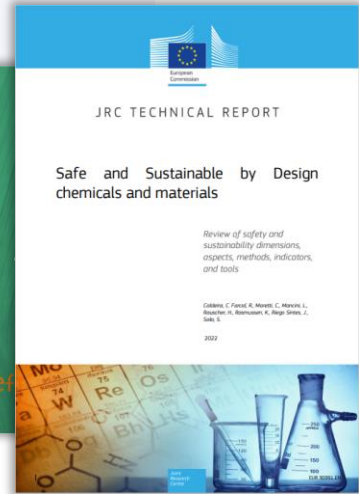
Why is transitioning to NGRA increasingly urgent?

1. Citizen concerns about the potential impacts of chemicals on their health & environment are high

> 85% / 90% EU citizens are worried about the impact of chemicals present in everyday products on their health / the environment
> **Special Eurobarometer 501**

✓ Let's use NAMs & NGRA to **rebuild citizen trust that chemical regulatory frameworks are protective**

2. Move to more sustainable sources of chemicals (e.g. bio-based) **is transforming chemical innovation & use**

SAFE AND SUSTAINABLE-BY-DESIGN: BOOSTING INNOVATION AND GROWTH WITHIN THE EUROPEAN CHEMICAL INDUSTRY
OCTOBER 2021

JRC TECHNICAL REPORT

Safe and Sustainable by Design chemicals and materials

Review of safety and sustainability dimensions, aspects, methods, indicators, and tools

Caldeira, C; Farcal, R; Moretti, C; Mancini, L; Rauscher, H; Rasmussen, K; Riego Sintes, J; Sala, S

2022

✓ Let's use NAMs & NGRA to **ensure new chemicals are Safe & Sustainable by Design**

3. Regulatory Animal Testing of Chemicals is increasingly seen as unjustifiable / unethical by the majority of society
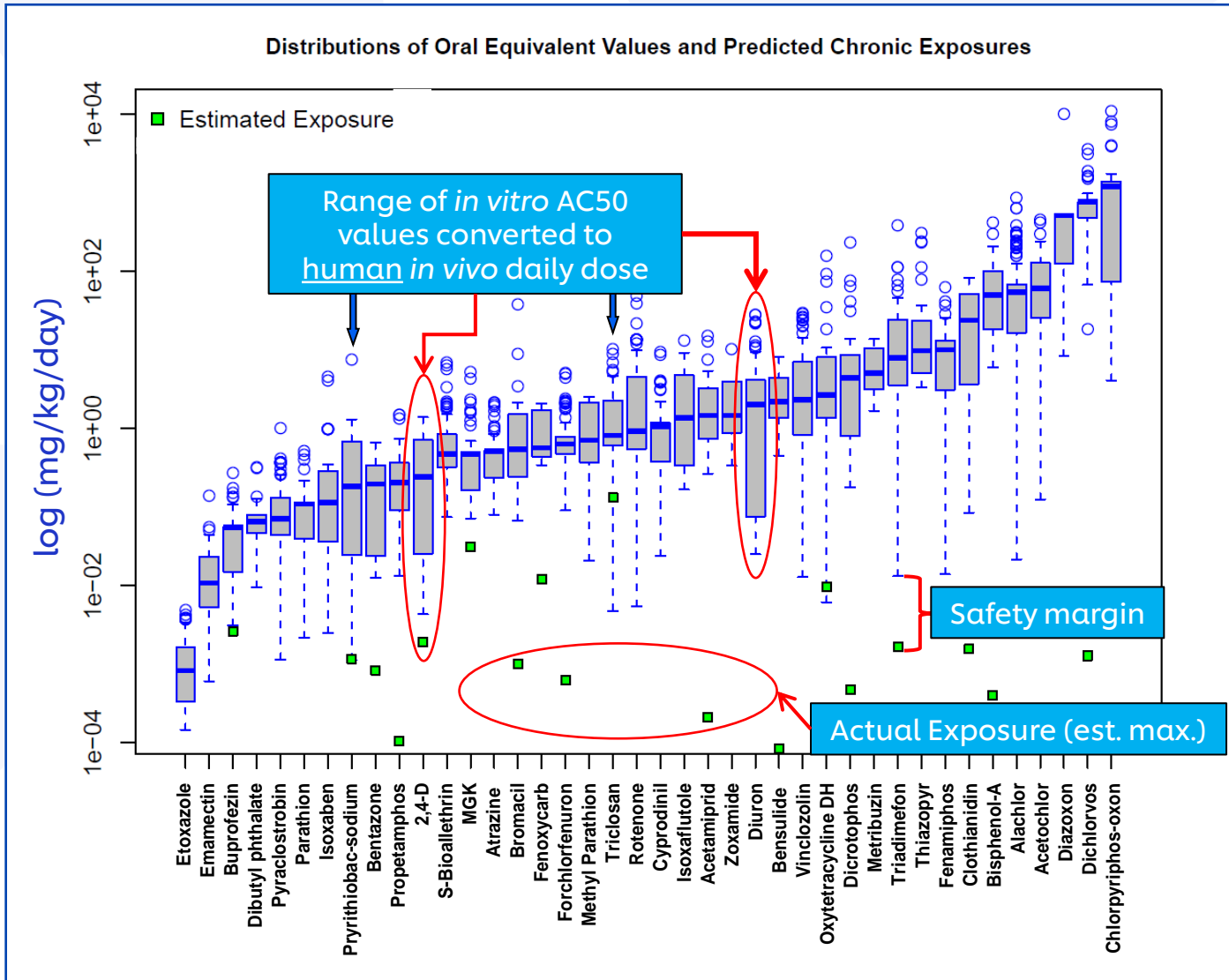
Aug 2021 – Aug 2022: 1.4M+ signatures

European Union
EUROPEAN CITIZENS' INITIATIVE

Save Cruelty Free Cosmetics

✓ Let's use NAMs & NGRA to **fully replace the need for chemical regulatory animal testing**

NGRA: aim is protection, not prediction of animal data

Distributions of Oral Equivalent Values and Predicted Chronic Exposures

The hypothesis underpinning NGRA is that **if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.**

At no point does NGRA attempt to predict the results of high dose toxicology studies in animals.

NGRA **uses new exposure science and understanding of human biology.**

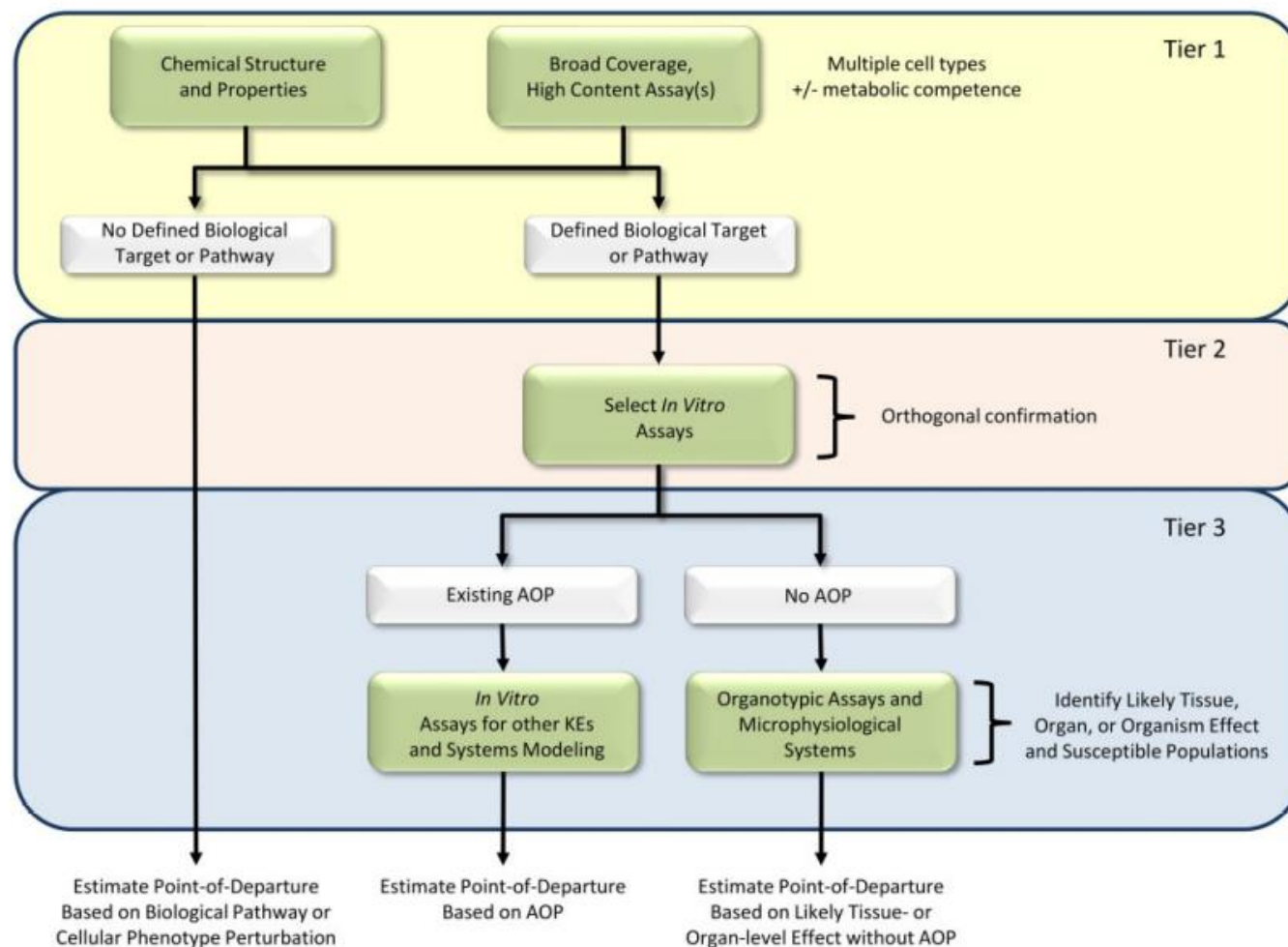# US EPA Next Generation Blueprint Tiered Testing Framework

Figure 2. Tiered testing framework for hazard characterization. Tier 1 uses both chemical structure and broad coverage, high content assays across multiple cell types for comprehensively evaluating the potential effects of chemicals and grouping them based on similarity in potential hazards. For chemicals from Tier 1 without a defined biological target / pathway, a quantitative point-of-departure for hazard is estimated based on the absence of biological pathway or cellular phenotype perturbation. Chemicals from Tier 1 with a predicted biological target or pathway are evaluated Tier 2 using targeted follow-up assays. In Tier 3, the likely tissue, organ, or organism-level effects are considered based on either existing adverse outcome pathways (AOP) or more complex culture systems. Quantitative points-of-departure for hazard are estimated based on the AOP or responses in the complex culture system.

FORUM

The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency

Russell S. Thomas,[*,1] Tina Bahadori,[†] Timothy J. Buckley,[‡] John Cowden,[*] Chad Deisenroth,[*] Kathie L. Dionisio,[‡] Jeffrey B. Frithsen,[§] Christopher M. Grulke,[*] Maureen R. Gwinn,[*] Joshua A. Harrill,[*] Mark Higuchi,[¶] Keith A. Houck,[*] Michael F. Hughes,[¶] E. Sidney Hunter, III,[¶] Kristin K. Isaacs,[‡] Richard S. Judson,[*] Thomas B. Knudsen,[*] Jason C. Lambert,[||] Monica Linnenbrink,[*] Todd M. Martin,[||] Seth R. Newton,[‡] Stephanie Padilla,[¶] Grace Patlewicz,[*] Katie Paul-Friedman,[*] Katherine A. Phillips,[‡] Ann M. Richard,[*] Reeder Sams,[*] Timothy J. Shafer,[¶] R. Woodrow Setzer,[*] Imran Shah,[*] Jane E. Simmons,[¶] Steven O. Simmons,[*] Amar Singh,[*] Jon R. Sobus,[‡] Mark Strynar,[‡] Adam Swank,[‡] Rogelio Tornero-Valez,[‡] Elin M. Ulrich,[‡] Daniel L. Villeneuve,[||] John F. Wambaugh,[*] Barbara A. Wetmore,[‡] and Antony J. Williams[*]

[*]National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, [†]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C. 20004, [‡]National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, [§]Chemical Safety for Sustainability National Research Program, U.S. Environmental Protection Agency, Washington, D.C. 20004, [¶]National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, [||]National

SEURAT-1 NGRA framework: tiered testing to support human health safety assessment

Berggren *et al* (2017) Computational Toxicology **4**, 31-44
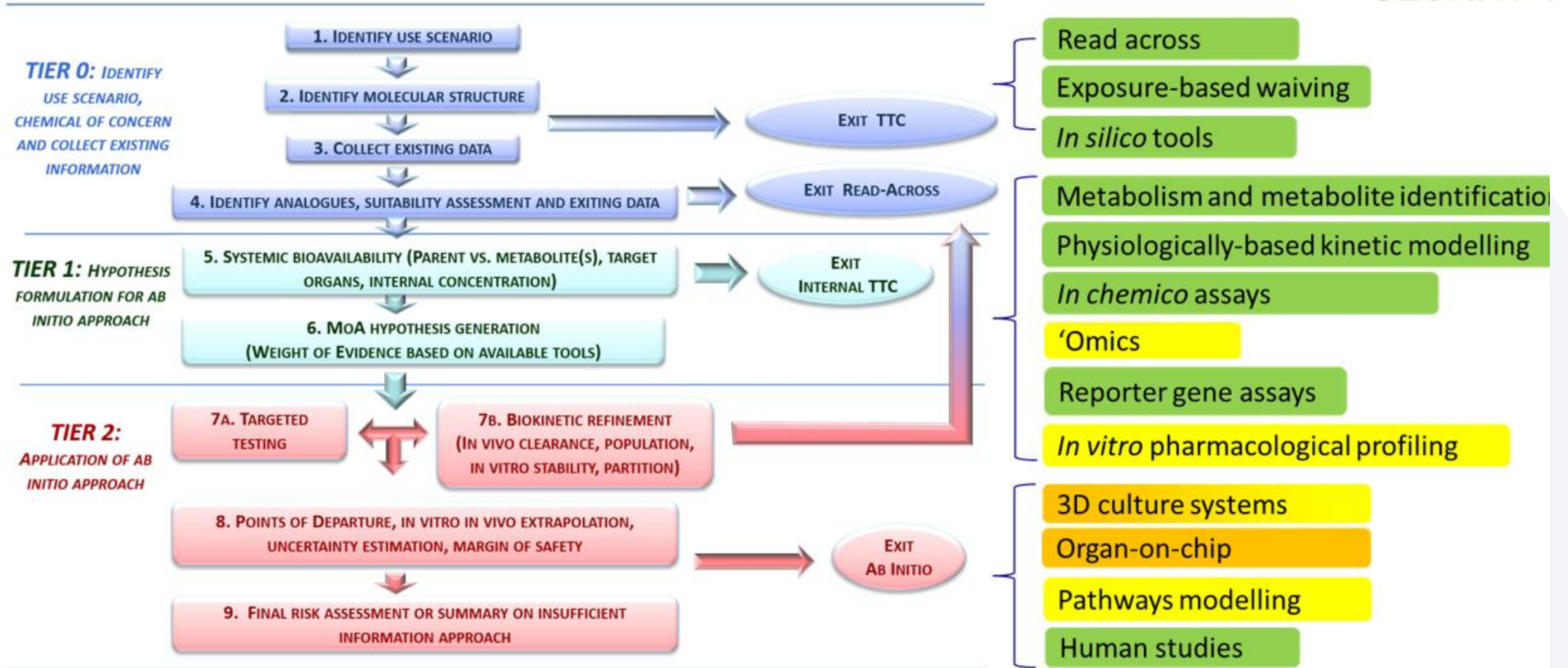
Tier 1: Chemical Screening & Assessment using NAMs

Friedmann et al. 2020 APCRA 'proof-of-concept' case study demonstrated the feasibility of applying a high throughput NAM-based approach for screening-level assessments

→ POD $_{NAM\ 95}$ value was less than or equal to the POD $_{traditional}$ value (derived from *in vivo* toxicology data) value for 89% chemicals

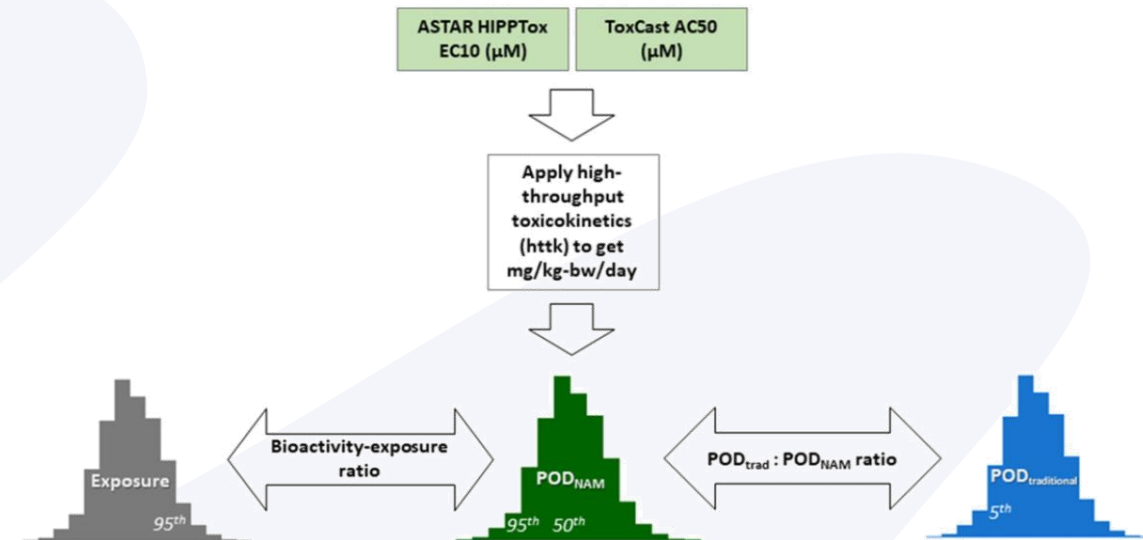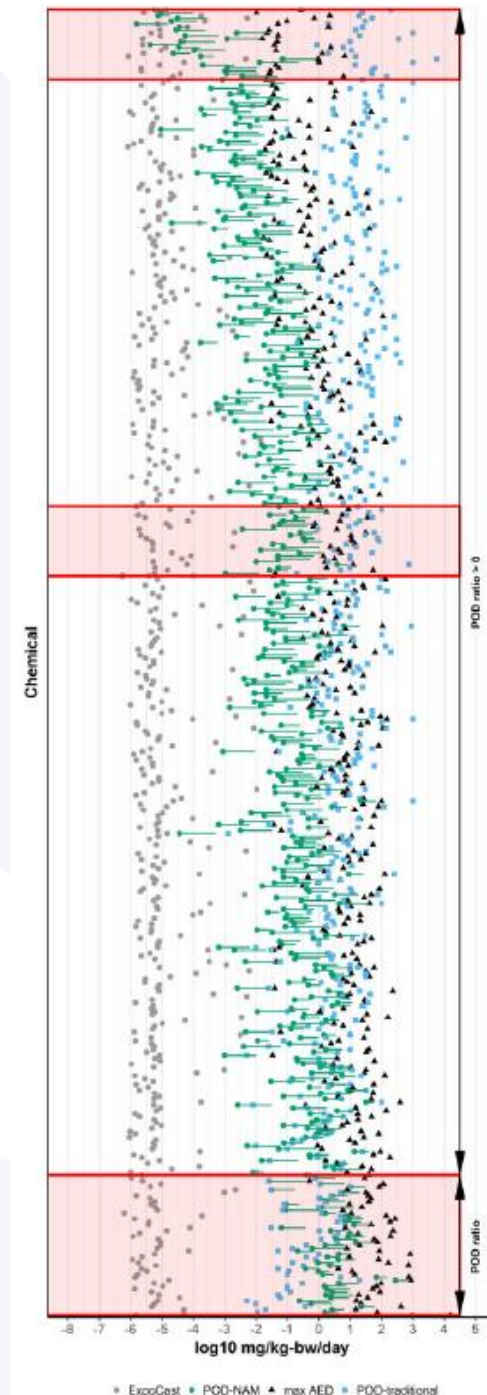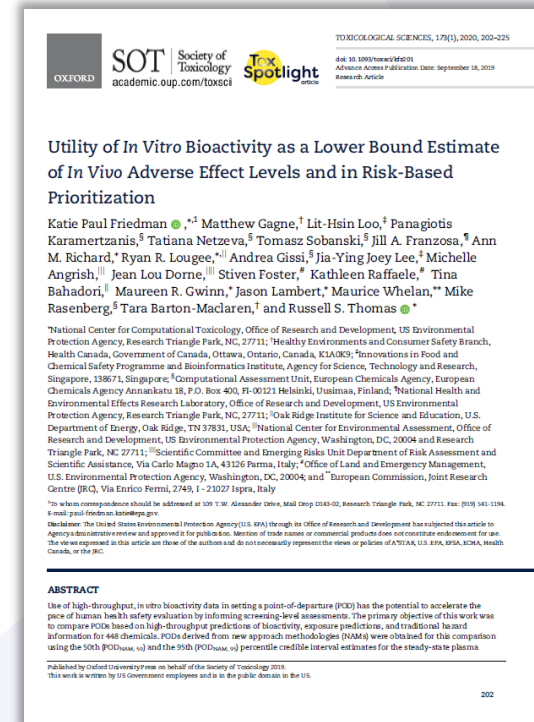→ Bioactivity-exposure ratio is a useful data-driven metric for chemical prioritization

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

ASTAR HIPPTox EC10 (μM)   ToxCast AC50 (μM)

Apply high-throughput toxicokinetics (httk) to get mg/kg-bw/day

Exposure — Bioactivity-exposure ratio — POD$_{NAM}$ — POD$_{trad}$: POD$_{NAM}$ ratio — POD$_{traditional}$

95th   95th 50th   5th

Figure 1. Overall workflow of the case study. This case study includes 448 substances with exposure predictions, *in vitro* assay data, HTTK information using the httk R package, and *in vivo* hazard information. The 50th and 95th percentile from the Monte Carlo simulation of interindividual toxicokinetic variability were used to estimate administered equivalent doses (AEDs), and the minimum of either the ToxCast or HIPPTox-based AEDs were selected as the POD$_{NAM,\ 50}$ or POD$_{NAM,\ 95}$. The POD$_{NAM}$ estimates were compared with the fifth percentile from the distribution of the POD$_{traditional}$ values obtained from multiple sources to obtain the log$_{10}$ POD ratio. The log$_{10}$ bioactivity:exposure ratio (BER) was obtained by comparing the POD$_{NAM}$ estimates to exposure predictions. All values used for computation were in log$_{10}$-mg/kg-bw/day units.

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 *

*National Center for Computational Toxicology, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, 27711; †Healthy Environments and Consumer Safety Branch, Health Canada, Government of Canada, Ottawa, Ontario, Canada, K1A0K9; ‡Innovations in Food and Chemical Safety Programme and Bioinformatics Institute, Agency for Science, Technology and Research, Singapore, 138671, Singapore; §Computational Assessment Unit, European Chemicals Agency, European Chemicals Agency Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Uusimas, Finland; ¶National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, 27711; ‖Oak Ridge Institute for Science and Education, U.S. Department of Energy, Oak Ridge, TN 37831, USA; ‖National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC, 20004 and Research Triangle Park, NC 27711; #Scientific Committee and Emerging Risks Unit Department of Risk Assessment and Scientific Assistance, Via Carlo Magno 1A, 43126 Parma, Italy; #Office of Land and Emergency Management, U.S. Environmental Protection Agency, Washington, DC, 20004; and **European Commission, Joint Research Centre (JRC), Via Enrico Fermi, 2749, I - 21027 Ispra, Italy

1To whom correspondence should be addressed at 109 T.W. Alexander Drive, Mail Drop D143-02, Research Triangle Park, NC 27711. Fax: (919) 541-1194. E-mail: paul-friedman.katie@epa.gov.

Disclaimer: The United States Environmental Protection Agency (U.S. EPA) through its Office of Research and Development has subjected this article to Agency administrative review and approved it for publication. Mention of trade names or commercial products does not constitute endorsement for use. The views expressed in this article are those of the authors and do not necessarily represent the views or policies of A*STAR, U.S. EPA, EFSA, ECHA, Health Canada, or the JRC.

ABSTRACT

Use of high-throughput, in vitro bioactivity data in setting a point-of-departure (POD) has the potential to accelerate the pace of human health safety evaluation by informing screening-level assessments. The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals. PODs derived from new approach methodologies (NAMs) were obtained for the comparison using the 50th (POD$_{NAM,\ 50}$) and the 95th (POD$_{NAM,\ 95}$) percentile credible interval estimates for the steady-state plasma

log10 mg/kg-bw/day

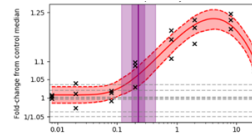ExpoCast   POD-NAM   max AED   POD-traditional

NGRA for consumer product safety assessment: integrating exposure & bioactivity information to estimate a safe Margin of Exposure (MoE) / Bioactivity Exposure Ratio (BER)
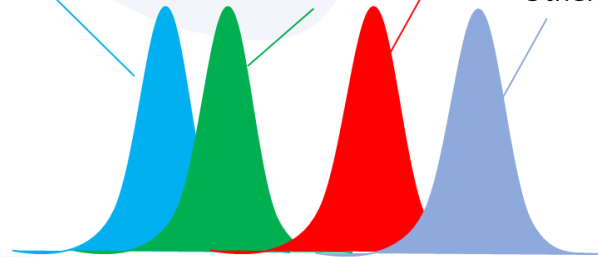
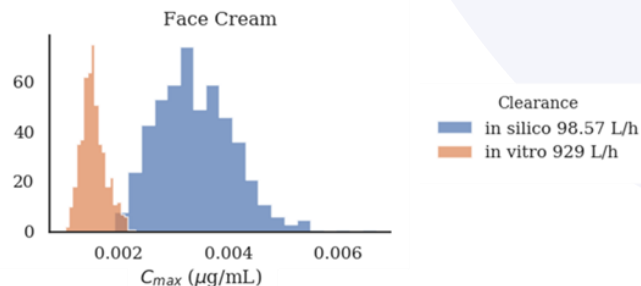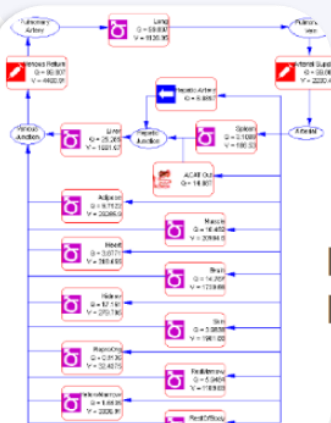# NGRA for Systemic Exposure & Effects: 0.1% coumarin in face cream
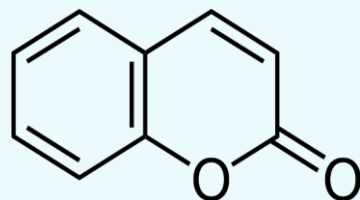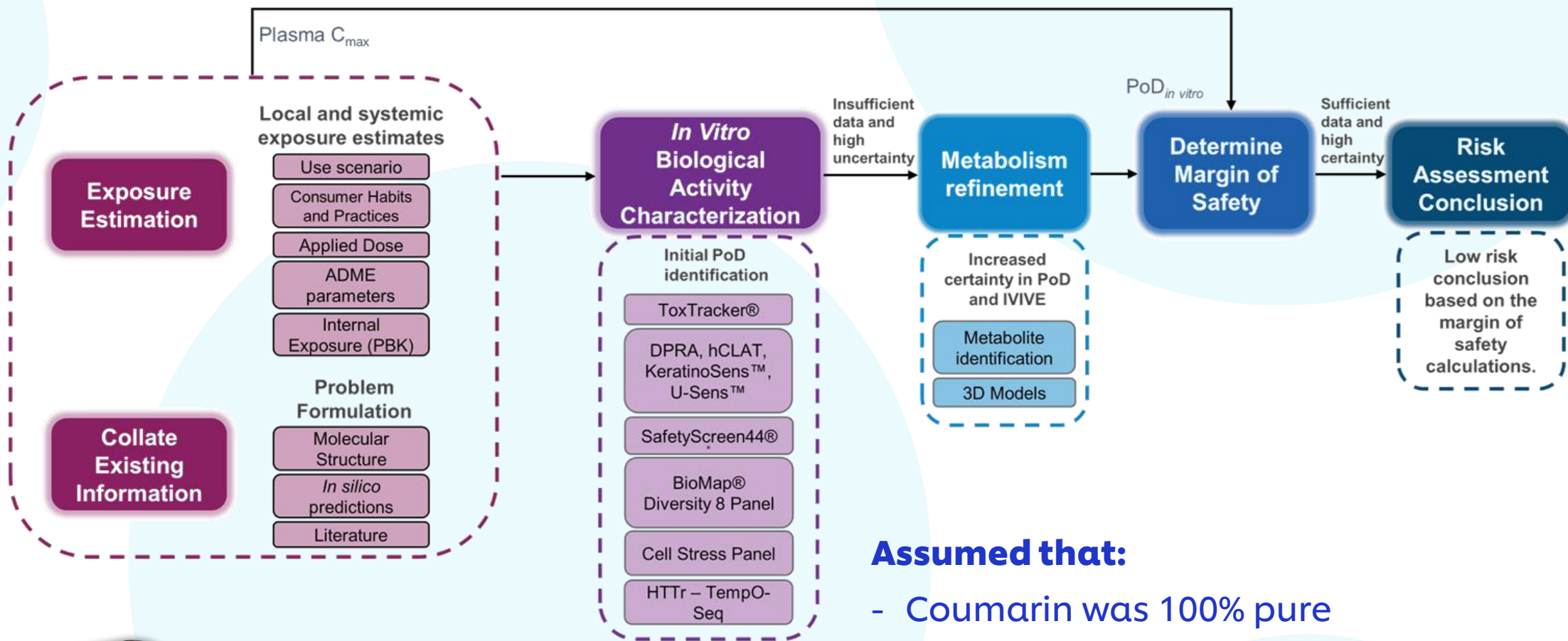
Assumed that:

- Coumarin was 100% pure

- No *in vivo* data was available such as animal data, history of safe use (HoSU) or clinical data or use of animal data in read across

Key NAMs used in Coumarin case study

PBK Modelling

Face Cream

Clearance
- in silico 98.57 L/h
- in vitro 929 L/h

C_{max} (μg/mL)

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

- Nuclear receptor panel
- GPCR panel
- Ion Channel panel
- Enzyme panel
- Transporter panel

eurofins | Cerep
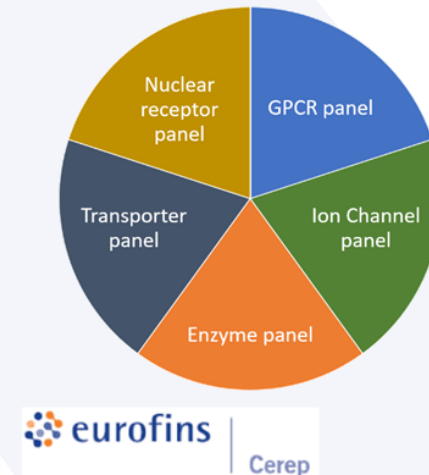
Transcriptomics

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

BMDexpress 2

Accumulative Number of Pathway Showing Dose response vs Calculated BMD mean value (μM)
- HepaRG 2D
- HepG2
- Biological oxidations
- Xenobiotics
- Cytochrome P450 - arranged by substrate type
- Phase I - Functionalization of compounds

BMD Express 2.2
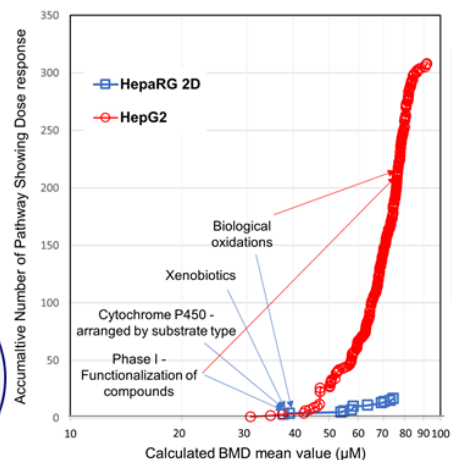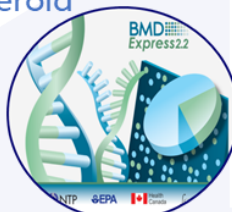
Cellular Stress Pathways

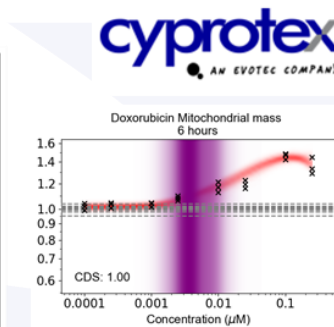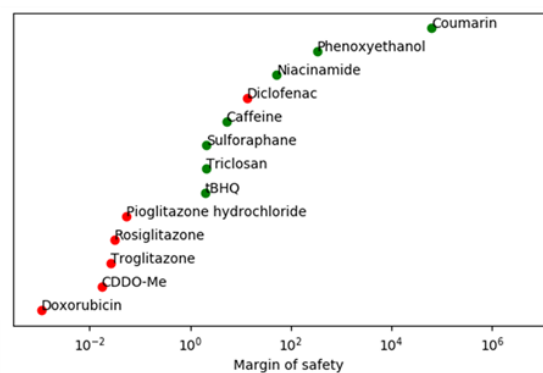**13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways**

Exposure scenario adopted for chemical is 'low risk' [from consumer goods perspective]:
- Niacinamide [food, cosmetics]
- Caffeine [beverages, cosmetics]
- Phenoxyethanol [cosmetics]
- Sulforaphan [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]

Margin of safety: Coumarin, Phenoxyethanol, Niacinamide, Diclofenac, Caffeine, Sulforaphane, Triclosan, tBHQ, Pioglitazone hydrochloride, Rosiglitazone, Troglitazone, CDDO-Me, Doxorubicin

cyprotex AN EVOTEC COMPANY

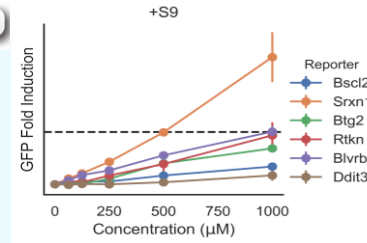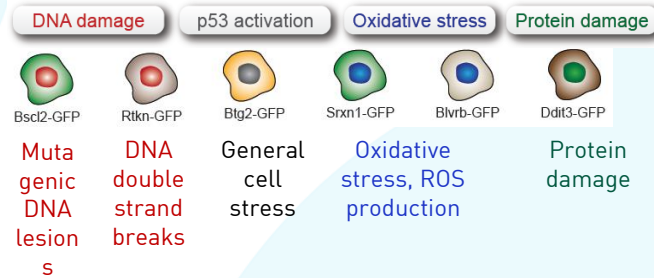Doxorubicin Mitochondrial mass 6 hours

CDS: 1.00

Concentration (μM)

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

Unilever

Examples of bespoke NAMs used in Coumarin case study

Genotoxicity assessment: ToxTracker®

- **Coumarin and its metabolites triggered genotoxicity alerts**

6 GFP reporter mouse embryonic stem (mES) cells

Immunomodulatory screening assay: BioMap® Diversity 8 Panel

- **Coumarin predicted to have anti-inflammatory properties**
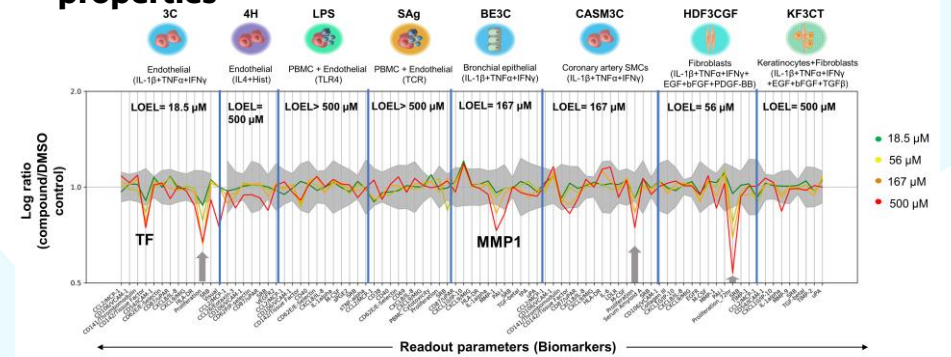
Metabolite identification & PoD refinement

Human *In vitro* metabolism

Coumarin is preferentially detoxified to hydroxycoumarin

Cell stress & HTTr in 3D HepaRG models
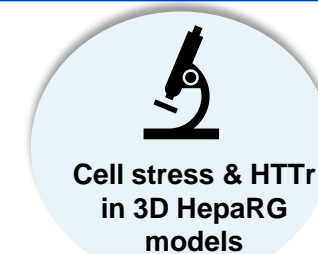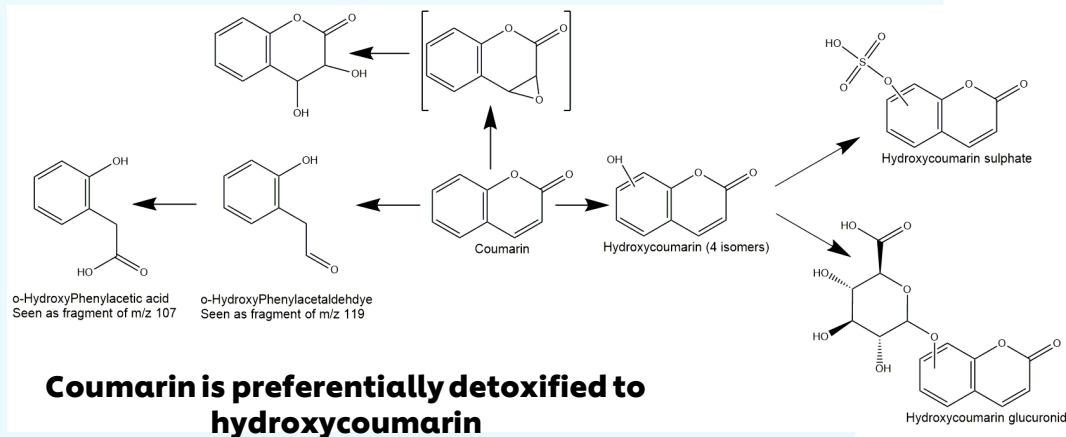
- Low bioactivity also found in a metabolic competent cell model (HepaRG 3D)

- PoDs range: 41-871 µM – similar range as in from 2D cells

NGRA for Systemic Exposure & Effects: 0.1% coumarin in face cream

Determine Margin of Safety
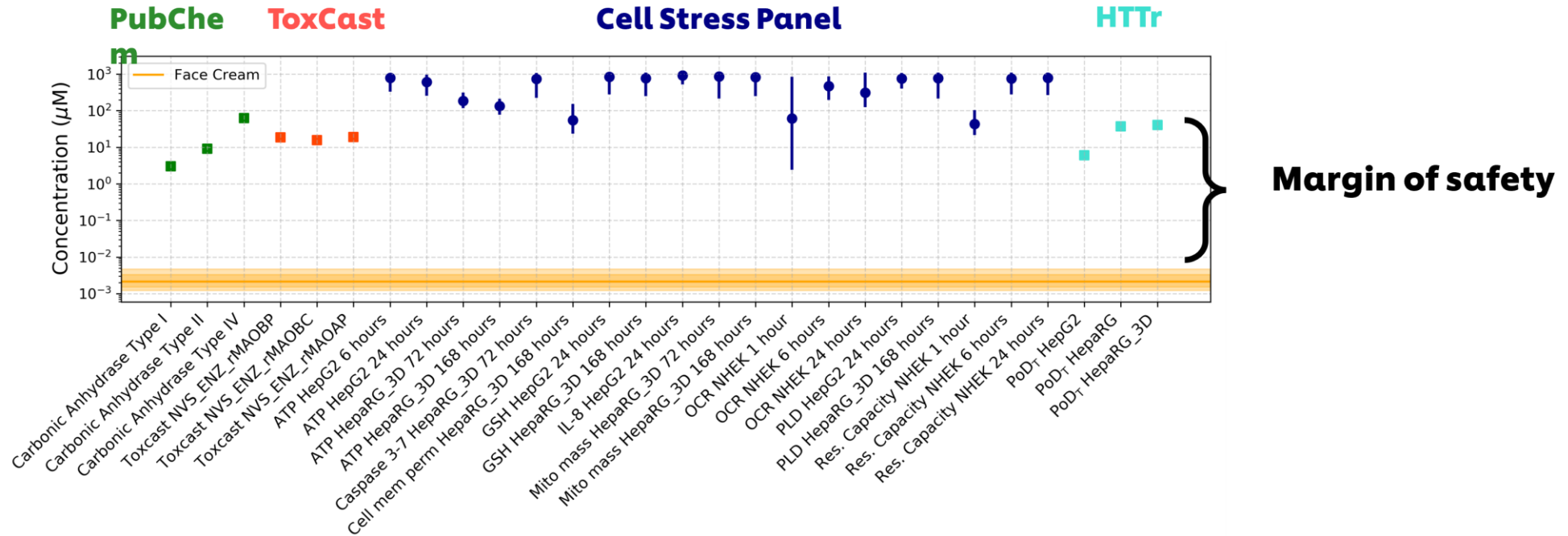
The 5th percentile of the MoS distribution ranged between 706 and 96738

In this case study:

- **Weight of evidence suggested that the inclusion of 0.1% coumarin in face cream is safe for the consumer**

Can we develop a general toolbox for estimating BERs?

PBK models
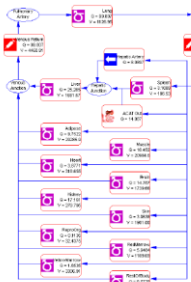
Free concentration
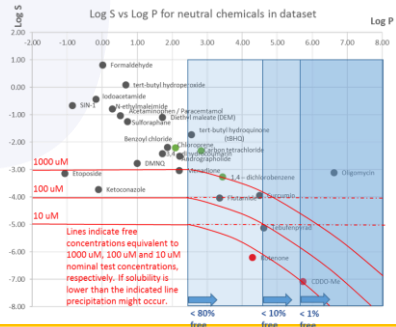
Conc. Resp. models
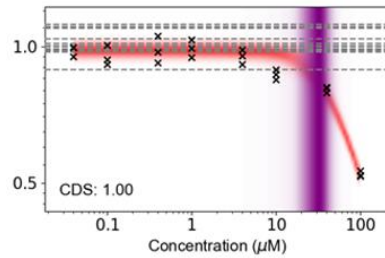
HTTr
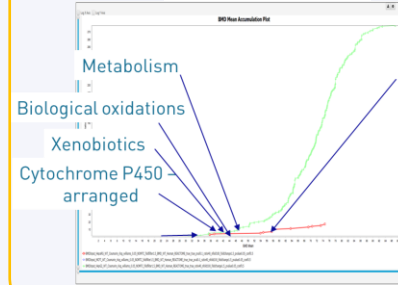
CSP
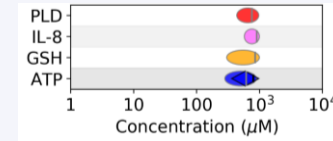
IPP

Bioactivity exposure ratio
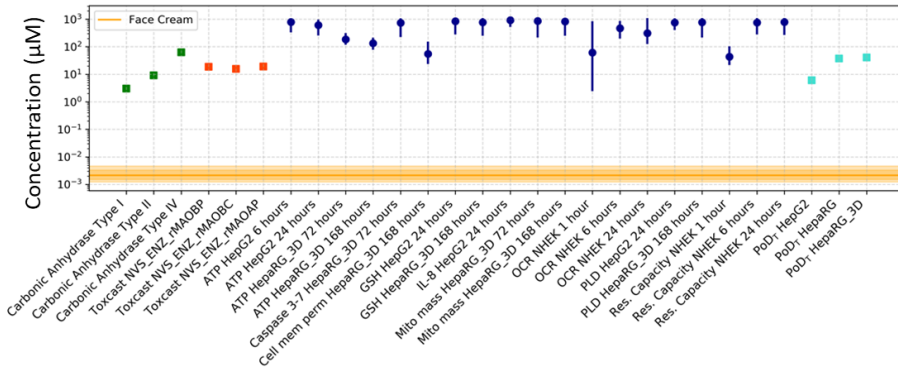
Inform safety decision

HTTr: High-throughput transcriptomics   **CSP:** Cell Stress Panel   **IPP:** In vitro pharmacological profiling

An approach for evaluating the Systemic NGRA toolbox

Chemical exposures scenarios

🟢 'Low' risk (from consumer goods perspective) – e.g. foods, cosmetics

🔴 'High' risk (from consumer goods perspective) – e.g. drugs

BER threshold

Low risk?

Rank order

Bioactivity exposure ratio

0.01   1   100   1000
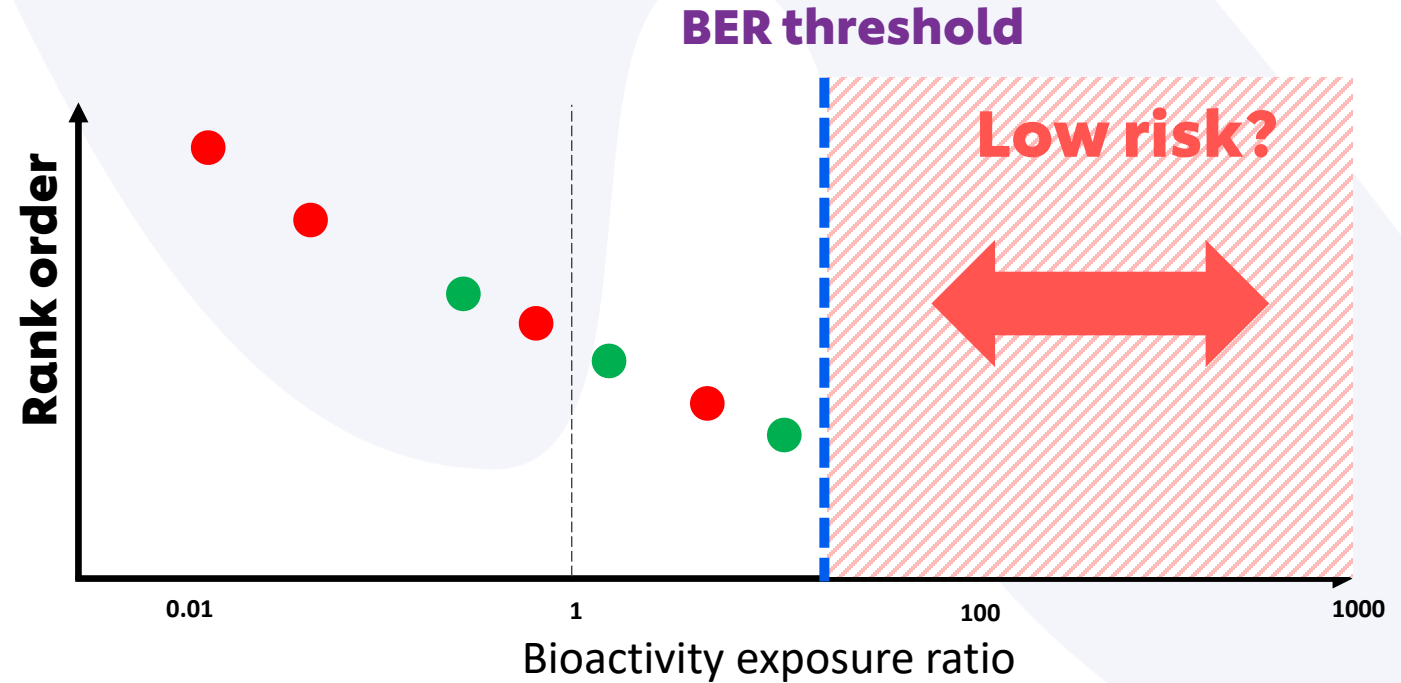
Define typical use-case scenarios benchmark chemical-exposures; Mixture of High and low risk
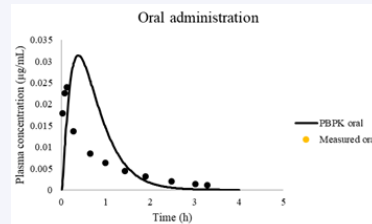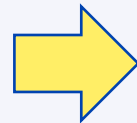
PBK models of systemic exposure
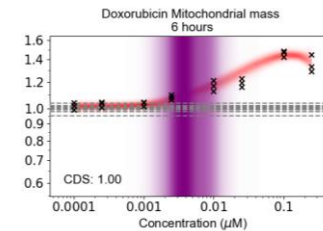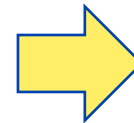
In-vitro cell assays, estimate PoDs
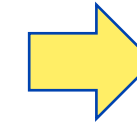
Calculate the bioactivity exposure ratio

Ongoing: Systemic NGRA toolbox evaluation
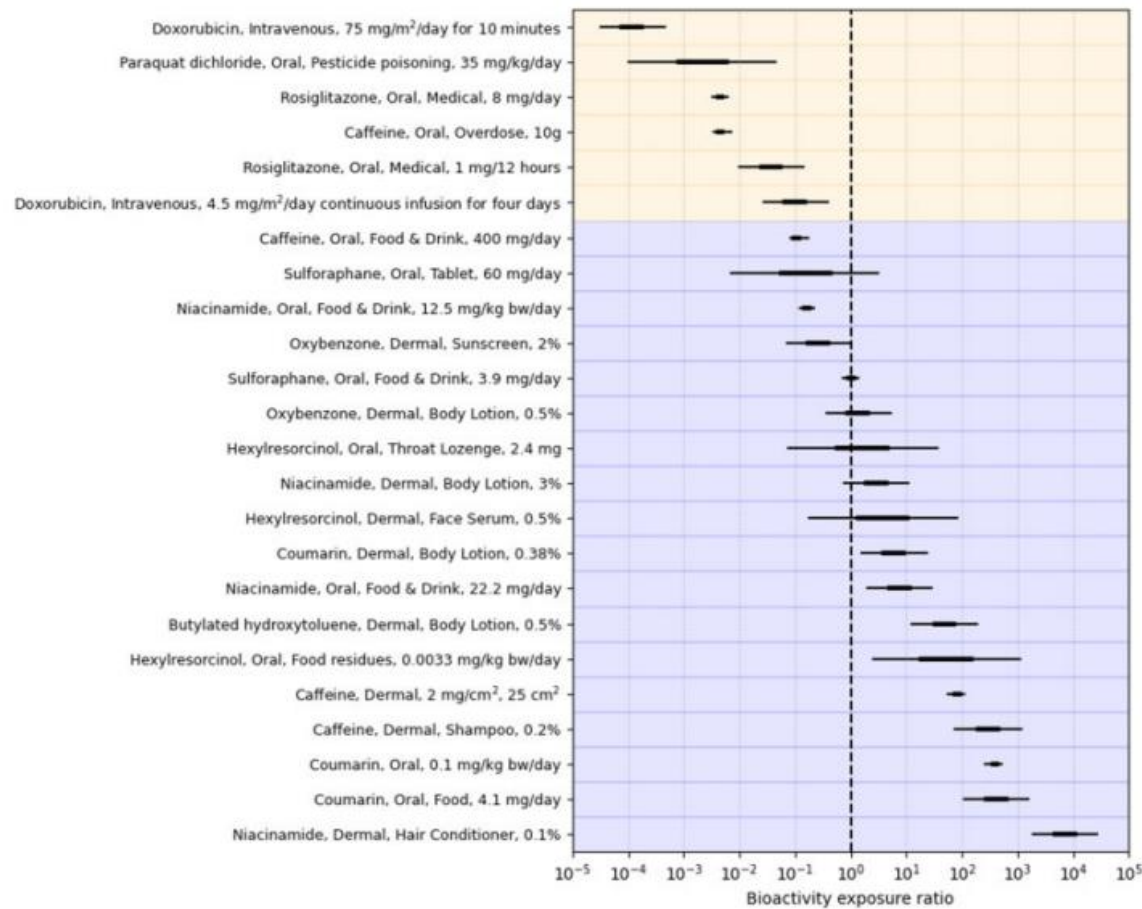
Figure 5. Centered 50% and 95% credible intervals summarizing the distribution of the bioactivity exposure ratio (BER) when using all available predicted C_{max} estimates. Background colors indicate the assigned risk category for each benchmark chemical-exposure scenario assigned at stage 1 (blue—low, yellow—high). The vertical dashed line indicates a BER equal to 1.

Blue: low risk chemical-exposure scenario

Yellow: high risk chemical-exposure scenario

[Middleton *et al.* 2022. Tox. Sci. 189. 124-147](#)

NGRA for Skin Allergy: coumarin, 0.1% face cream & 1% deodorant

For the purposes of the case study, *in vivo* data and read-across were not used, and the use of dermal sensitisation threshold (DST) was not appropriate.

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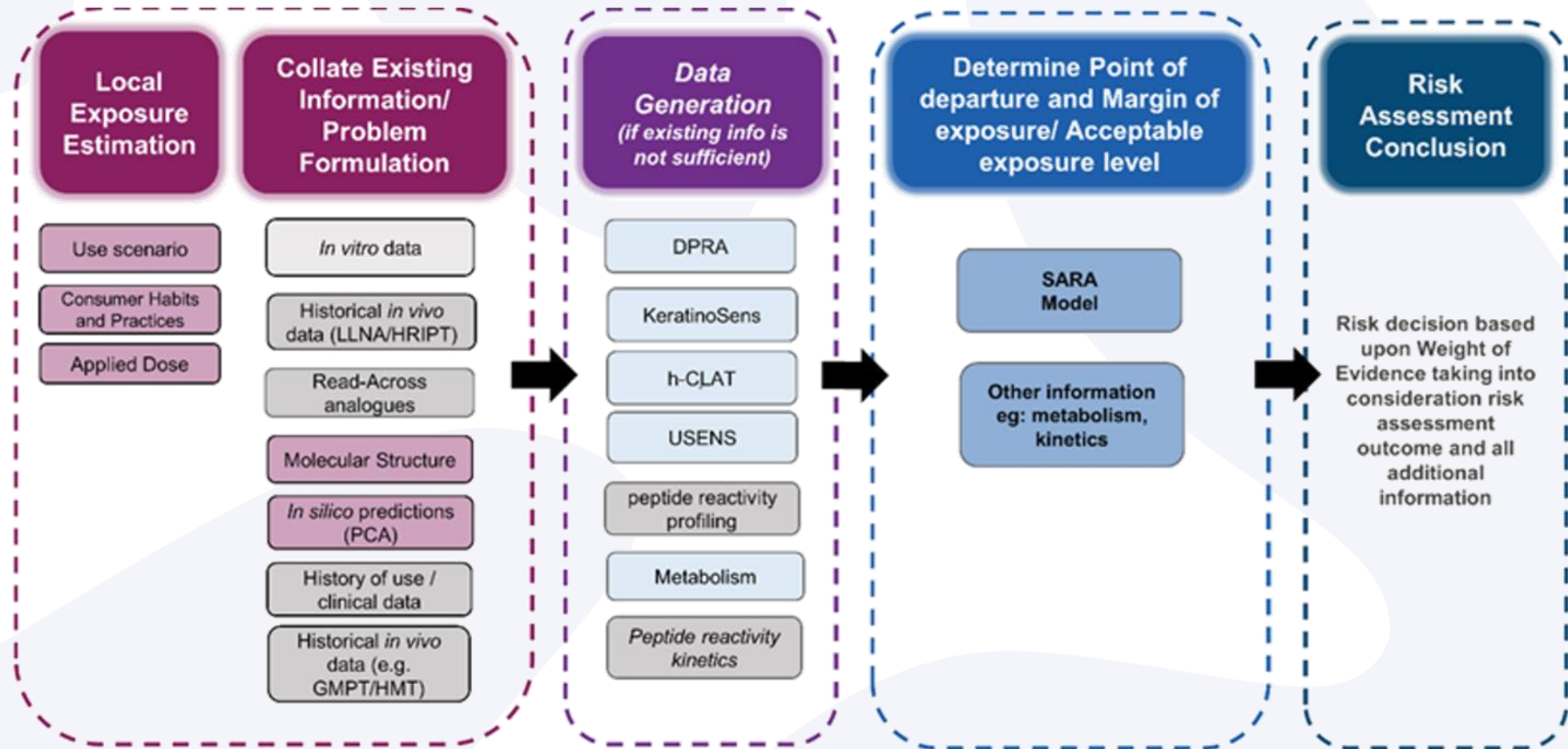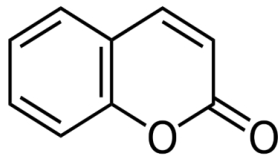
Skin Allergy Bioactivity

OECD

Data Generation (if existing info is not sufficient)

- DPRA
- KeratinoSens
- h-CLAT
- USENS
- peptide reactivity profiling
- Metabolism
- *Peptide reactivity kinetics*

Electrophilic Chemicals	→	Covalent Binding to Skin Proteins	→	Keratinocyte Activation	→	Dendritic Cell Activation	→	T-cell Activation and Proliferation	→	Skin Sensitisation
		Key Event 1 (KE1)		KE2		KE3		KE4		Adverse Outcome (AO)

Predictive Chemistry

For example:
- DEREK-NEXUS
- OECD QSAR Toolbox
- TIMES
- ToxTree

Protein Reactivity

OECD TG 442C
Includes:
- ADRA
- DPRA

Keratinocyte Activation

OECD TG 442D
Includes:
- KeratinoSens™
- LuSens

DC Activation

OECD TG 442E
Includes:
- h-CLAT
- IL-8 Luc Assay
- U-Sens™

T Cell Proliferation

For Example:
- Human T cell proliferation assays (hTCPA)

Skin Sensitisation

OECD TG 429: mouse local lymph node assay (LLNA) & variants TG442A & 442B

OECD TG 406: Buehler & Guinea Pig Maximisation Test (GPMT)

Human evidence e.g. Human Repeat Insult Patch Test (HRIPT)

	DPRA (TG442C)		KeratinoSens™ (TG 442D)	h-CLAT (TG 442E)		U-SENS™ (TG 442E)
	%cys depl.	%lys depl.	EC1.5 (µM)	CD86 (EC200 µg/mL)	CD54 (EC150 µg/mL)	CD86 (EC150 µg/mL)
Coumarin	1.3	0	187.5	<178	>637	95.5

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

Unilever

Skin Allergy Risk Assessment (SARA) Defined Approach

- Bayesian probabilistic model, which estimates human sensitiser potency using data covering AOP KEs 1-3, Adverse Outcome & risk benchmarks
  - original publication: Reynolds et al. 2019: https://doi.org/10.1016/j.comtox.2018.10.004
  - latest publication: Reynolds et al. 2022: https://doi.org/10.1016/j.yrtph.2022.105219
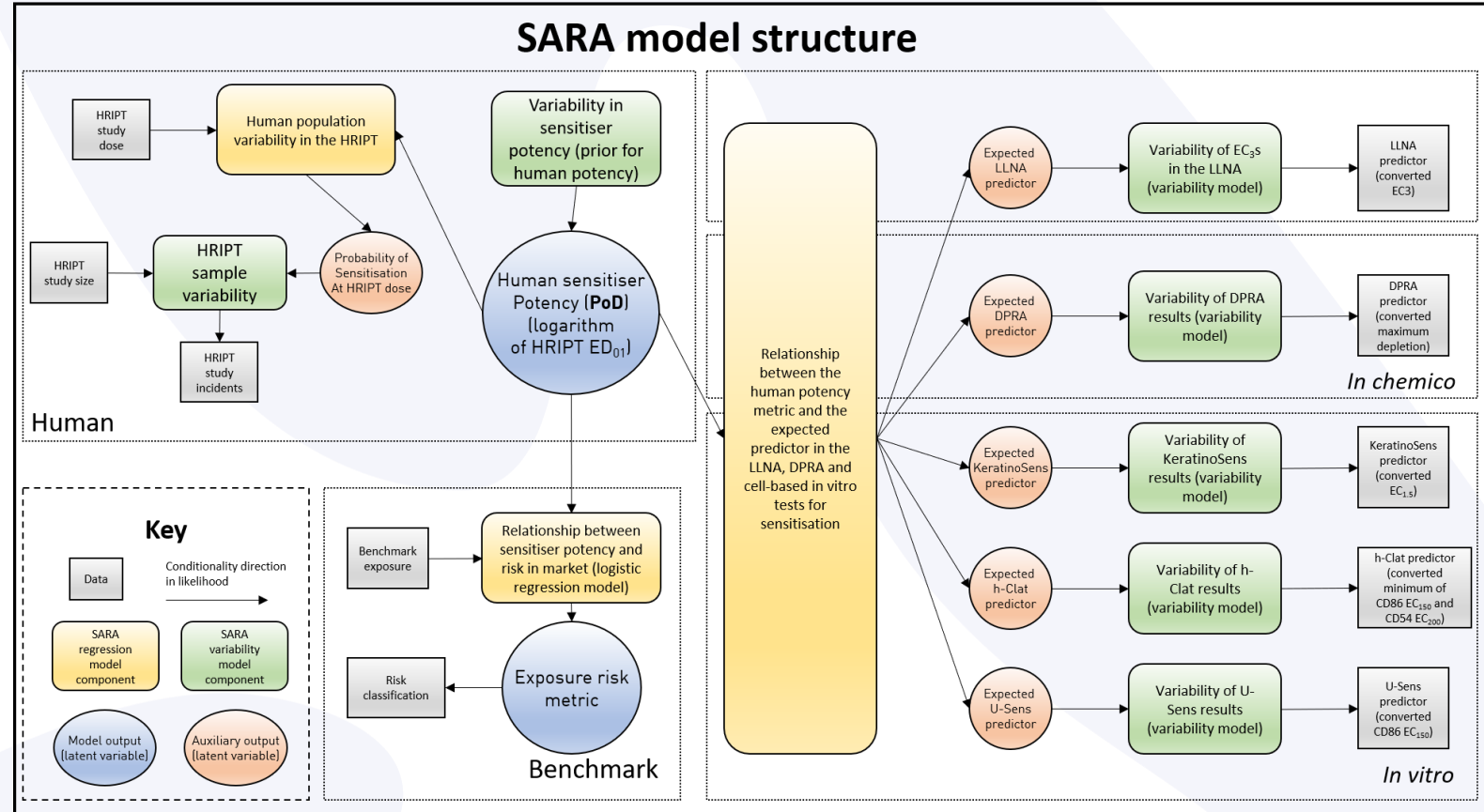
- Ongoing collaboration with NICEATM to adapt, expand and evaluate to predict GHS categories

SARA model structure

Key Event 1 (KE1)	KE2	KE3	Adverse Outcome (AO)
Protein Reactivity **OECD TG 442C** • DPRA	**Keratinocyte Activation** **OECD TG 442D** • KeratinoSens™	**DC Activation** **OECD TG 442E** • h-CLAT • U-Sens™	**_Skin Sensitisation_** • **OECD TG 429**: mouse local lymph node assay (LLNA) • Human evidence:. Human Repeat Insult Patch Test (HRIPT)

NGRA Skin Allergy: coumarin case study conclusion

- DPRA, KeratinoSens™, hCLAT and USens™ data were used as SARA DA inputs to define a human relevant PoD (ED_{01} i.e the 1% sensitising dose for a HRIPT population).

- The MoE was calculated from the ED_{01} for coumarin and the dermal exposures for each product type using SARA DA

  - 0.1% coumarin in face cream MoE ranks with the low-risk benchmarks
  - 1% coumarin in deodrant MoE ranks with the high-risk benchmarks.

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

Unilever NGRA frameworks for Consumer Safety decisions

Developmental & Reproductive

Inhalation

Rajagopal et al (2022) *Frontiers in Toxicology*, doi: 10.3389/ftox.2022.838466

Skin Sensitisation

Systemic

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

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

Ongoing Evaluations

EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

Use of NAMs and NGRA in Chemical Regulation: translation of NGRA concepts into regulatory frameworks & guidance is underway but needs to accelerate

- Stucki et al. 2022 reviewed US, Canada and EU strategic plans, guidance and documentation supporting use of NAMs to assess the human health effects of chemicals

Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health

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CITATION
Stucki AO, Barton-Maclaren TS,
Bhuller Y, Henriquez JE, Henry TR,

TABLE 1 US, Canada, and EU: industrial chemicals and household products.

Agency	Strategic plans, guidance, and other documentation for the implementation of NAMs referenced in this manuscript
EPA OPPT	• Interim science policy: use of alternative approaches for skin sensitization as a replacement for laboratory animal testing EPA, (2018b)
	• Strategic plan to promote the development and implementation of alternative test methods within the TSCA program EPA, (2018d)
	• Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization Paul Friedman et al. (2020) [a]
	• List of alternative test methods and strategies (or new approach methodologies [NAMs]), Second update: 4 February 2021 EPA, (2021d)
	• New approach methods work plan, reducing use of animals in chemical testing EPA, (2021e) [b]
	• A WoE Approach for Evaluating, in Lieu of Animal Studies, the Potential of a Novel Polysaccharide Polymer to Produce Lung Overload Ladics et al. (2021)
CPSC	• Recommended Procedures Regarding the CPSC's Policy on Animal Testing (16 CFR Part 1500)
	• Guidance on Alternative Test Methods and Integrated Testing Approaches CPSC, (2022)
HC HECSB	• Fact sheet series: Topics in risk assessment of substances under CEPA HC, (2016b)
	• Guidance document for the notification and testing of new chemicals and polymers HC, (2021c)
	• Canadian regulatory perspective on next generation risk assessments for pest control products and industrial chemicals Bhuller et al. (2021)
	• Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization Paul Friedman et al. (2020)
	• Science approach documents HC, (2016c), HC, (2021f), HC, (2022c), HC, (2021f), HC, (2022c)
ECHA	• How to use alternatives to animal testing to fulfil the information requirements for REACH registration ECHA, (2016a)
	• Read-across assessment framework ECHA, (2017)
	• 4th report on the use of alternatives to testing on animals for REACH ECHA, (2020)
	• Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization Paul Friedman et al. (2020)
	• Skin sensitization ECHA, (2021)

[a]EPA Office of Research and Development (ORD) involved.
[b]Applicable to all EPA offices.
CEPA, Canadian Environmental Protection Act; CFR, Code of Federal Regulations; CPSC, Consumer Products Safety Commission; ECHA, European Chemicals Agency; EPA OPPT, Environmental Protection Agency Office of Pollution Prevention and Toxics; HC HECSB, Health Canada Healthy Environments and Consumer Safety Branch; NAM, new approach methodologies; TSCA, Toxic Substances Control Act; WoE, weight-of-evidence.

How can we accelerate the NGRA paradigm shift?

1. **We need more scientific exchange between industry and regulatory scientists to accelerate knowledge exchange & necessary adaptations to regulatory frameworks & guidance** (e.g. OECD, EPAA, APCRA, PARC, ASPIS...)

2. **We need to re-focus validation / confidence-building activities on our NGRA frameworks to ensure they are protective / fit for purpose** (e.g. OECD DA Skin Sens. & Integrated Approaches for Testing & Assessment (IATA) activities)

3. **We need to greater harmonization / coordination to aid transition to animal-free sustainable innovation** (e.g. International Collaboration for Cosmetics Safety (ICCS), Save Cruelty Free Cosmetics EU Citizens Initiative)
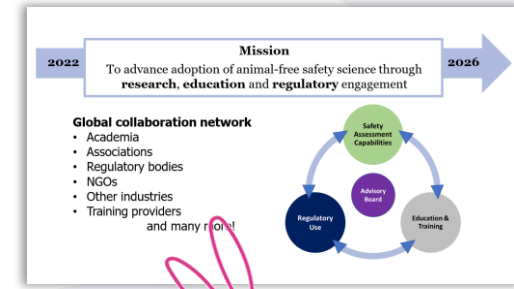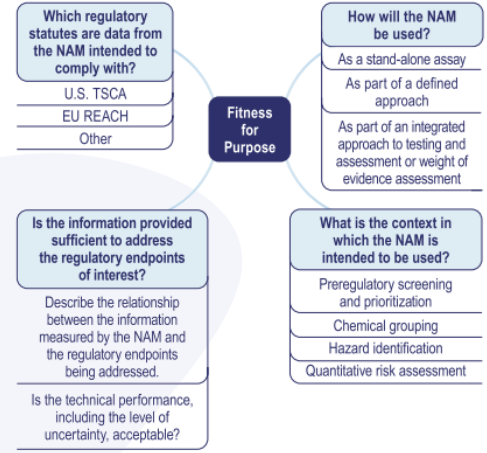
Accelerating the transition to animal-free, sustainable innovation
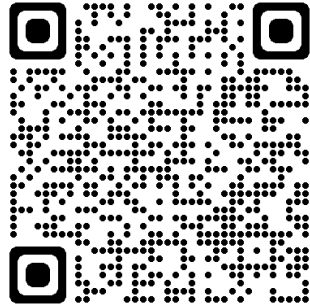## e.g. Save Cruelty Free Cosmetics European Citizen Initiative (ECI) proposal

Suggested actions to re-think & strengthen
EU Commission **"AT as a last resort"** commitment:

We call on the European Commission to do the following:

1. Protect and strengthen the cosmetics animal testing ban.
Initiate legislative change to achieve consumer, worker, and environmental protection for all cosmetics ingredients without testing on animals for any purpose at any time.

2. Transform EU chemicals regulation.
Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.

3. Modernise science in the EU.
Commit to a legislative proposal plotting a roadmap to phase-out all animal testing in the EU before the end of the current legislative term.
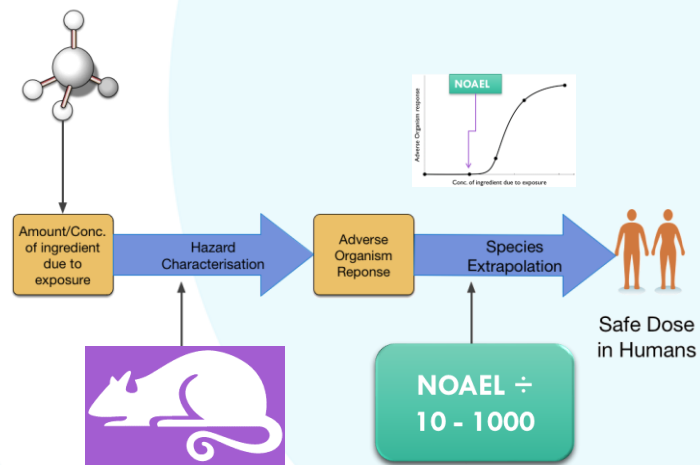
1. **immediately pause all animal tests** on existing cosmetics ingredients; safety can be assured without AT

2. **ensure return on EU investment** >€1.5B over past 20 years in developing alternatives to AT

3. **establish open dialogue on, and transparent scientific evaluation of, NAM strategies for specific chemicals / chemical groups**, facilitating application of advanced safety science

4. **accelerate knowledge transfer & training in advanced safety science and NAM-based chemical assessments with EU regulators**, sharing expertise across JRC, EFSA, EMA & ECHA and accessing leading edge NAMs chemical safety assessment capability of US EPA & other authorities

5. **stimulate EU capacity building in NAMs** to increase the number of service providers of new "NAMs toolbox"

6. **develop a modern, science-based, chemicals regulatory framework**, which facilitates use of 21C science & technology to better protect people and the environment, under the *Chemicals Strategy for Sustainability*

7. **define a roadmap to phase out AT** for EU chemicals regulatory compliance purposes & deliver against that
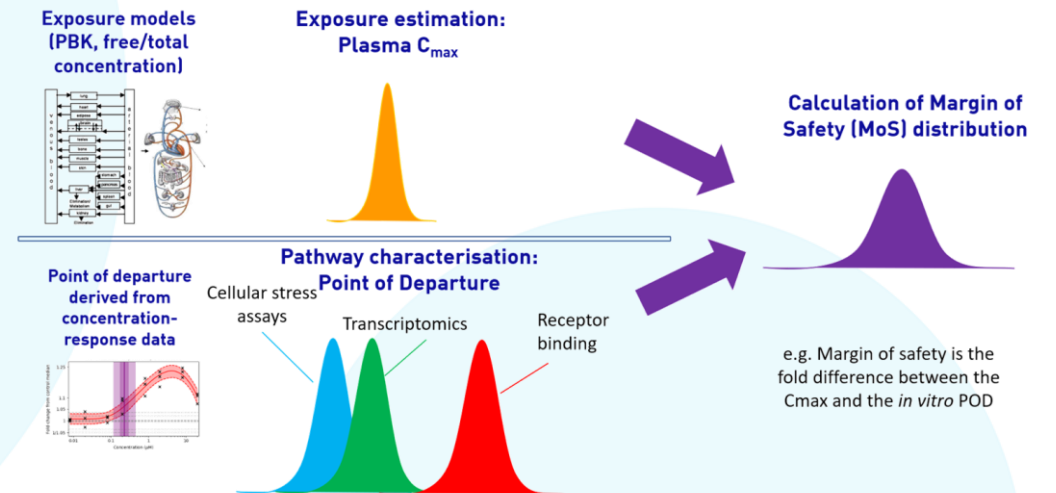
Conclusions

- **A paradigm shift is underway** as use of non-animal safety science increases & safety assessment frameworks evolve to embed NAMs & NGRA

- **Translation of NGRA concepts into chemical regulatory frameworks**, strategic plans & guidance is moving forward steadily but needs to accelerate

- **We can accelerate the NGRA paradigm shift** through working together to facilitate the transition to animal-free, sustainable innovation

'Traditional' Risk Assessment

Amount/Conc. of ingredient due to exposure → Hazard Characterisation → Adverse Organism Reponse → Species Extrapolation → Safe Dose in Humans

NOAEL

NOAEL ÷ 10 - 1000

'Next Generation' Risk Assessment

Exposure models (PBK, free/total concentration)

Exposure estimation: Plasma C_{max}

Point of departure derived from concentration-response data

Pathway characterisation: Point of Departure

Cellular stress assays

Transcriptomics

Receptor binding

Calculation of Margin of Safety (MoS) distribution

e.g. Margin of safety is the fold difference between the Cmax and the *in vitro* POD

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Collaborators:

TT21c.org: