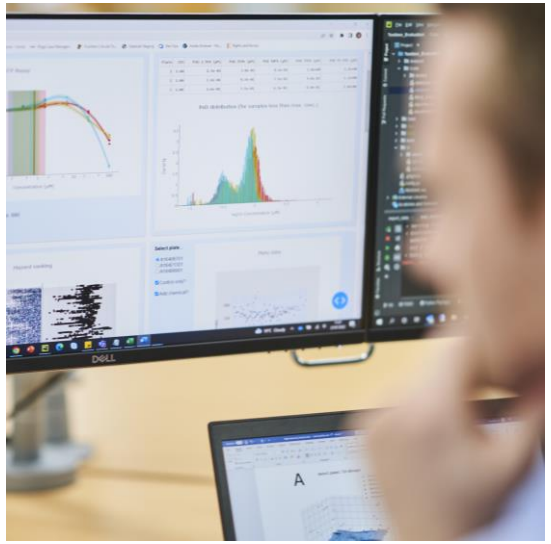
Next generation risk assessment – principles and tools

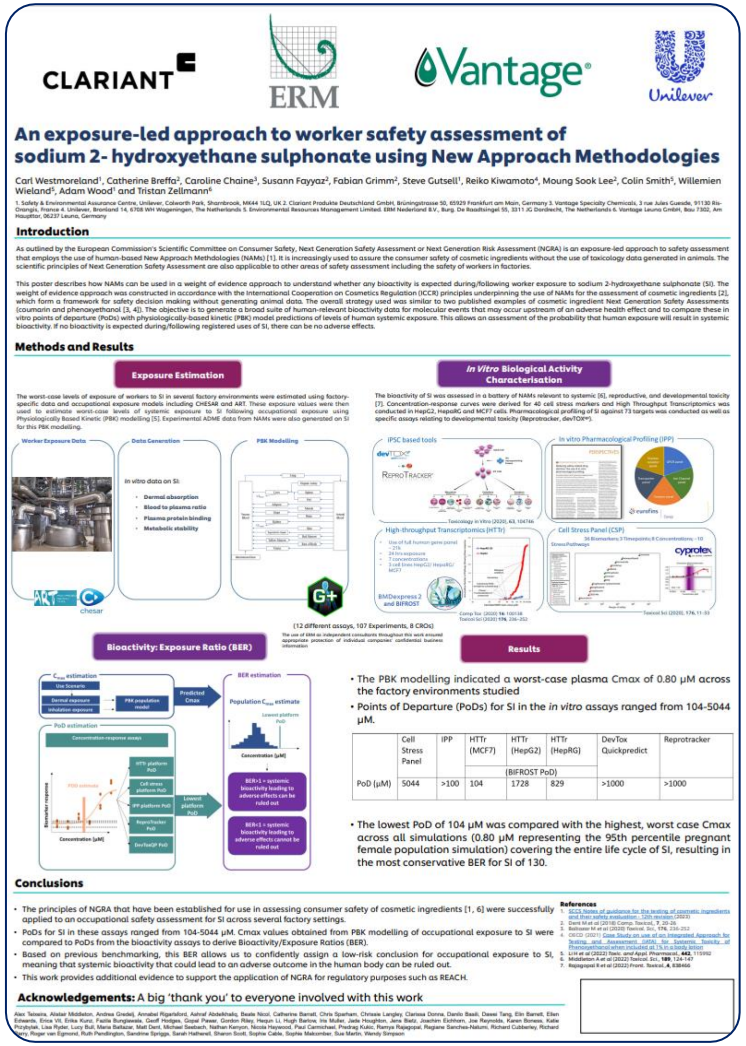
Matt Dent, Unilever Safety and Environmental Assurance Centre, UK

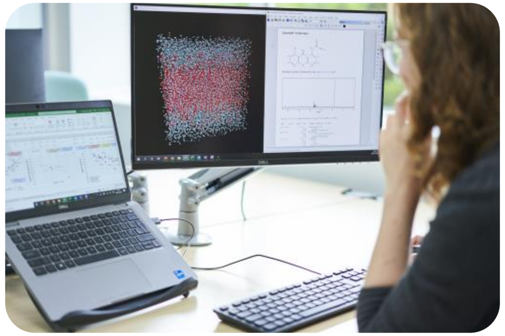


Unilever

Unilever's Safety and Environmental Assurance Centre

SEAC performs assessments across Unilever's product portfolio (personal care, home care, foods) and provides expert support to regulatory submissions

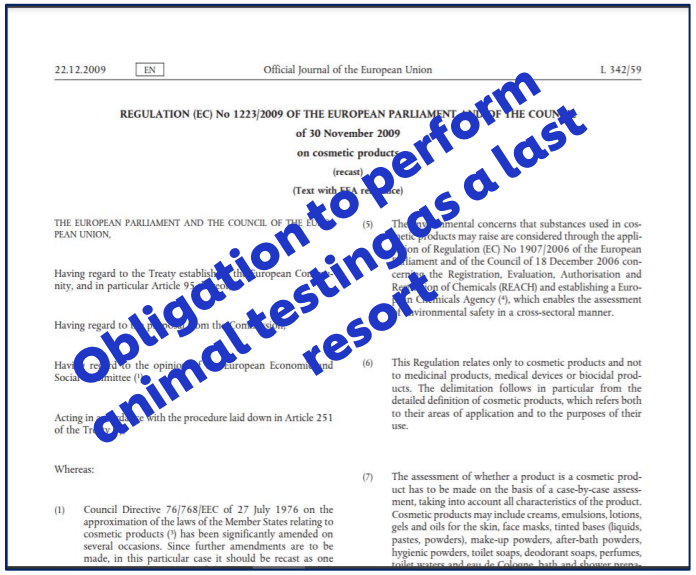




The need for non-animal safety assessments

Societal Attitudes/Consumer Preference

Biological Relevance



Regulatory Change

Key health effects to cover in a toxicological safety assessment

✅ Well-accepted non-animal approaches (e.g. OECD guidelines, Defined Approaches)

✅ Non-animal approaches available for <u>exposure-led safety</u> assessment but more evaluation to be done

Local effects	Systemic Effects
✅ Corrosion/irritation (skin/eye)	✅ Mutagenicity and genotoxicity
✅ Phototoxicity	✅ Systemic Toxicity
✅ Skin Sensitisation	✅ Reproductive Toxicity
✅ Local lung toxicity	✅ Carcinogenicity

Why are there no ❌?!

Unilever

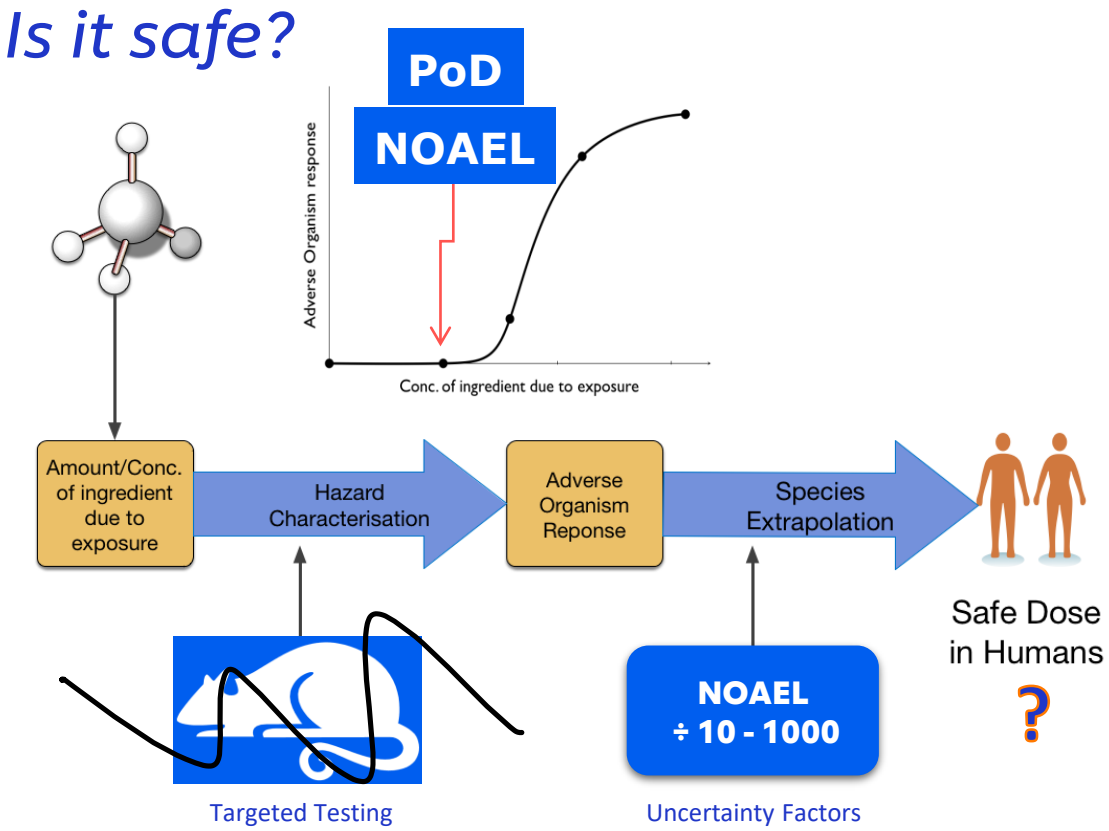
Are non animal safety assessments even possible for systemic toxicity?

Systemic toxicity isn't like local toxicity

Many possible adversities

ADME considerations

Homeostasis



Unilever

Well-established approaches for systemic toxicity

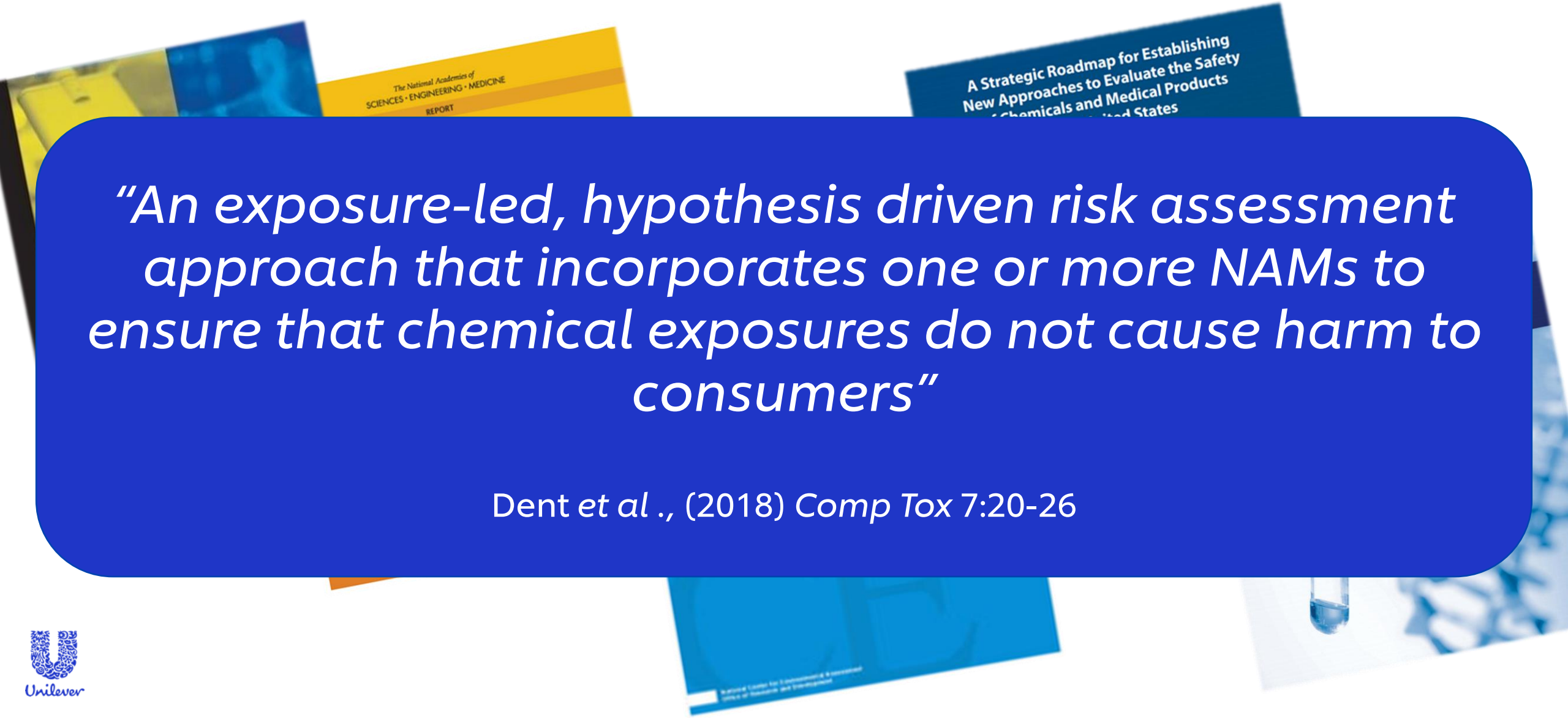
Threshold of Toxicological Concern
(Yang et al 2017) https://doi.org/10.1016/j.fct.2017.08.043

Read across
(Alexander-White et al 2022)
https://doi.org/10.1016/j.yrtph.2021.105094

History of Safe Use
(Neely et al 2011) PMID: 22025816

For 'significant' exposures to a novel ingredient a new non-animal paradigm is needed...

What is next generation risk assessment (NGRA)?



"An exposure-led, hypothesis driven risk assessment approach that incorporates one or more NAMs to ensure that chemical exposures do not cause harm to consumers"

Dent *et al* ., (2018) *Comp Tox* 7:20-26

Unilever

Principles of NGRA from ICCR*

4 Main overriding principles:

- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

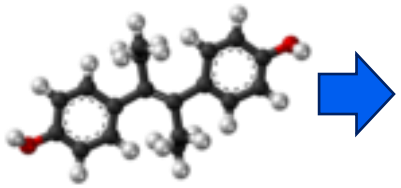
- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparent and documented

Unilever

Dent *et al* ., (2018) *Comp Tox* 7:20-26

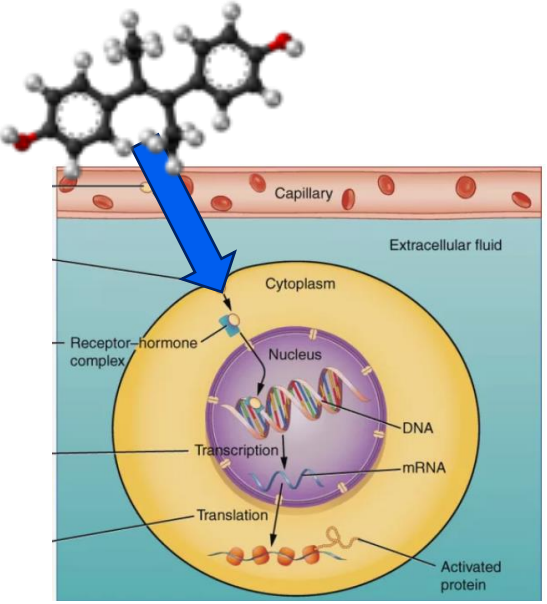
*International Cooperation on Cosmetics Regulation

Illustrating the adverse outcome pathway (AOP) concept: estrogens and breast cancer

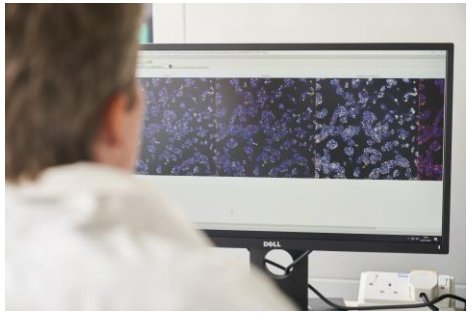


Breast Cancer

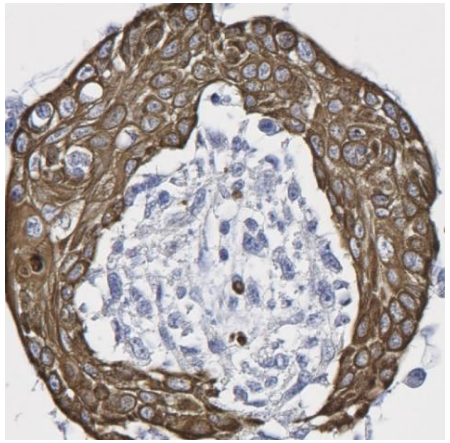
Illustrating the adverse outcome pathway (AOP) concept: estrogens and breast cancer



Binding to estrogen receptor



Genes activated, cells proliferate

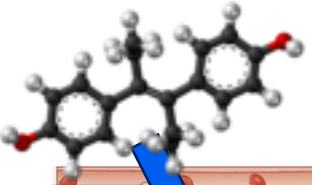


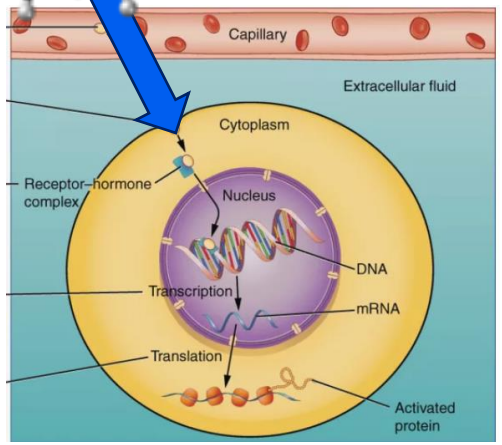
Cells transform

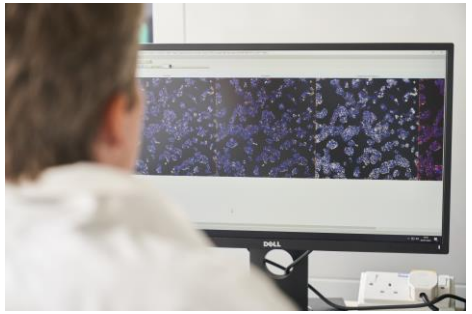
Breast Cancer

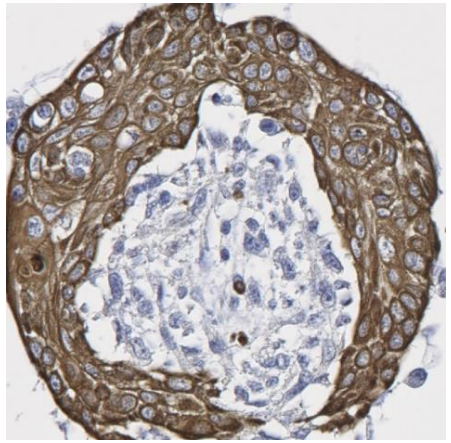
Unilever

The difference between bioactivity and adversity







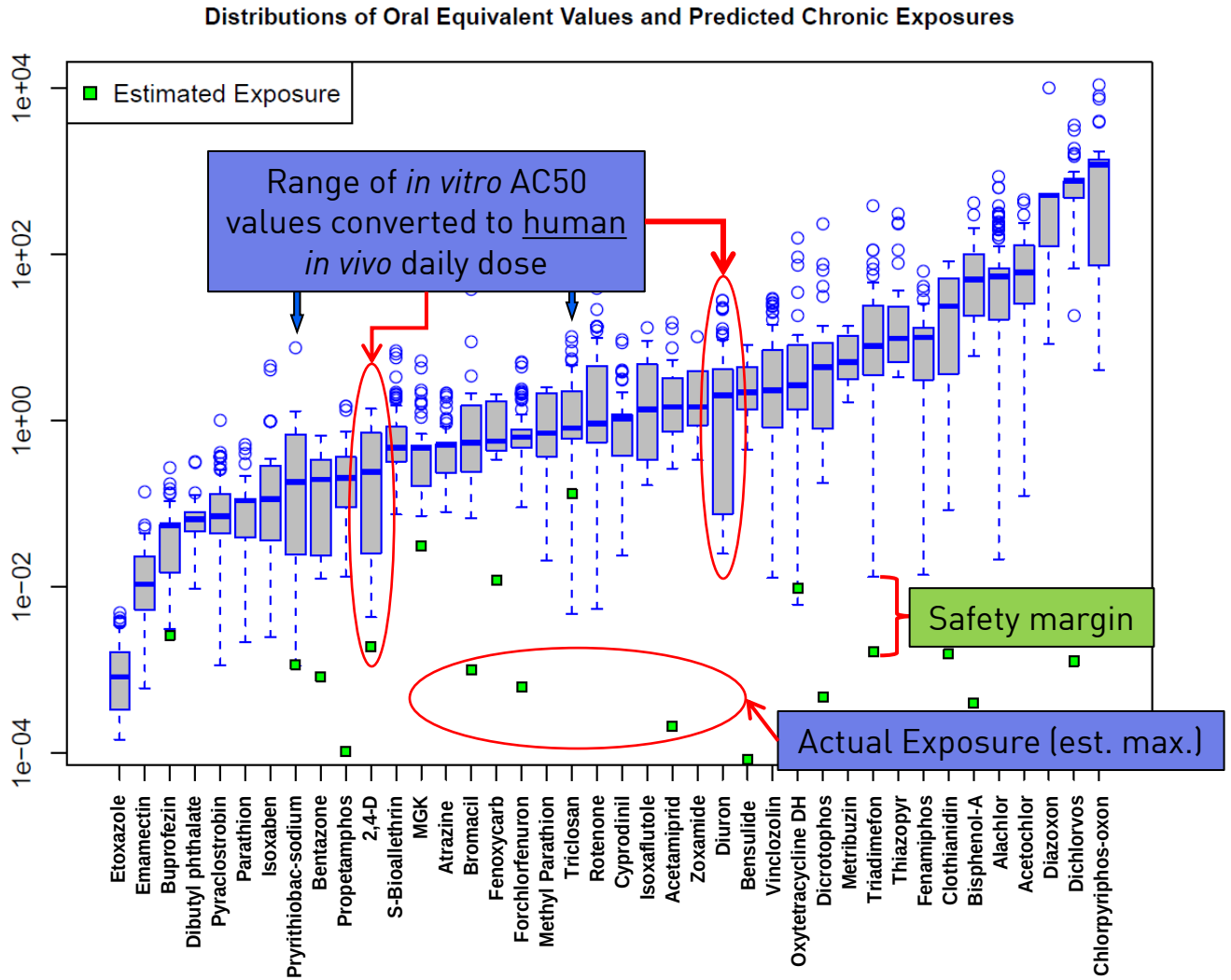


~~~~78 Major human organs × 5 ways a chemical could be toxic to each one × 5 Key Events ≈ 2000 assays~~~~
(Carmichael et al., 2022)

If the MIE does not occur at relevant doses, neither can the AO

If the MIE occurs, this may or may not lead to the AO
~~~~

Paradigm shift for systemic safety - Protection not Prediction

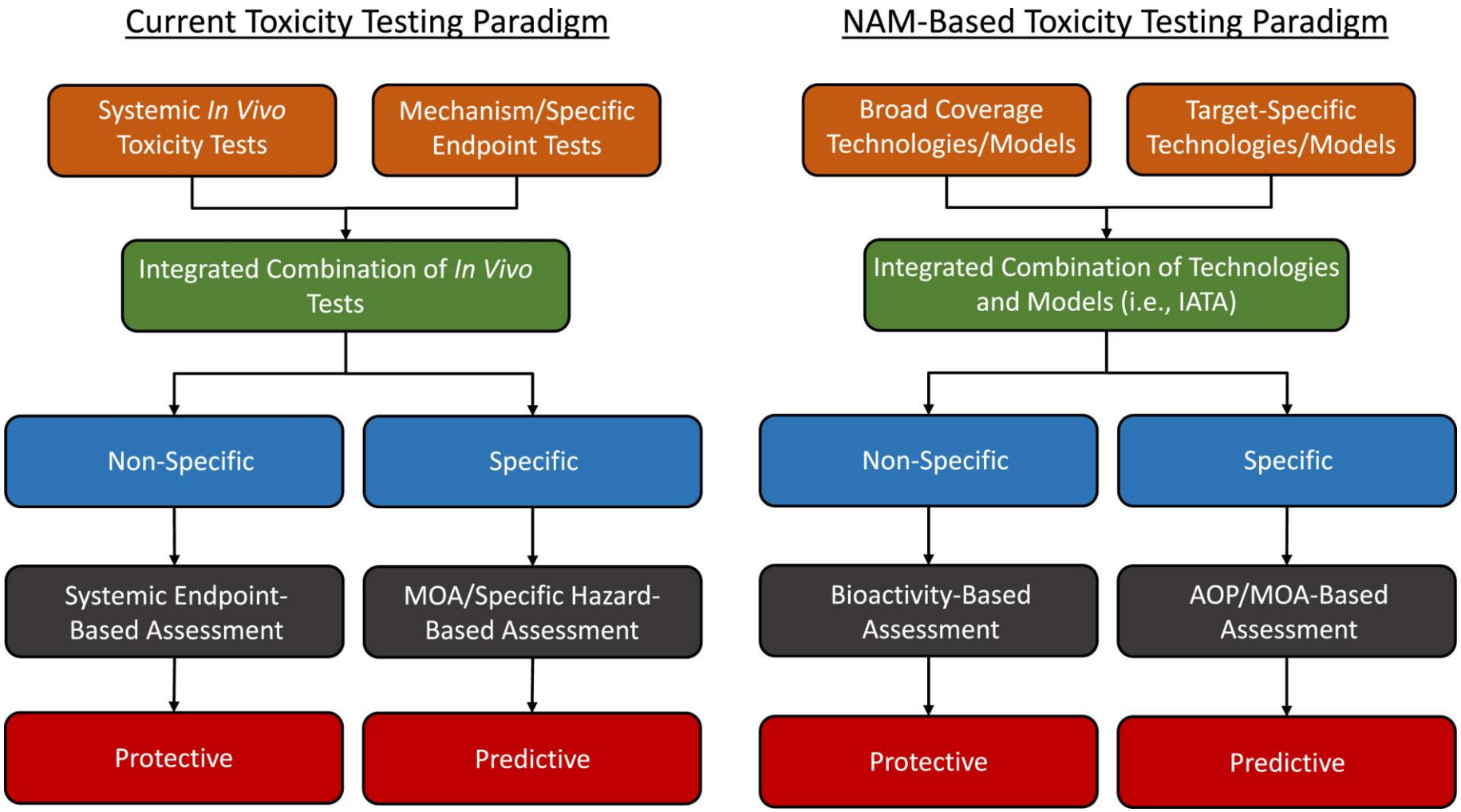


Graphic from Dr Rusty Thomas, EPA, with thanks

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.**

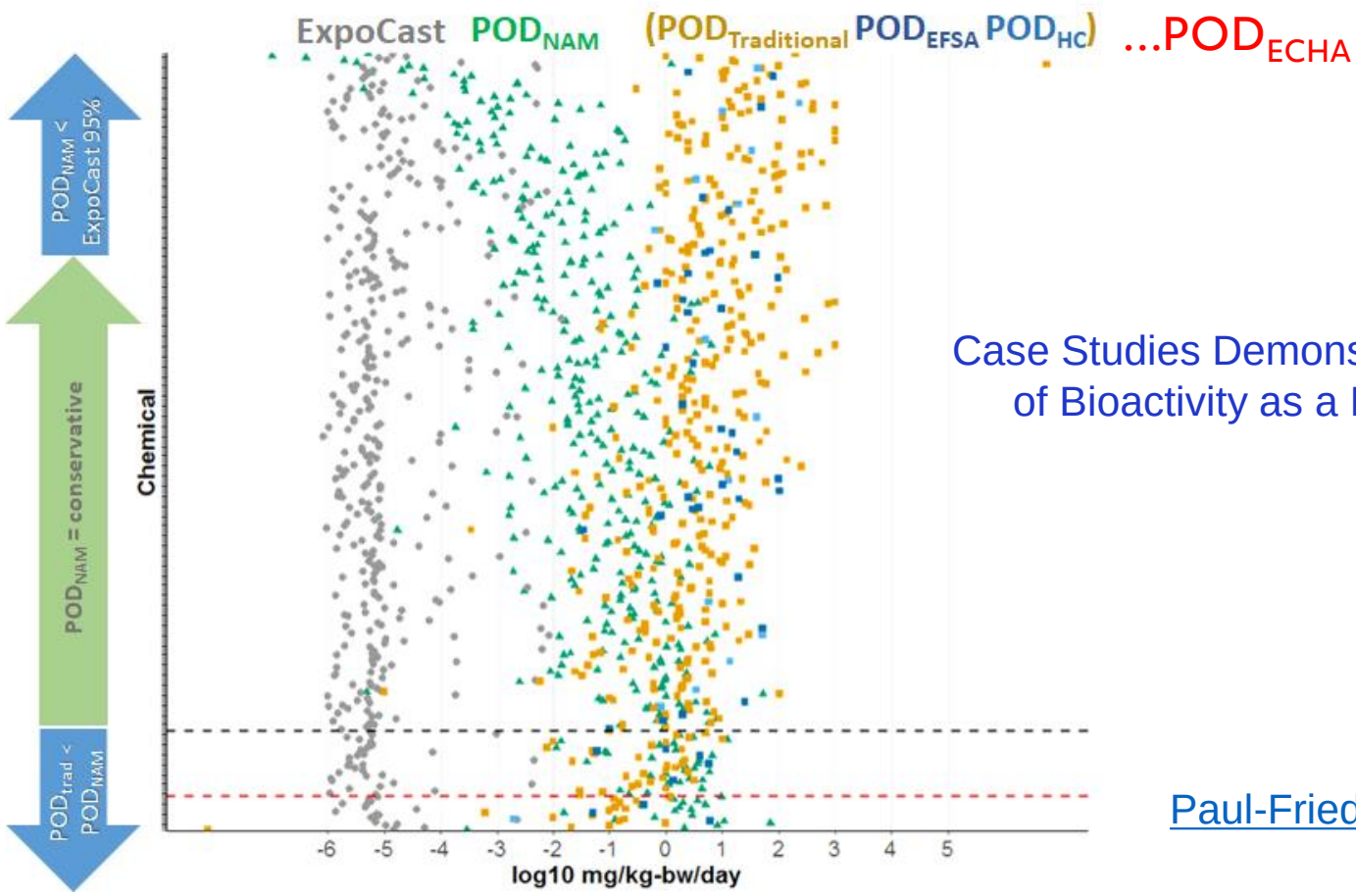
Rotroff, *et al.* Tox.Sci 2010

Protection and prediction in current and future assessment approaches



Browne et al., 2024 Reg Tox Pharm https://doi.org/10.1016/j.yrtph.2024.105579

Points of Departure from NAMs can be protective



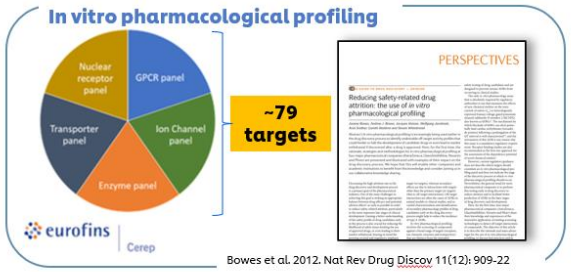
Case Studies Demonstrating Application of Bioactivity as a Protective POD

Paul-Friedman et al., 2020

Unilever

Risk Assessment Outcome

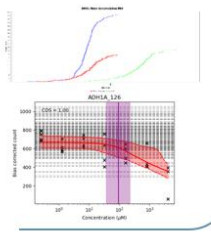
BIOACTIVITY



Bowes et al. 2012. Nat Rev Drug Discov 11(12): 909-22

High-Throughput transcriptomics (HTTr)

- TempO-seek technology – full gene panel
- 24hr exposure
- 7 concentrations
- Various cell models (e.g. HepG2, MCF7, HepaRG)
- Dose-response analysis using BMDExpress2 and BIFROST model



Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1): 236–252

Cell stress panel (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
- Dose-response analysis using BIFROST model

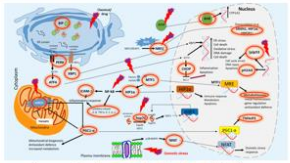
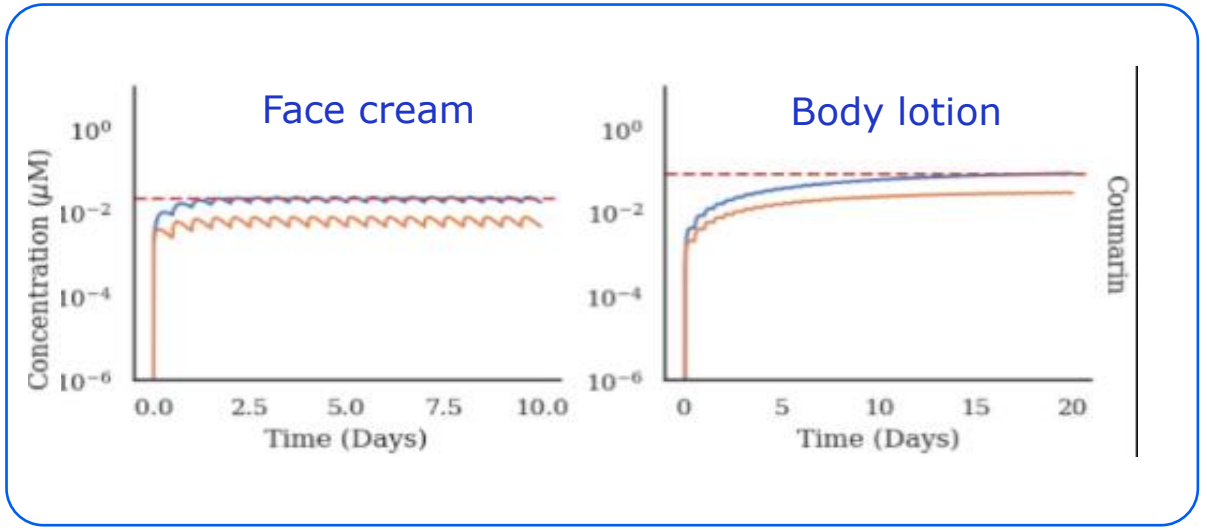


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

EXPOSURE



Identify lowest (most sensitive) point of departure, expressed in μM

Identify realistic worst-case plasma exposure (C_{max}) expressed as μM

$$\text{BIOACTIVITY EXPOSURE RATIO} = \frac{\text{BIOACTIVITY}}{\text{EXPOSURE}}$$

The bigger the BER, the greater the confidence that bioactivity will not occur in exposed consumers

Unilever

What do we still need to do?

1. Increase confidence in exposure predictions (including metabolites)
2. Determine whether tools give us enough biological coverage
3. Be explicit about the level of confidence in the assessment
4. Develop agreed standards for using tools and reporting data
5. Distinguish between adaptation and adversity
6. Develop an updated risk assessment workflow
7. More case studies

Regulatory Toxicology and Pharmacology 125 (2021) 105026

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Paving the way for application of next generation risk assessment to safety decision-making for cosmetic ingredients

M.P. Dent [a,*], E. Vaillancourt [b], R.S. Thomas [c], P.L. Carmichael [a], G. Ouedraogo [d], H. Kojima [e], J. Barroso [f], J. Ansell [g], T.S. Barton-Maclaren [b], S.H. Bennekou [h], K. Boekelheide [i], J. Ezendam [j], J. Field [b], S. Fitzpatrick [k], M. Hatao [l], R. Kreiling [m], M. Lorencini [n,1], C. Mahony [o], B. Montemayor [p], R. Mazaro-Costa [q], J. Oliveira [r], V. Rogiers [s], D. Smegal [k], R. Taalman [t], Y. Tokura [u], R. Verma [k], C. Willett [v], C. Yang [w]

What do we still need to do?

1. Increase **confidence** in exposure predictions (including metabolites)
2. Determine whether tools give us enough biological coverage
3. Be explicit about the level of **confidence** in the assessment
4. Develop **agreed standards** for using tools and reporting data
5. Distinguish between adaptation and adversity
6. Develop an updated risk assessment workflow
7. **More case studies**

Use of NGRA for decision making, sharing with regulators etc.

Regulatory Toxicology and Pharmacology 125 (2021) 105026

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Check for updates

Paving the way for application of next generation risk assessment to safety decision-making for cosmetic ingredients

M.P. Dent [a,*], E. Vaillancourt [b], R.S. Thomas [c], P.L. Carmichael [a], G. Ouedraogo [d], H. Kojima [e], J. Barroso [f], J. Ansell [g], T.S. Barton-Maclaren [b], S.H. Bennekou [h], K. Boekelheide [i], J. Ezendam [j], J. Field [b], S. Fitzpatrick [k], M. Hatao [l], R. Kreiling [m], M. Lorencini [n,1], C. Mahony [o], B. Montemayor [p], R. Mazaro-Costa [q], J. Oliveira [r], V. Rogiers [s], D. Smegal [k], R. Taalman [t], Y. Tokura [u], R. Verma [k], C. Willett [v], C. Yang [w]

New assessment paradigms need flexible regulatory frameworks

Conclusion

- Use of tiered, exposure-led approaches allows safety decisions to be made without animal test data
- The ICCR Principles help to formulate the problem and direct the assessment
- New regulatory frameworks are needed to make use of the best available safety science
- Our knowledge will never be complete, but we know enough to apply these approaches and to prevent unnecessary animal use

Acknowledgements

Julia Fentem
Maria Baltazar
Sophie Cable
Paul Carmichael
Richard Cubberley
Jade Houghton
Predrag Kukic
Sophie Malcomber
Alistair Middleton
Beate Nicol
Joe Reynolds
Sharon Scott
Ruth Pendlington
Katie Przybylak
Sandrine Spriggs
Carl Westmoreland
Andrew White
And many other members of Team SEAC

Unilever

Thank You

seac.unilever.com

Unilever