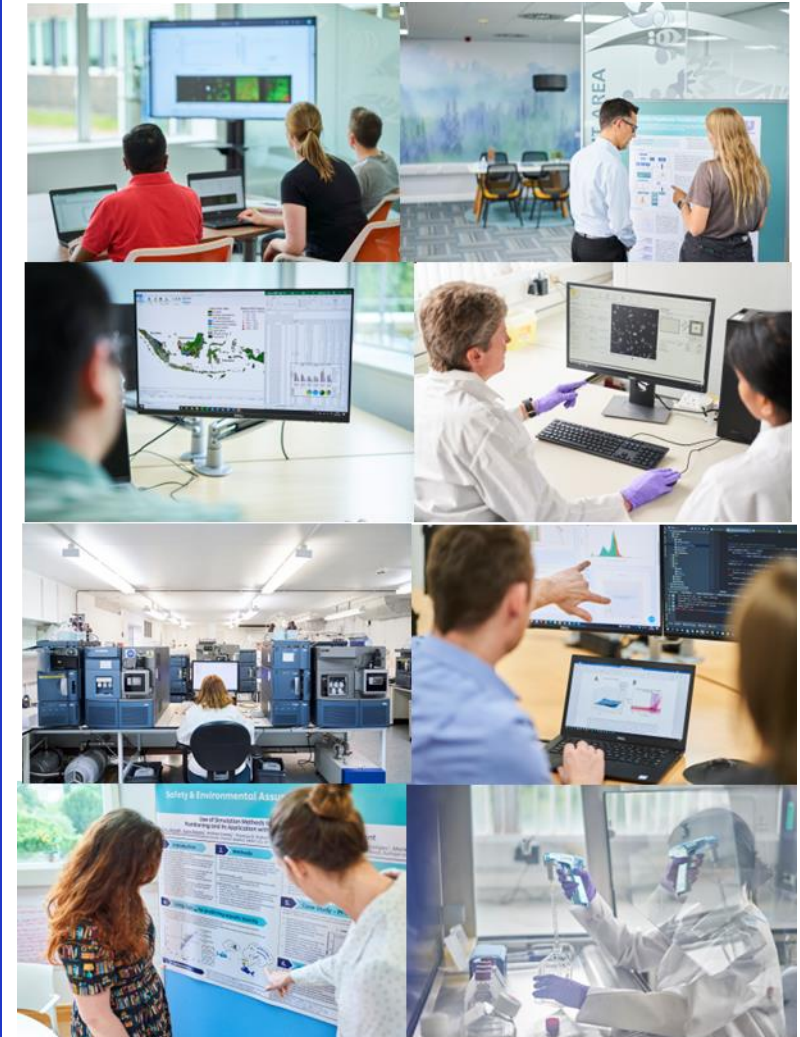# Closing the gap between advanced safety science and regulatory requirements

Dr Gavin Maxwell & Dr Julia Fentem MBE

CERJ Networking Day – 21st June 2024

Acknowledgement: >80 eco/toxicologists, biologists, chemists, computational modellers, data scientists & exposure / risk assessors in **Unilever's Safety & Environmental Assurance Centre (SEAC – seac.unilever.com)**

A good track record of collaboration over many years

1. **Unilever Policy and Approach**
2. Next Generation Risk Assessment (NGRA)
3. Applying NGRA to Cosmetic Safety Assessment
4. Accelerating the Transition

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**
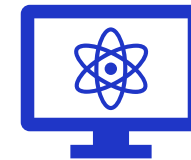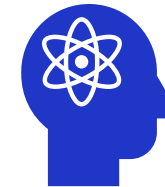- **Animal testing is not needed to assess ingredient & product safety** –wide range of non-animal alternatives available
- **We work to accelerate the global adoption of animal-free cosmetic safety assessment approaches**
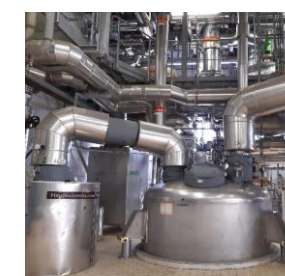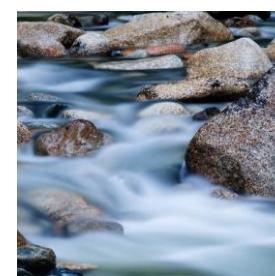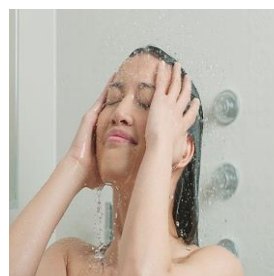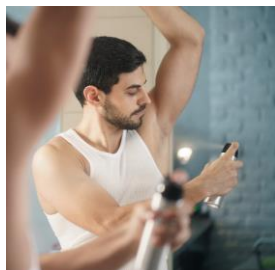
How we do it

40+ years of developing non-animal safety science

70+ collaborations

600+ publications

20 years of "Assuring Safety without Animal Testing" research & advocacy

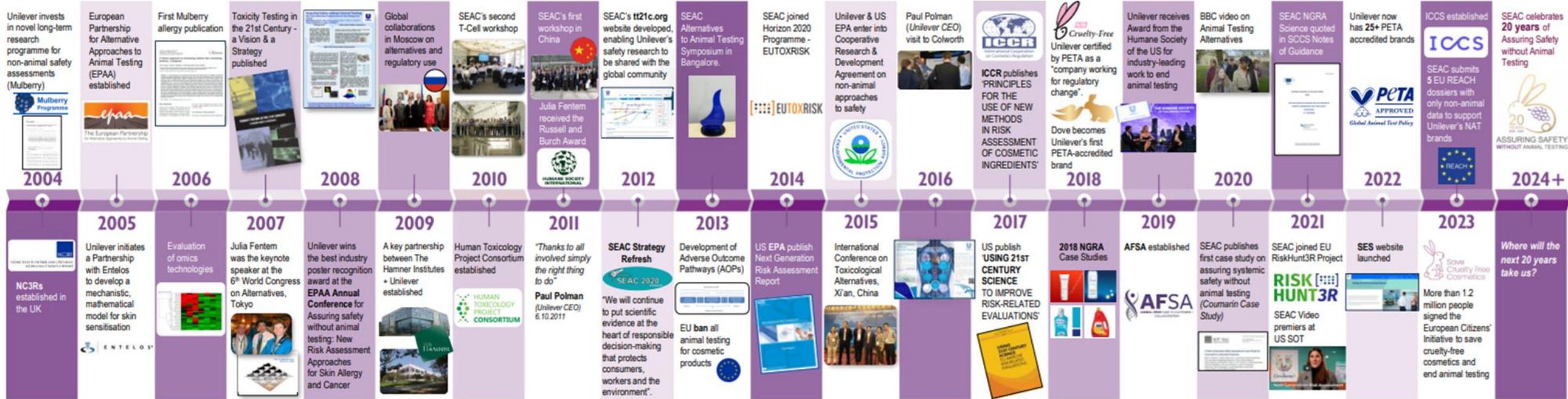> *Altern Lab Anim.* 2004 Dec;32(6):617-23. doi: 10.1177/026119290403200612.

The feasibility of replacing animal testing for assessing consumer safety: a suggested future direction

Julia Fentem [1], Mark Chamberlain, Bart Sangster

Toxicology 506 (2024) 153835

Next generation risk assessment for occupational chemical safety – A real world example with sodium-2-hydroxyethane sulfonate

Adam Wood [a,*], Catherine Breffa [b], Caroline Chaine [c], Richard Cubberley [a], Matthew Dent [a], Joachim Eichhorn [b], Susann Fayyaz [b], Fabian A. Grimm [b], Jade Houghton [a], Reiko Kiwamoto [d], Predrag Kukic [a], MoungSook Lee [b], Sophie Malcomber [a], Suzanne Martin [a], Beate Nicol [a], Joe Reynolds [a], Gordon Riley [a], Sharon Scott [a], Colin Smith [e], Carl Westmoreland [a], Willemien Wieland [f], Mesha Williams [a], Kathryn Wolton [a], Tristan Zellmann [g], Steve Gutsell [a]

My background:
NGRA for Skin Sensitisation
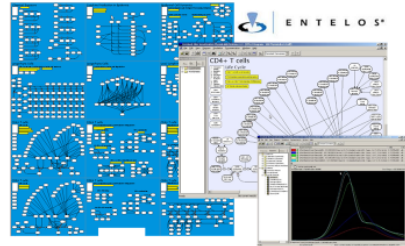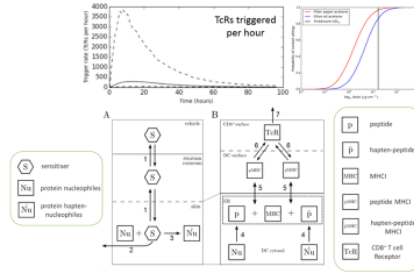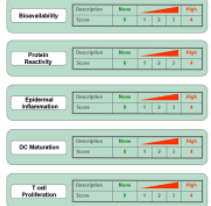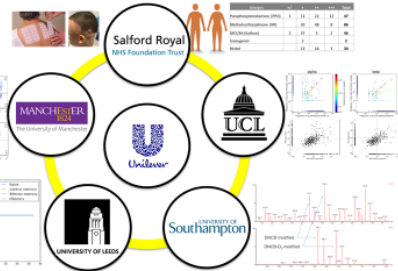
My current roles:

Regulatory Science Strategy & Advocacy Lead, SEAC

Industry co-chair, EPAA

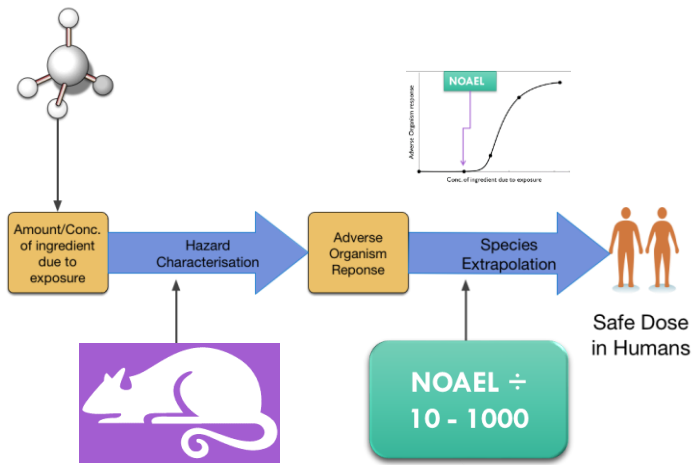**Core Acceptance Team vice chair, ICCS**
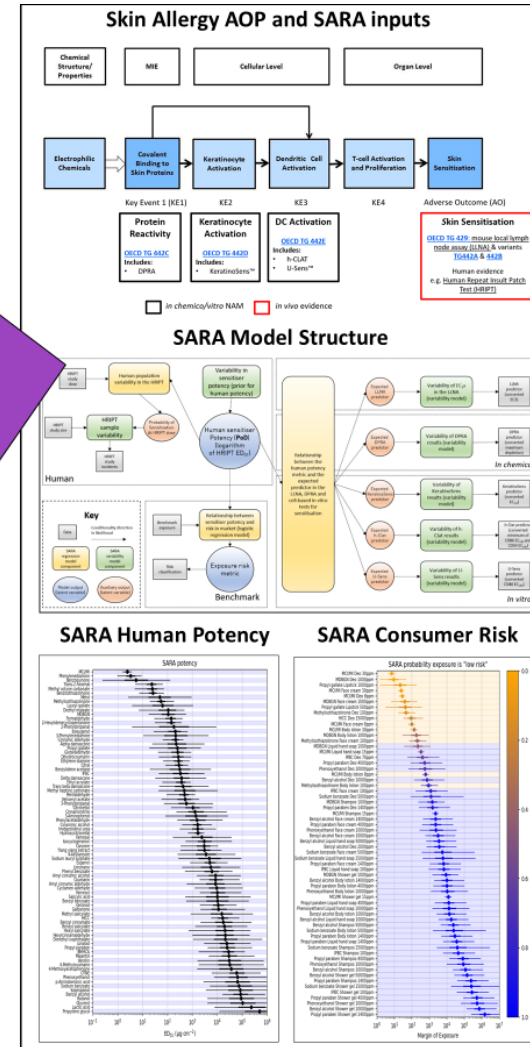
1. Unilever Policy and Approach
2. **Next Generation Risk Assessment (NGRA)**
3. Applying NGRA to Cosmetic Safety Assessment
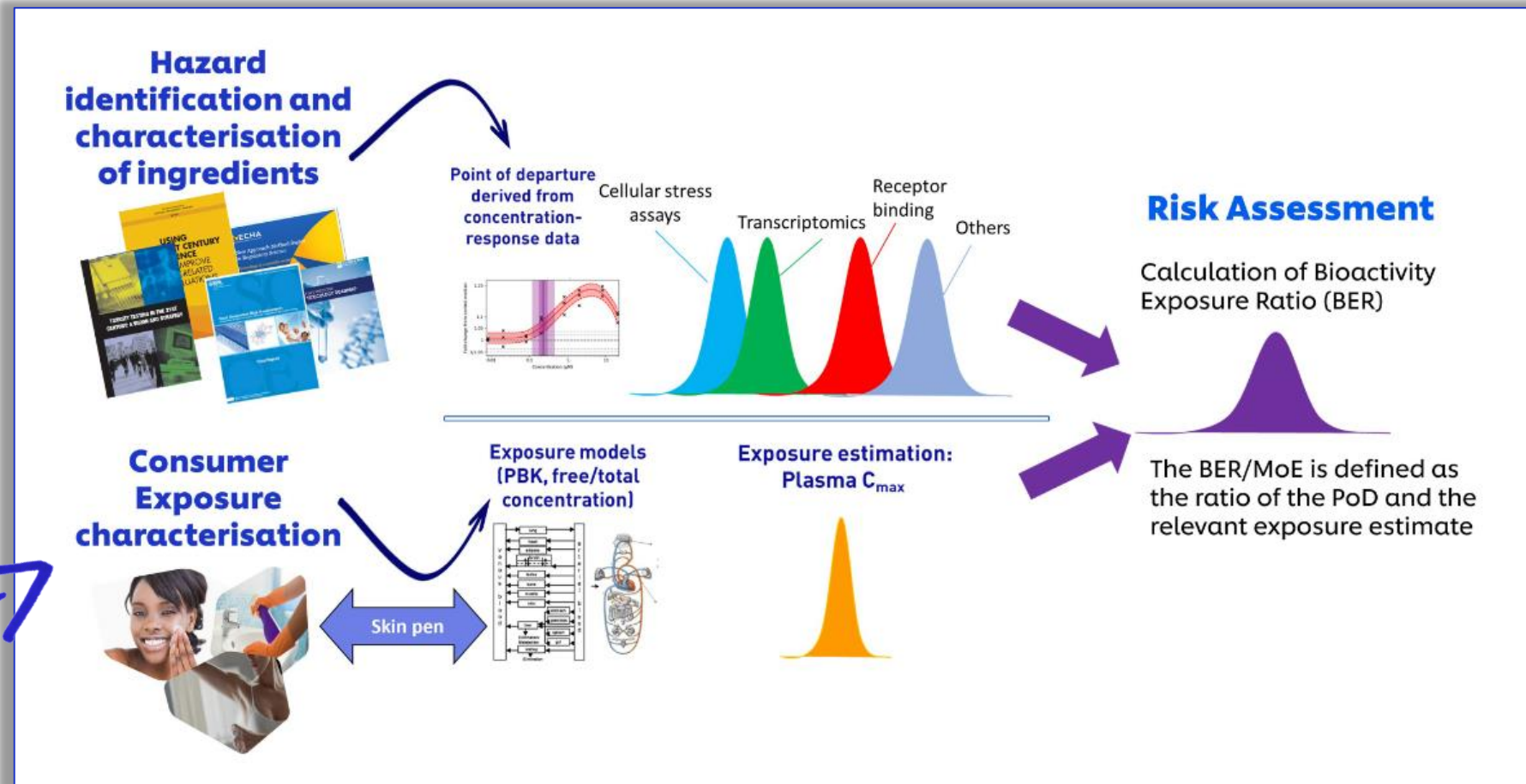4. Accelerating the Transition
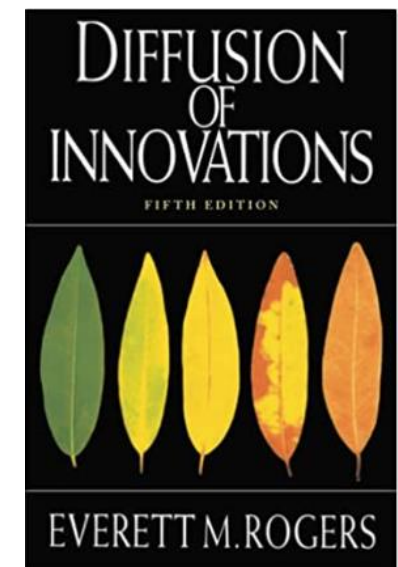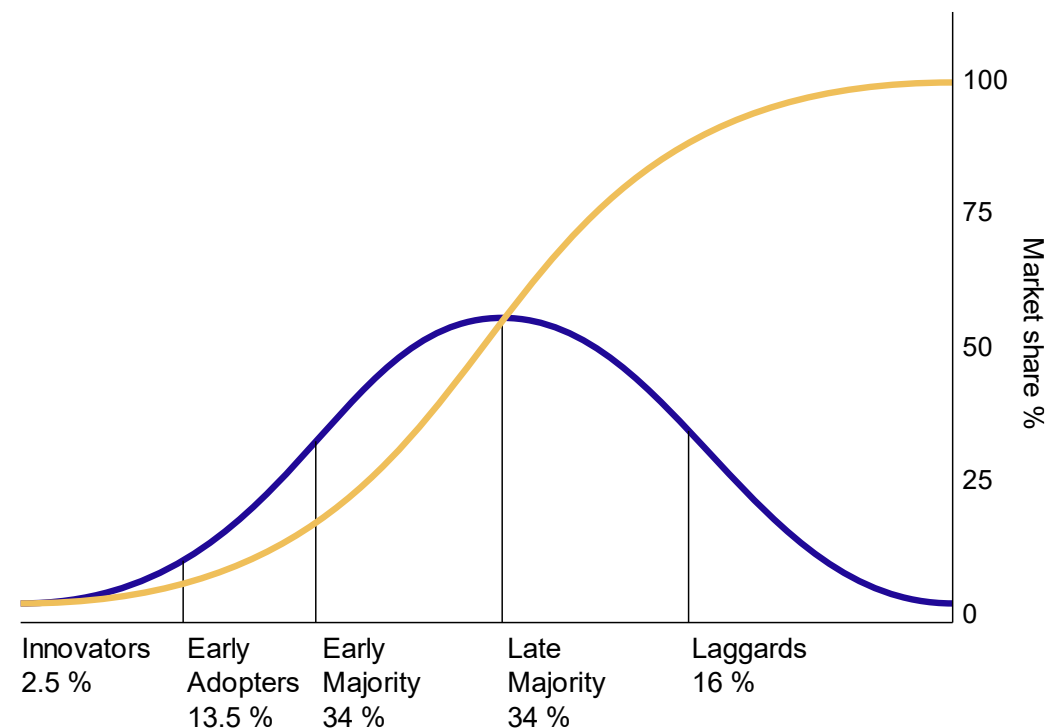
A global transition is underway as use of non-animal safety science increases & regulatory safety frameworks start to embed NAMs & NGRA approaches
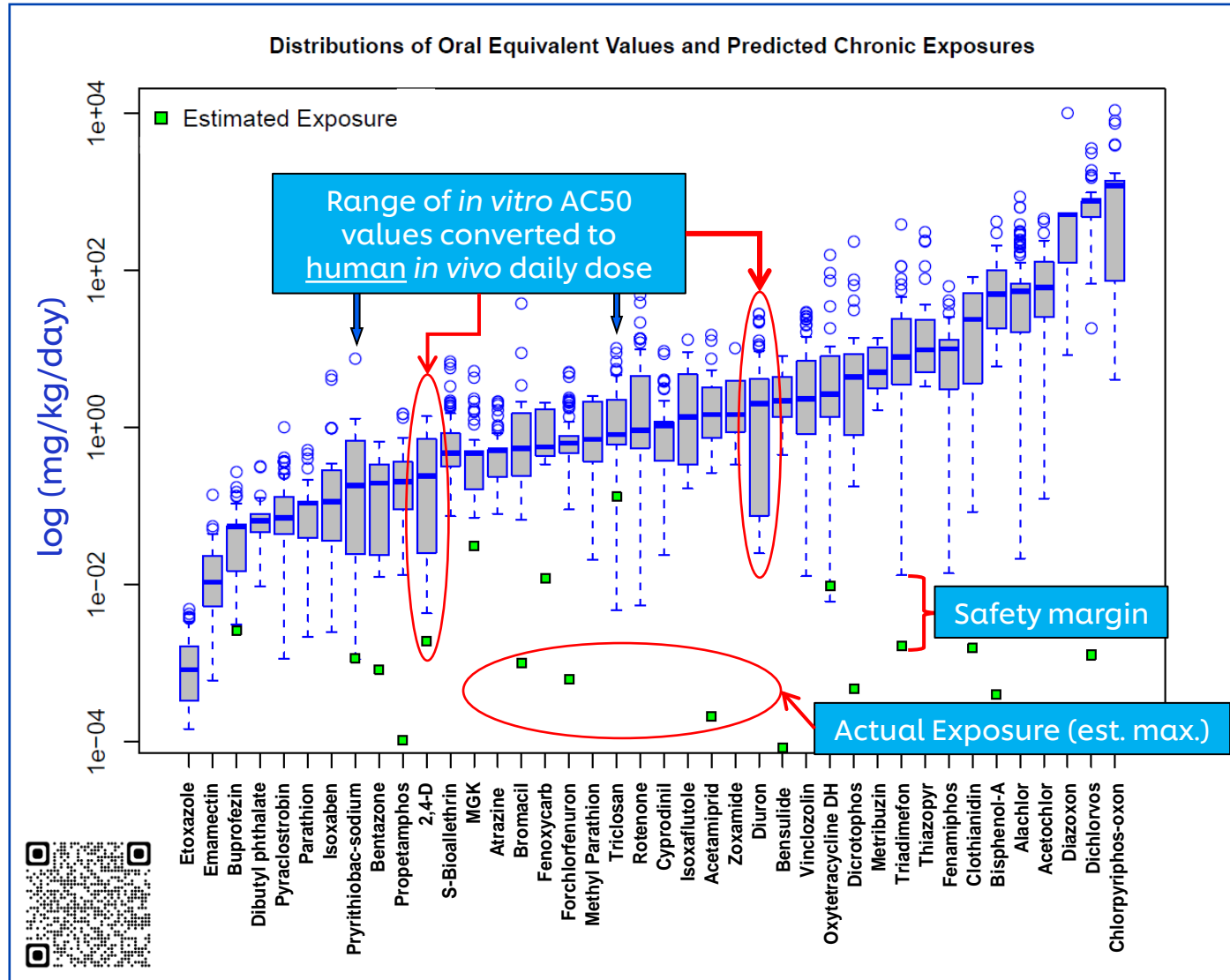
'Traditional' Risk Assessment

'Next Generation' Risk Assessment (NGRA)

NGRA: aim is protection, not prediction of animal data

Distributions of Oral Equivalent Values and Predicted Chronic Exposures

- Estimated Exposure
- Range of *in vitro* AC50 values converted to <u>human</u> *in vivo* daily dose
- Safety margin
- Actual Exposure (est. max.)

y-axis: log (mg/kg/day)

x-axis labels: Etoxazole, Emamectin, Buprofezin, Dibutyl phthalate, Pyraclostrobin, Parathion, Isoxaben, Pryrithiobac-sodium, Bentazone, Propetamphos, 2,4-D, S-Bioallethrin, MGK, Atrazine, Bromacil, Fenoxycarb, Forchlorfenuron, Methyl Parathion, Triclosan, Rotenone, Cyprodinil, Isoxaflutole, Acetamiprid, Zoxamide, Diuron, Bensulide, Vinclozolin, Oxytetracycline DH, Dicrotophos, Metribuzin, Triadimefon, Thiazopyr, Fenamiphos, Clothianidin, Bisphenol-A, Alachlor, Acetochlor, Diazoxon, Dichlorvos, Chlorpyriphos-oxon

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.**

Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

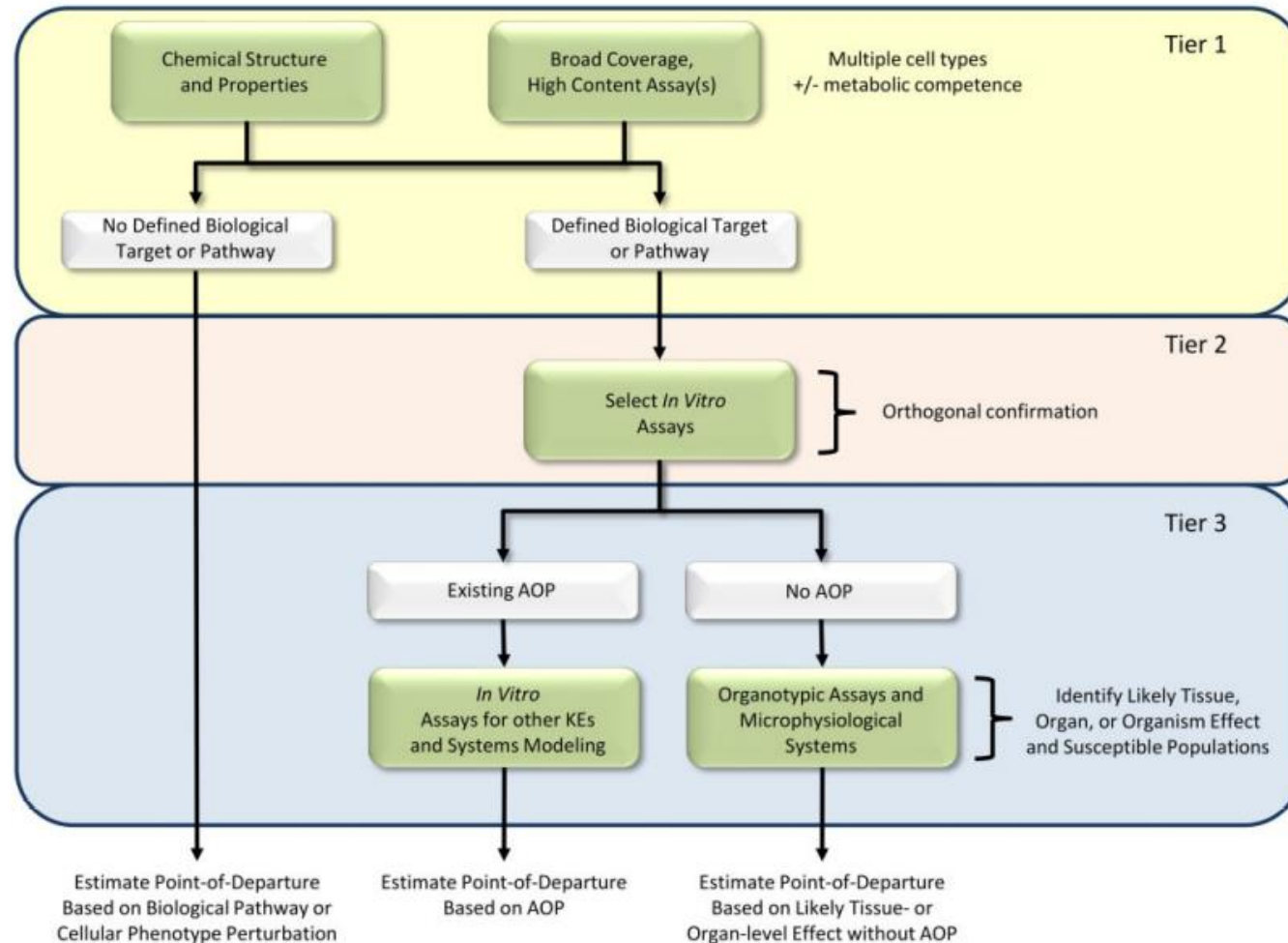# US EPA Next Generation Blueprint Tiered Testing Framework

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.

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

Use of NAMs/NGRA for Chemical Screening & Safety Assessment:
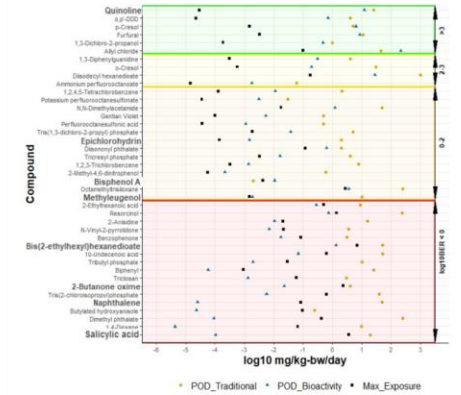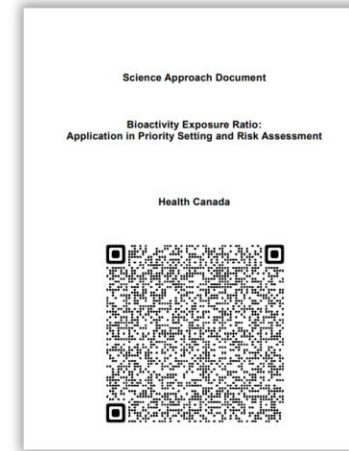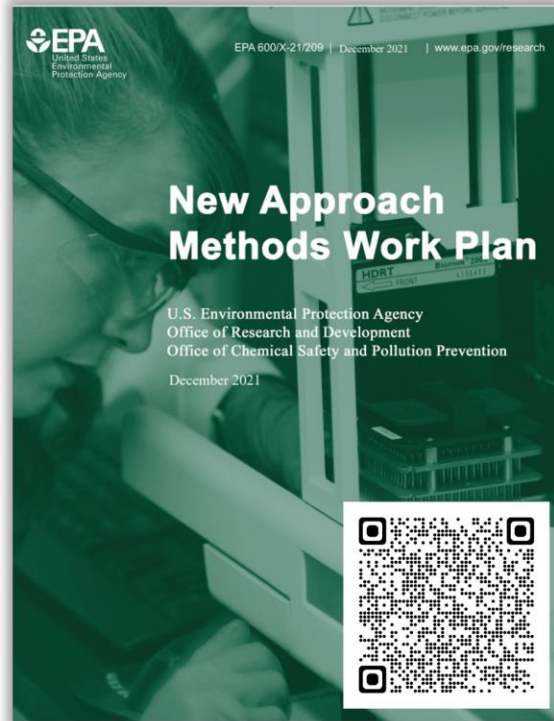## Current status of regulatory acceptance
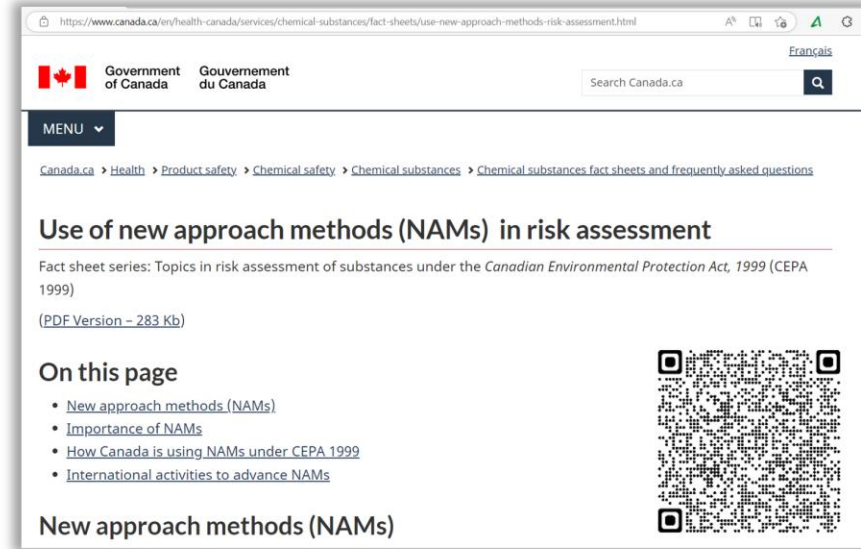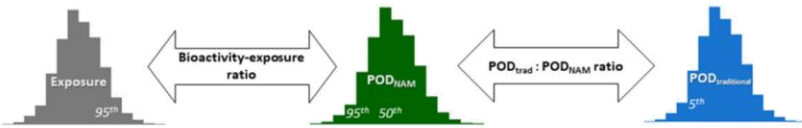
Paul Friedman et al. 2020

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 less than or equal to the $POD_{traditional}$ value for 89% chemicals. **Bioactivity-exposure ratio** useful metric for chemical prioritization

New Approach Methods Work Plan (epa.gov)

1. Unilever Policy and Approach
2. Next Generation Risk Assessment (NGRA)
3. **Applying NGRA to Cosmetic Safety Assessment**
4. Accelerating the Transition
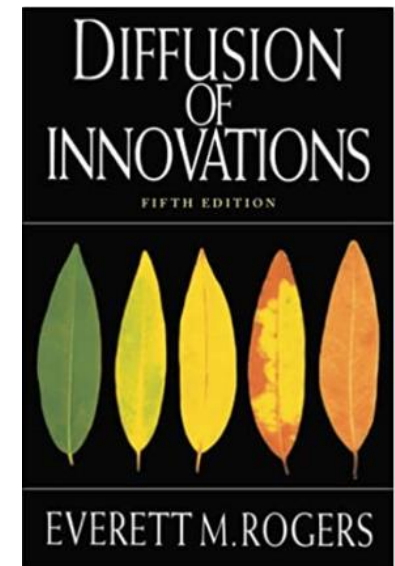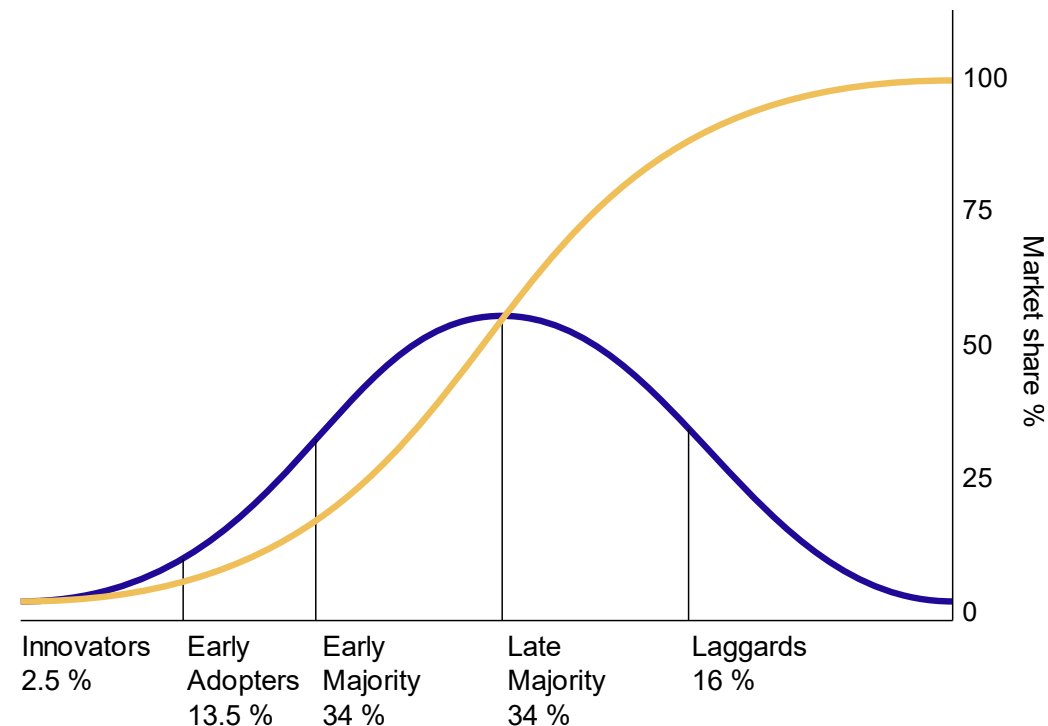
SEURAT-1 NGRA framework: tiered testing to support human health safety assessment

Berggren *et al* (2017) Computational Toxicology **4**, 31-44
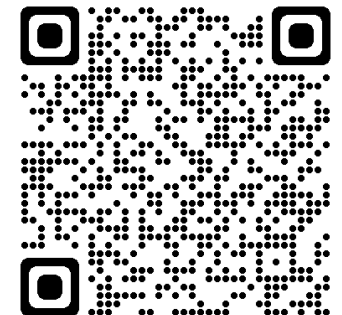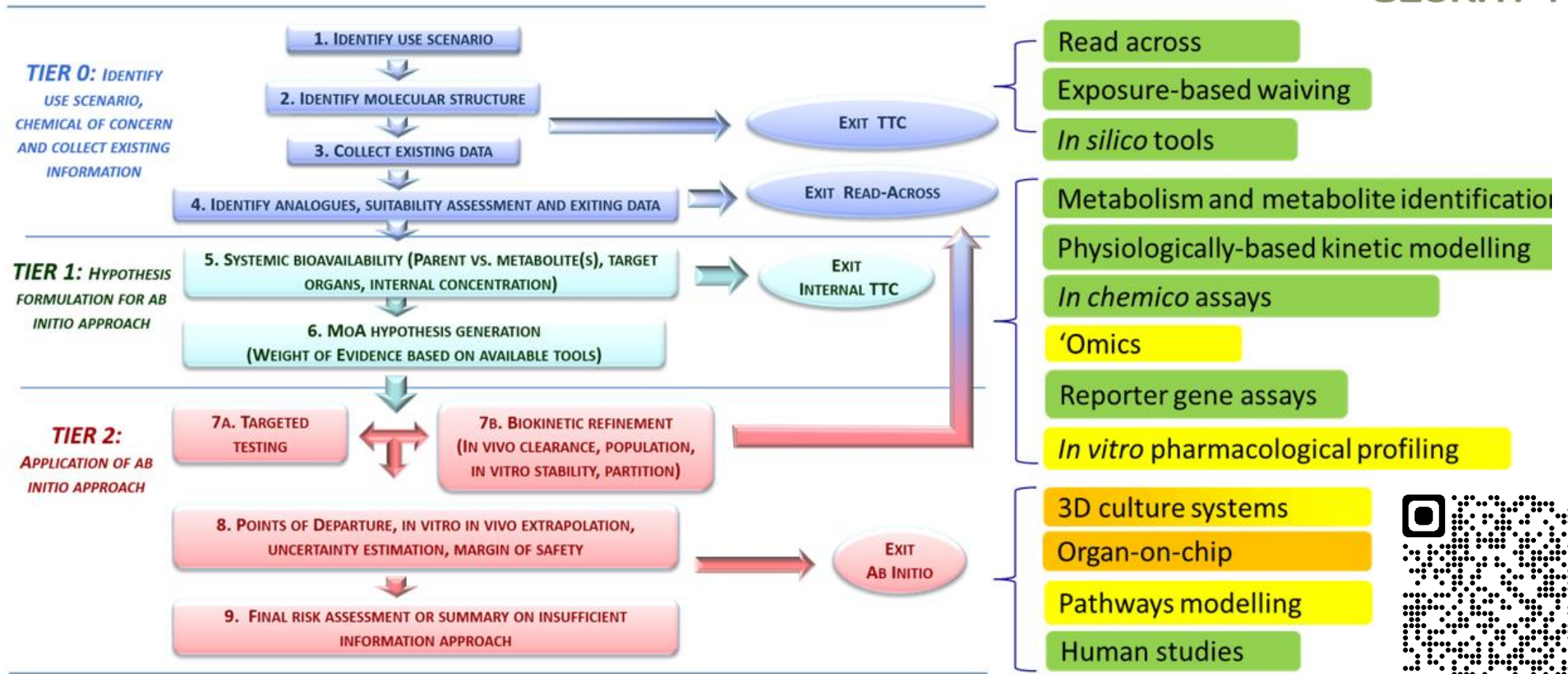
Unilever NGRA frameworks for Consumer Safety   Ongoing Evaluations

Systemic
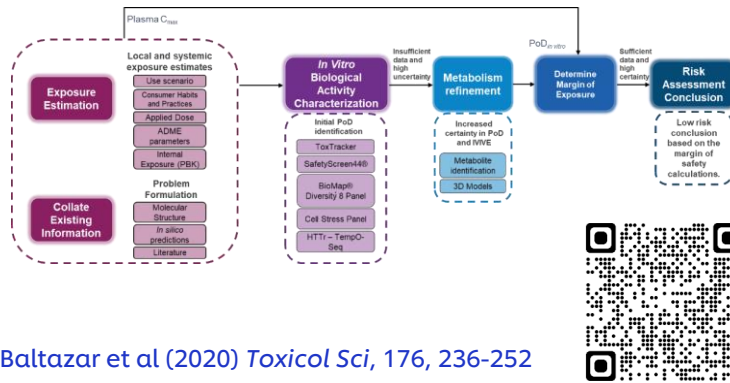
Baltazar et al (2020) *Toxicol Sci*, 176, 236-252
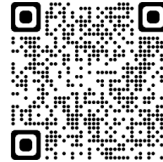
Developmental & Reproductive
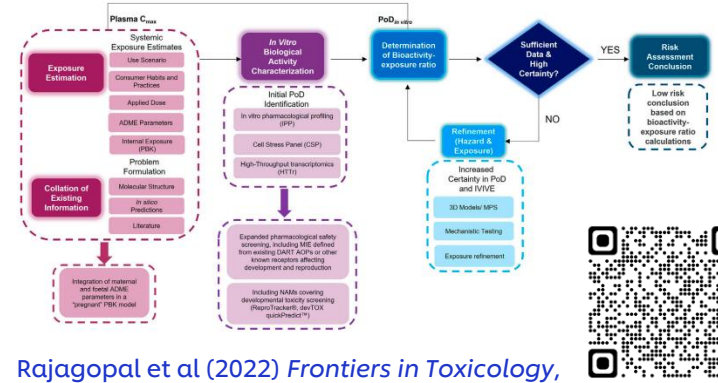
Rajagopal et al (2022) *Frontiers in Toxicology*,
doi: 10.3389/ftox.2022.838466

Skin Sensitisation

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

Inhalation

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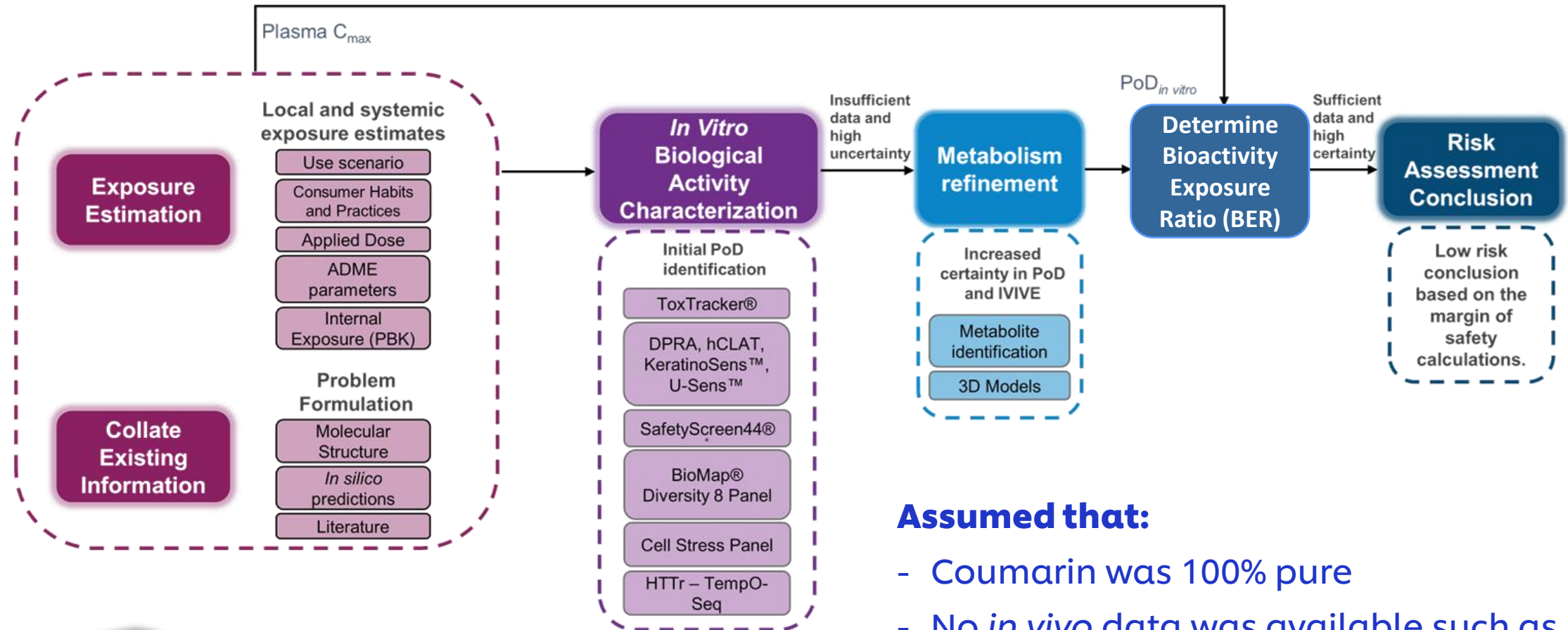
Assumed that:

- 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

Baltazar *et al.,* (2020) *Tox Sci* Volume 176, Issue 1, 236–252
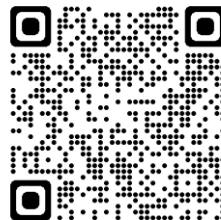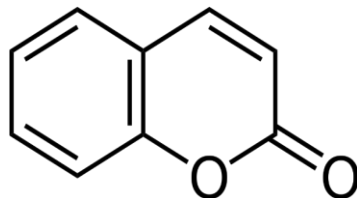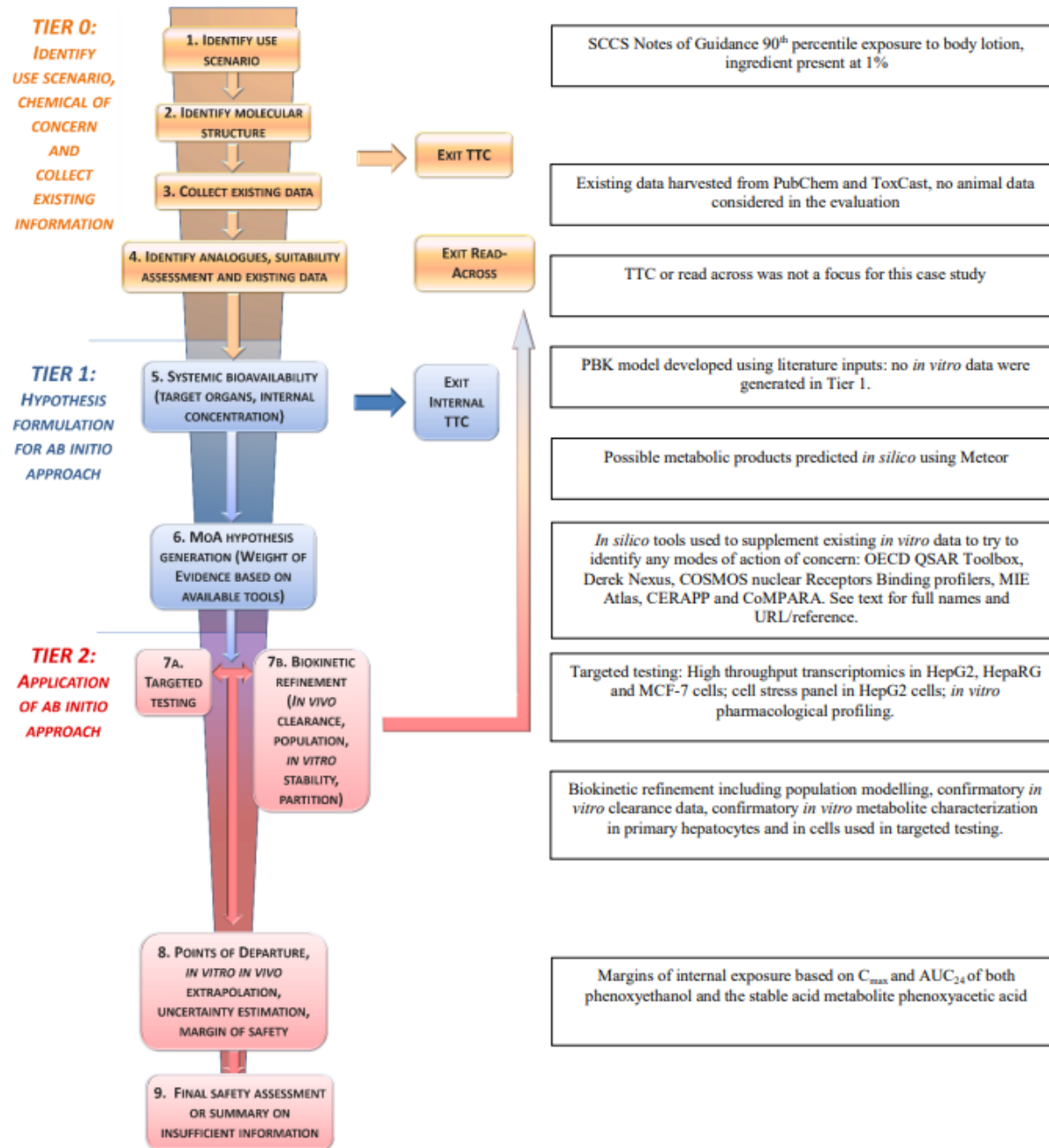
Case Study on use of an IATA for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion
Testing and Assessment Series, # 349
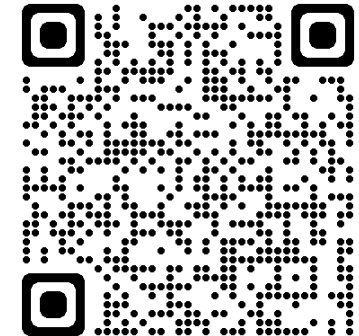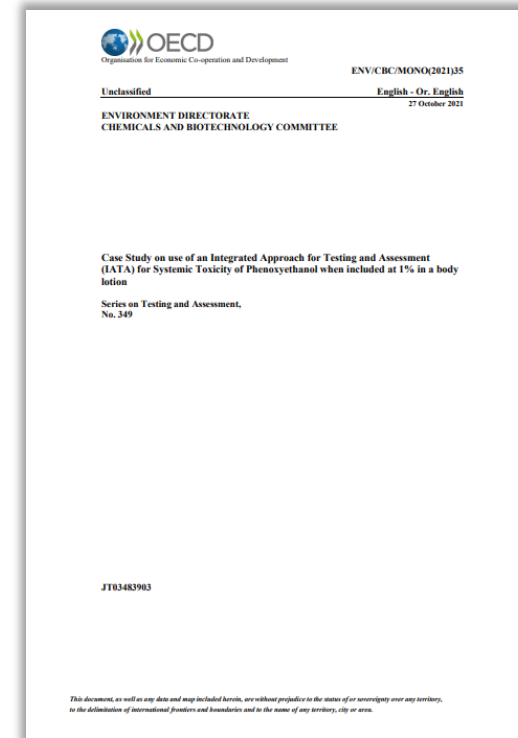
Making Safety Decisions for a Sunscreen Active Ingredient Using NGRA:
Benzophenone-4 Case Study

Gathering information
- Identified use scenario
- Identified molecular structure
- Collected existing data
- Route of exposure, habits & practises Literature, databases, In silico QSARs

Module 1 – Exposure estimation
- Estimate systemic exposure concentration (SEC) (plasma C_{max})

Hypothesis Generation

Generic Core tools[1]

Module 2 – Bioactivity characterisation
- Broad suite of assays and analysis used as part of the systemic toolbox (Cell stress panel, pharmacological profiling, transcriptomics)
- Tools to address specific risk assessment questions

Module 3 - Risk characterisation
- Calculation of Bioactivity-Exposure ratio (BER). Assessment based on lowest of POD_{NAM} together with weight of evidence
- Risk evaluation and risk assessment documentation

https://seac.unilever.com/files/10f53eed-f24a-4529-9a14-951a55a7a873/seac-pdf-making-safety-decisions-for-a-sunscreen-active-ingredient-using-next-generation-risk-assessment-benzophenone-4-case-study.pdf

Use of NAMs/NGRA for Cosmetic Safety Assessment:
Current status of regulatory acceptance

1. Unilever Policy and Approach
2. Next Generation Risk Assessment (NGRA)
3. Applying NGRA to Cosmetic Safety Assessment
4. **Accelerating the Transition**

'mind the gap' between
early adoption & regulatory use

Market share %

100

75

50

25

0

| Innovators 2.5 % | Early Adopters 13.5 % | Early Majority 34 % | Late Majority 34 % | Laggards 16 % |

DIFFUSION OF INNOVATIONS
FIFTH EDITION
EVERETT M. ROGERS

Why accelerate the transition to Animal-Free Safety Assessment?

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

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

3. **Regulatory Animal Testing of Chemicals is increasingly seen as unjustifiable / unethical by the majority of society**

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

Special Eurobarometer 501

Safe and Sustainable by Design chemicals and materials - Methodological Guidance
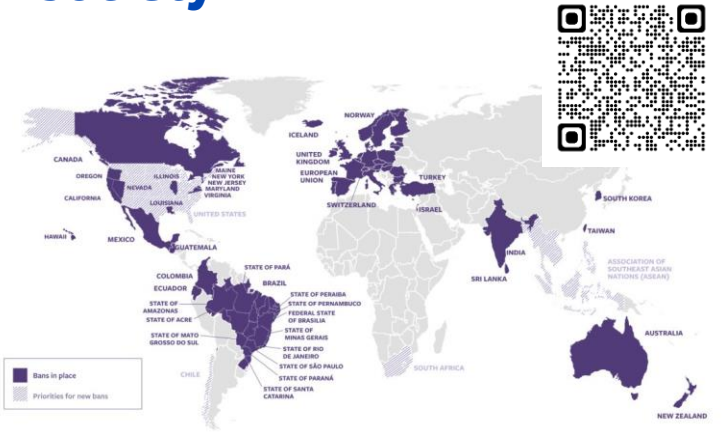
✓ Let's use Animal-free Safety Science to **rebuild consumer trust in cosmetic safety**

✓ Let's use Animal-free Safety Science to **ensure new chemicals are Safe & Sustainable**

✓ Let's use Animal-free Safety Science to **fully replace the need for regulatory animal testing**

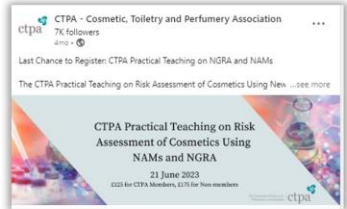# 1. Build confidence in NGRA frameworks by validating whether or not they are 'fit for regulatory use'

Fitness for Purpose

Human Biological Relevance

Framework for Establishing Scientific Confidence in NAMs

Independent Review

Technical Characterization

Data Integrity and Transparency

Which regulatory statutes are data from the NAM intended to comply with?
- U.S. TSCA
- EU REACH
- Other

How will the NAM be used?
- As a stand-alone assay
- As part of a defined approach
- As part of an integrated approach to testing and assessment or weight of evidence assessment

Fitness for Purpose

Is the information provided sufficient to address the regulatory endpoints of interest?
- Describe the relationship between the information measured by the NAM and the regulatory endpoints being addressed.
- Is the technical performance, including the level of uncertainty, acceptable?

What is the context in which the NAM is intended to be used?
- Preregulatory screening and prioritization
- Chemical grouping
- Hazard identification
- Quantitative risk assessment

[A framework for establishing scientific confidence in new approach methodologies](#)

2. Co-create NGRA best practice through open industry: regulator scientific dialogue using NGRA case studies

3. Update toxicological training to include NGRA concepts and approaches

Risk Assessment Process

Collate Existing Information → Exposure Estimation → Biological activity characterisation → Exposure Refinement → Risk Assessment Conclusion

0: Master Class and Risk Assessment Overview

1. Problem Formulation | 2. Consumer Exposure | 3. Predictive Chemistry | 6. Internal Exposure | 7. Integration into Risk Assessment

4a. Exposure Based Waiving | 4b. Safety of Botanicals History of Safe Use | 5. In Vitro Assay Synthesis | AFSA **Master Class Modules**

Global Regulatory Environment

Module release date 2023	Online now	Aug '23	Fall '23
0: Intro: course overview			
1: Problem formulation			
2: Consumer exposure			
3: In silico tools			
4a: Exposure-based waiving			
4b: Safety of Botanicals: History of Safe Use			
8: Regulatory landscape			
5: In vitro data synthesis			
6: Internal Exposure: Dosimetry			
7: Risk assessment			

4. Collaborate to pool resources, learn together & manage the change (EU Roadmap, UK NAMs strategy, EPA NAM workplan)

EPAA 'NAM Designathon' Challenge for human systemic toxicity

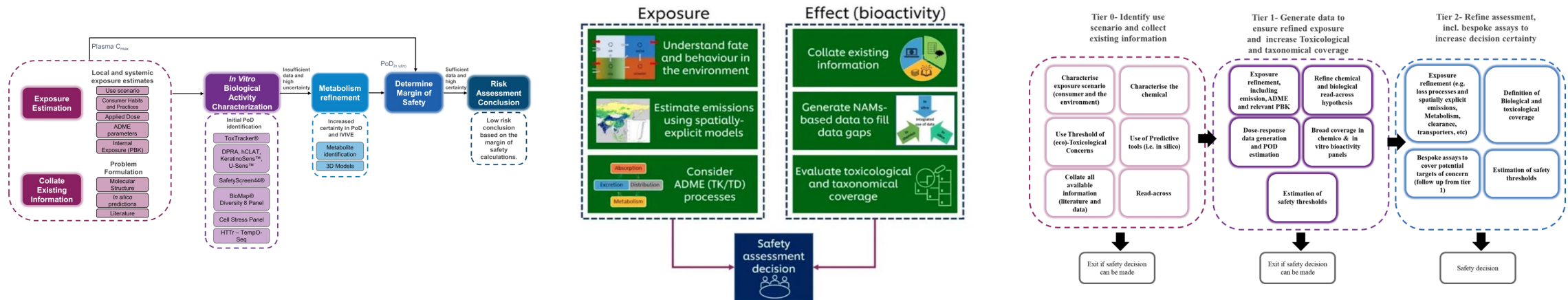EPAA 'Use of NAMs in Environmental Safety Assessment' Partners Forum
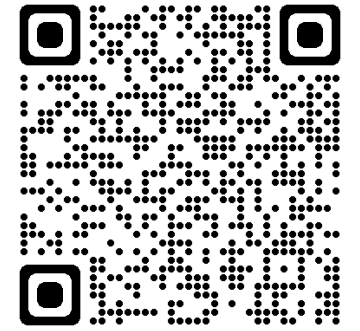
EPAA NAM User Forum

Conclusions

- **A paradigm shift is well underway** as use of NAMs and NGRA increases & moves beyond innovators/early adopters

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

- **We can accelerate the NGRA paradigm shift** through increasing industry: regulator exchange, re-focusing validation, supporting training platforms & increased collaboration

Acknowledgements

Collaborators:

seac.unilever.com

Thank You for your attention!

seac.unilever.com

Unilever