

# Development and Application in the use of NAMs for Next Generation Risk Assessment

## Learnings from Industry case studies

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Unilever

# Outline

- **What is NGRA?**
- **Examples of how it could be applied?**
- **How Protective is this?**

# The need for non-animal approaches



Societal Attitudes/Consumer Preference



Scientific Relevance

22.12.2009 EN Official Journal of the European Union L 342/59

**REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance)**

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Economic and Social Committee (1),

Acting in accordance with the procedure laid down in Article 2 of the Treaty (2),

Whereas:

(1) Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (3) has been significantly amended on several occasions. Since further amendments are to be made, in this particular case it should be recast as a Regulation.

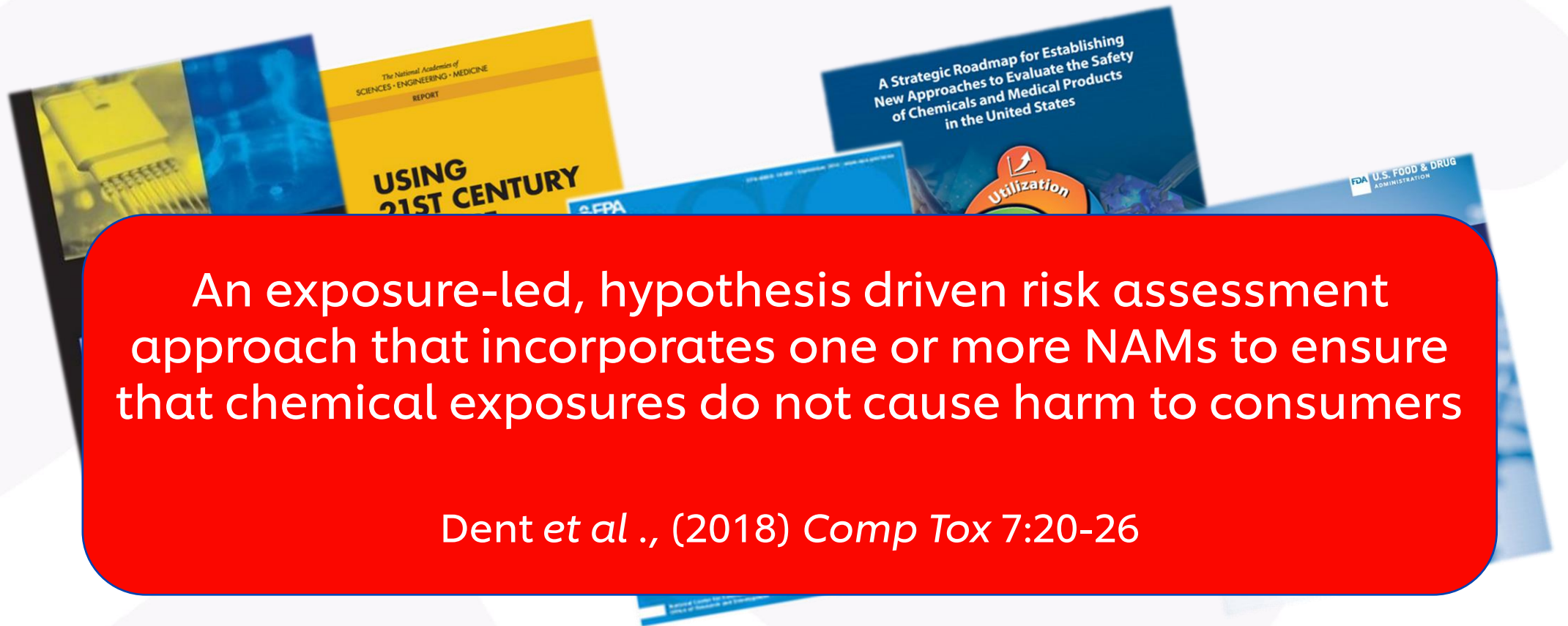
(5) The environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency (4), which enables the assessment of environmental risks in a cross-sectoral manner.

*Is it safe?*

The diagram illustrates the process of determining a safe dose for humans. It starts with 'Amount of ingredient due to exposure' leading to 'Targeted Testing' (represented by a microscope icon). This leads to 'Adverse Organism Response' (represented by a cell icon). From there, it goes to 'Species Extrapolation' (represented by a person icon) and finally to 'Safe Dose in Humans'. A box labeled 'NOAEL + 10-1000' is shown as an input to the extrapolation step. A red diagonal line with the text 'e.g. 90 Day Repeat Dose Study' is drawn across the diagram.

Regulatory Change

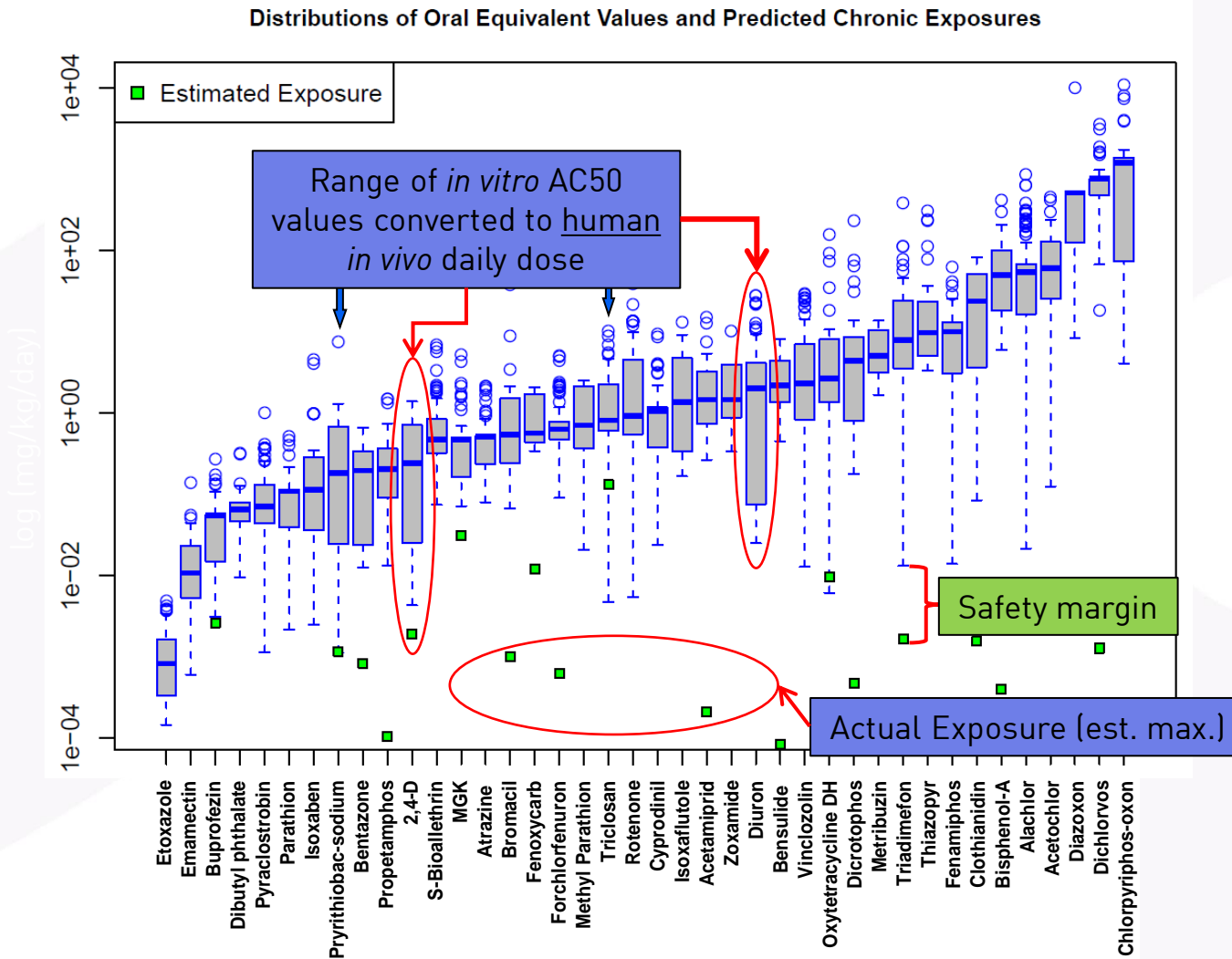
# What is NGRA?



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

# Paradigm shift for systemic safety - Protection not Prediction



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.**



Slide from Dr Rusty Thomas, EPA, with thanks

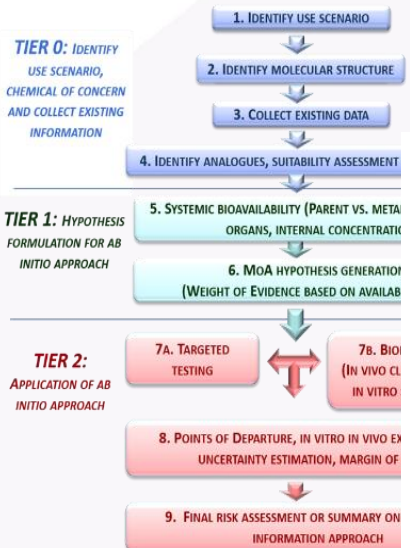
Rotroff, et al. Tox.Sci 2010

Thomas RS et al., 2019. Tox Sci. 1;169(2):317-332.

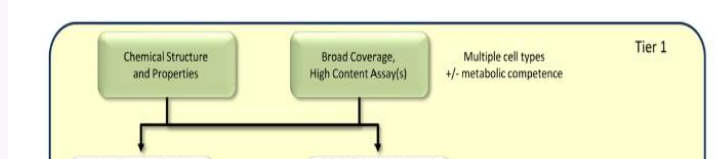




# Framework Approach: The overall goal is a human safety risk assessment



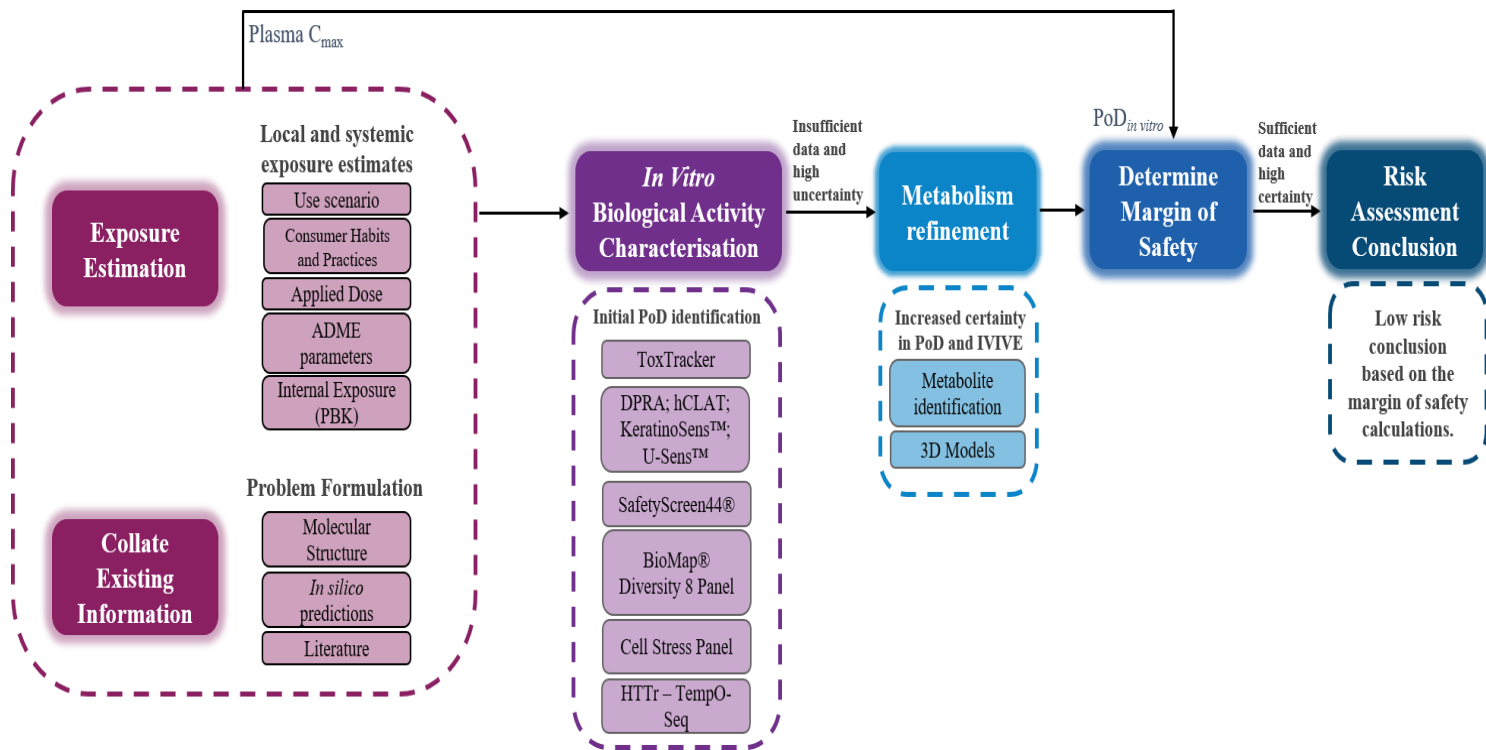
Berggren



## ICCR 9 principles of NGRA



## ICCR NINE PRINCIPLES OF NGRA



- principles:**
  - is a human safety risk assessment
  - is exposure led
  - is hypothesis driven
  - is designed to prevent harm
- define how a NGRA should be conducted:**
  - appropriate appraisal of existing information
  - iterative approach
  - relevant methods and strategies
- documenting NGRA:**
  - uncertainty should be characterized and documented
  - approach should be transparent and documented

Dent et al. 2018 Computational Toxicology, 7, 20-26.

# Case Study approach – Human Health Safety Assessment required for ...

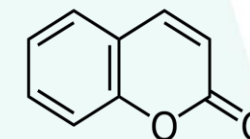
## 0.1% COUMARIN IN FACE CREAM

Can we safely use **x%** of ingredient **y** in product **z**?

### Assumed that:

- Coumarin was 100% pure
- no *in vivo* data was available such as animal data, History of Safe Use (HoSU) info. or Clinical data
- no use of animal data in Read Across
- *In silico* alerts known to be based on animal or *in vivo* data or on the structure of Coumarin itself were excluded

Problem Formulation



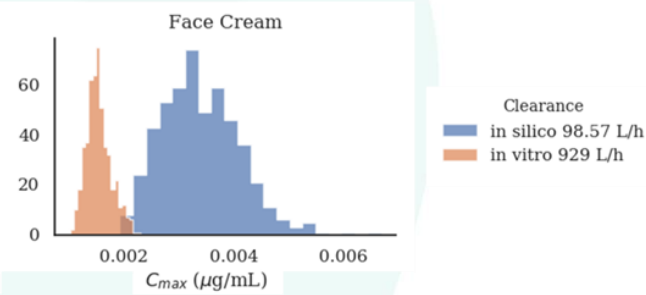
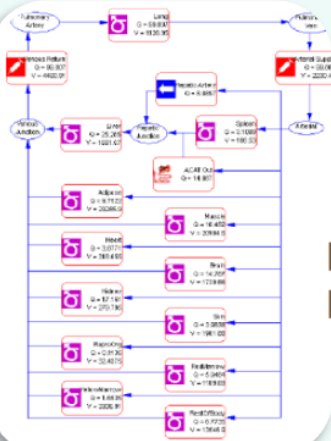
Exposure Led

All safety assessments of cosmetic ingredients are exposure-driven:

Baltazar et al., (2020) *Tox Sci* (vol 176: 236–252)  
<https://doi.org/10.1093/toxsci/kfaa048>

# Some key elements in the NGRA toolbox

## 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 Héran, 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 if discovered 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.

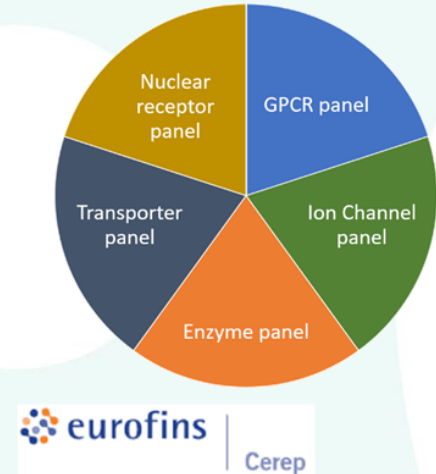
Decreasing the high attrition rate in the drug discovery and development process is a primary goal of the pharmaceutical industry. One of the main challenges in achieving this goal is striking an appropriate balance between drug efficacy and potential adverse effects as early as possible in order to reduce safety-related attrition, particularly in the more expensive late stages of clinical development. Gaining a 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 financial and regulatory costs of new clinical and regulatory submissions.

target (or targets), whereas 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 only *in vitro* pharmacology assay that is absolutely required by regulatory authorities is one that measures the effects of new chemical entities on the ionotropic calcium ( $Ca_v1$ ) or heteromultimeric expressed human voltage-gated potassium channel subfamily B member 2 (hKCNH2), also known as hERG. The mechanism by which blockade of hERG can elicit potentially fatal cardiac arrhythmias (torsades de pointes) following a prolongation of the QT interval is well characterized<sup>1,2</sup>, 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 entities<sup>3</sup>. 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, the general need for most 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 discuss their production and to

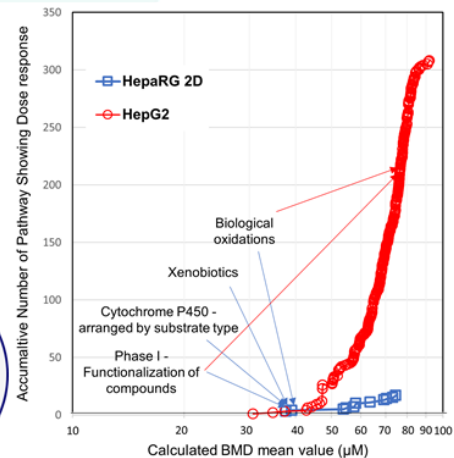
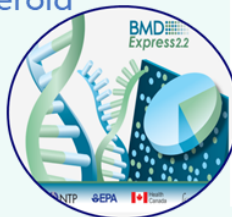


eurolins | Cerep

## Transcriptomics

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

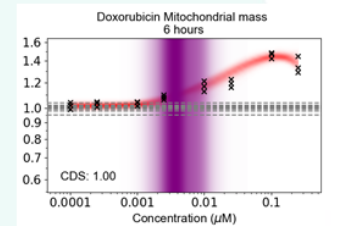
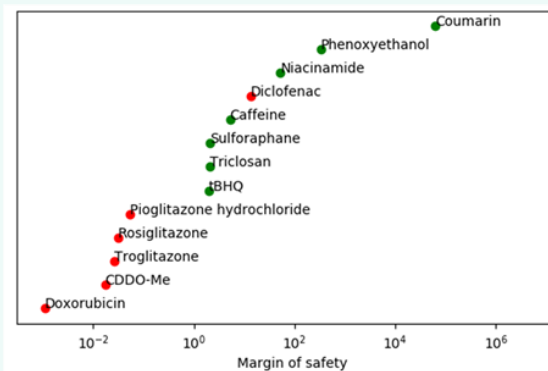
## BMDexpress 2



## Cellular Stress Pathways

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

- Exposure scenario adopted for chemical is 'low risk'** (from consumer goods perspective)
- Nicotinamide (food, cosmetics)
  - Caffeine (beverages, cosmetics)
  - Phenoxethanol (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



# NGRA for 0.1% coumarin in face cream: exposure estimation

Exposure Estimation

Local and systemic exposure estimates

- Use scenario
- Consumer Habits and Practices
- Applied Dose
- ADME parameters
- Internal Exposure (PBK)



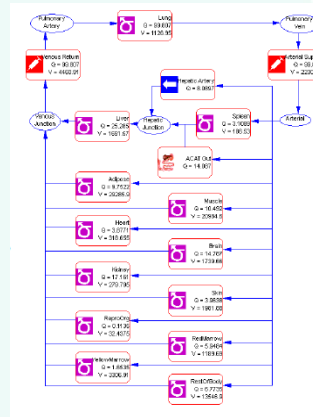
Table 2: Estimated daily exposure levels for different cosmetic product types according to Consumer Europe data (SCENARIOS 1/01; Hall et al., 2007, 2011).

| Product type              | Estimated daily amount applied (mg/d) | Relative absorption (%) | Relative exposure (mg/d) | Relative exposure (mg/d) |
|---------------------------|---------------------------------------|-------------------------|--------------------------|--------------------------|
| <b>Bathing, showering</b> |                                       |                         |                          |                          |
| Shower gel                | 18.67 g                               | 279.23                  | 0.01                     | 0.19                     |
| Hand water soap           | 70.00 g                               | 0.01                    | 0.20                     | 1.33                     |
| <b>Hair care</b>          |                                       |                         |                          |                          |
| Conditioner               | 10.11                                 |                         | 0.11                     | 1.51                     |



B. Hall et al./Food and Chemical Toxicology 49 (2011) 408–422

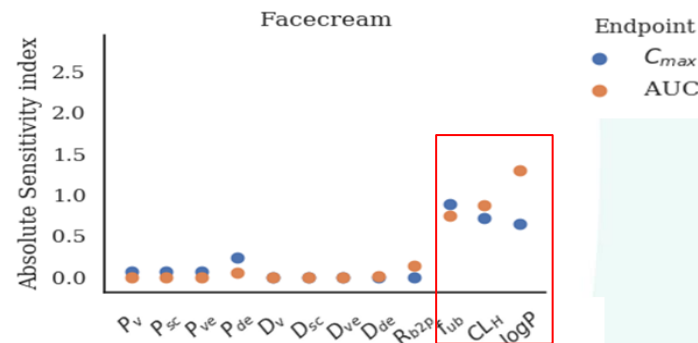
## GastroPlus® (Simulations Plus)



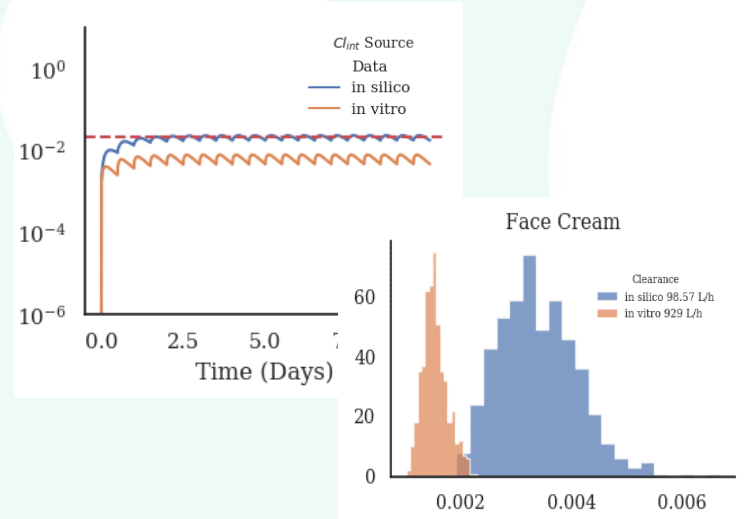
Physico-Chemical & ADME parameters

ADMET Predictor

- Hepatic Clearance rate
- ECCS Class
- logP,  $f_{ub}$ ,  $R_{bp}$  etc.
- Skin penetration parameters



## Level 2- Simulated plasma concentration of coumarin after dermal exposure.



Level 2. Uncertainty and population variability  
Distribution of  $C_{max}$  values after performing Monte Carlo simulation.

| Total Plasma $C_{max}$ ( $\mu$ M) | Mean   | Median | 90th percentile | 95th percentile | 97.5th percentile | 99th percentile |
|-----------------------------------|--------|--------|-----------------|-----------------|-------------------|-----------------|
| <b>Face Cream</b>                 | 0.0022 | 0.0021 | 0.004           | 0.0043          | 0.0046            | 0.005           |

**In Vitro Biological Activity Characterization**

- Initial PoD identification
- ToxTracker®
- DPRA, hCLAT, KeratinoSens™, U-Sens™
- SafetyScreen44®**
- BioMap® Diversity 8 Panel
- Cell Stress Panel
- HTTr – TempO-Seq

# NGRA for 0.1% coumarin in face cream: In vitro biological activity characterisation: In vitro binding and enzymatic assays: Eurofins SafetyScreen44

**To investigate possible interactions between coumarin and the 44 key targets involved in drug attrition**

## 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*

**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 if discovered 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<sup>1</sup> as early as possible in order to reduce safety-related attrition, particularly in the more expensive late stages of clinical development. Gaining a 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, bearing in mind the growing societal and regulatory emphasis

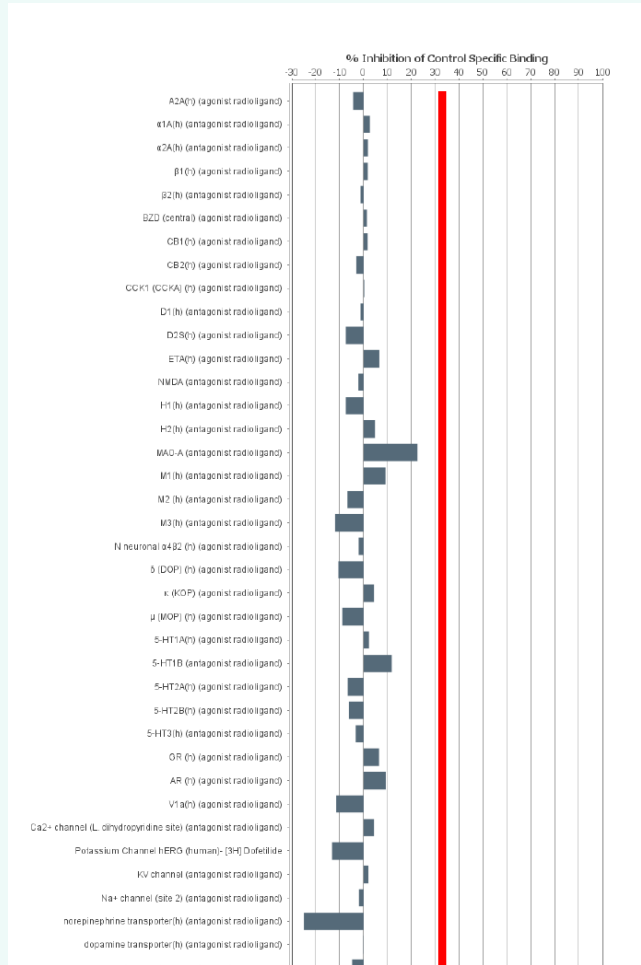
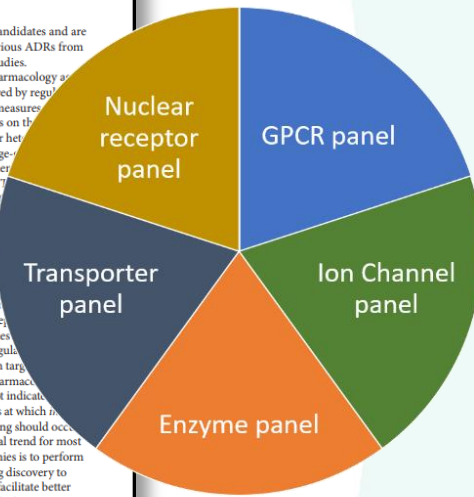
target (or targets), whereas secondary effects are due to interactions with targets other than the primary target (or targets) (that is, off-target interactions). Off-target interactions are often the cause of ADRs in animal models or clinical studies, and so careful characterization and identification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

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The only *in vitro* pharmacology assay that is absolutely required by regulatory authorities is one that measures the current of native ( $I_{Na}$ ) or heterologously expressed human voltage-gated sodium channel subfamily H member 1 (hNav1.5), also known as hERG<sup>2</sup>, which blockade of hERG is a potentially fatal cardiac arrhythmia (long QT syndrome) following a QT interval is well characterized. The seriousness of this ADR is such that this assay is a mandatory part of the assessment of the drug candidate. However, current regulatory guidance does not describe which targets should constitute an *in vitro* pharmacological profiling panel and does not indicate the extent of the discovery process at which *in vitro* pharmacological profiling should occur. Nevertheless, the general trend for most pharmaceutical companies is 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 experiences 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 discuss best practices and to

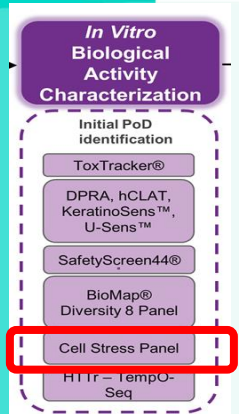


**Results:**

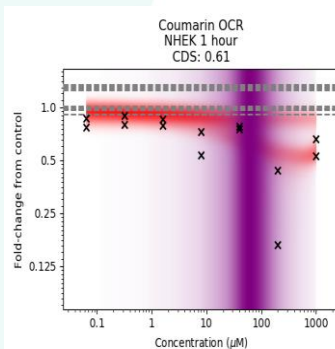
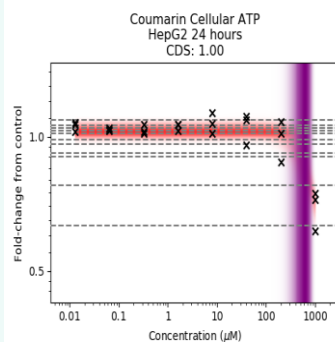
**All binding and enzymatic assay results were negative at 10 μM**

# In vitro biological activity characterisation: In vitro cell stress panel

- Cellular stress response assays are useful to **characterize non-specific biological activity** which is not mediated via a specific protein/receptor interaction
- Measures a range of biomarkers covering **~10 cell stress pathways**
- Single exposure; 8 concentrations; 1h, 6h & 24hr timepoints; HepG2 & NHEK cells



- **Mitochondrial Toxicity:** MitoSOX, PGC1 $\alpha$ , MMP, ATP, Glu/Gal
- **Oxidative Stress:** GSH, ROS, SRXN1, NRF2
- **DNA damage:** p $H2AX$ , p53
- **Inflammation:** TNFAIP3, ICAM1, NF $\kappa$ B p65, IL-1 $\beta$ , IL-8, HMGB1
- **ER Stress:** PERK, ATF4, CHOP, XBP1, BiP, ER Tracker
- **Metal Stress:** MTF-1, Metallothionein
- **Osmotic Stress** (NFAT5);
- **Heat Shock** (HSP70);
- **Hypoxia** (HIF1 $\alpha$ )
- **Cell Health:** LDH, Phospholipidosis, Steatosis, pH rodo indicator, apoptosis (caspase-3/7) & necrosis (ToPro-3)



| Biomarkers                    | Cell type | Stress pathway         | PoD (µM)       | Effect | Concentration dependency score (CDS) |
|-------------------------------|-----------|------------------------|----------------|--------|--------------------------------------|
| <b>ATP (6h)</b>               | HepG2     | cell health            | 794 (363-977)  | down   | 0.98                                 |
| <b>ATP (24h)</b>              | HepG2     |                        | 617 (282-891)  | down   | 1                                    |
| <b>Phospholipidosis (24h)</b> | HepG2     | cell health            | 759 (437-977)  | down   | 0.93                                 |
| <b>GSH (24h)</b>              | HepG2     | oxidative stress       | 851 (301-1000) | up     | 0.92                                 |
| <b>IL-8 (24h)</b>             | HepG2     | inflammation           | 912 (575-1000) | down   | 0.61                                 |
| <b>OCR (1h)</b>               | NHEK      | mitochondrial toxicity | 62 (2.6-776)   | down   | 0.6                                  |
| <b>OCR (6h)</b>               |           |                        | 468 (214-794)  |        | 1                                    |
| <b>OCR (24h)</b>              |           |                        | 309 (138-1000) |        | 0.52                                 |
| <b>Reserve capacity (1h)</b>  | NHEK      | mitochondrial toxicity | 44 (23-96)     | down   | 1                                    |
| <b>Reserve capacity (6h)</b>  |           |                        | 759 (302-1000) |        | 0.9                                  |
| <b>Reserve capacity (24h)</b> |           |                        | 794 (295-1000) |        | 0.55                                 |

**In Vitro Biological Activity Characterization**

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- SafetyScreen44®
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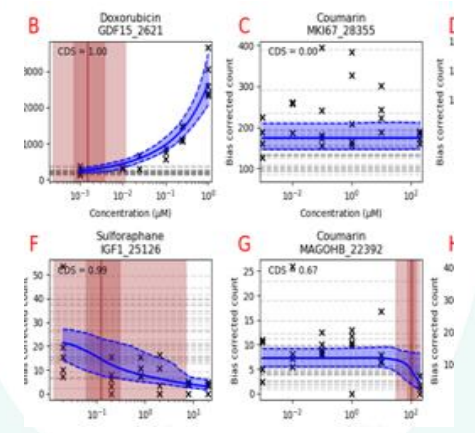
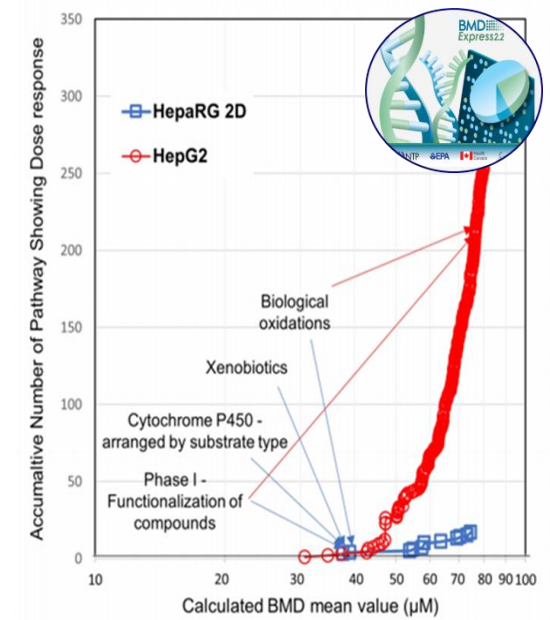
# In vitro biological activity: High-Throughput Transcriptomics (HTTr)

**Provide screen for biological activity across a broad biological coverage**

- *Tempo-Seq*
- *Human gene panel ver1 ~ 21k*
- *3 cell lines*

**Results:**

- The MCF7 PoD<sub>T</sub> were not considered to be sufficiently robust to derive a MoS
- The lowest PoD<sub>T</sub> for each cell model was selected for the MoS calculation



| Cell model   | HepG2          | MCF7         | HepaRG 2D     |
|--|----------------|--------------|---------------|
| Pathway level tests PoD <sub>T</sub> (μM)  | (308 pathways) | (0 pathways) | (17 pathways) |
| 20 pathways with the lowest p value Reactome                                       | 70             | NA           | 58*           |
| 20 pathways with the lowest BMD Reactome   | 44             | NA           | 58*           |
| BMD of Reactome pathway with lowest BMD that meets significance threshold criteria | 31             | NA           | 38            |
| Gene level tests PoD <sub>T</sub> (μM)   | (1570 genes)   | (47 genes)   | (87 genes)    |
| Mean BMD of 20 genes with largest fold change                                      | 6              | 3            | 54            |
| Mean BMD of genes between 25 <sup>th</sup> and 75 <sup>th</sup> percentile         | 17             | 1            | 59            |





# Tier 2 refinement: Metabolism prediction and activity

Metabolism refinement

Increased certainty in PoD and IVIVE

Metabolite identification

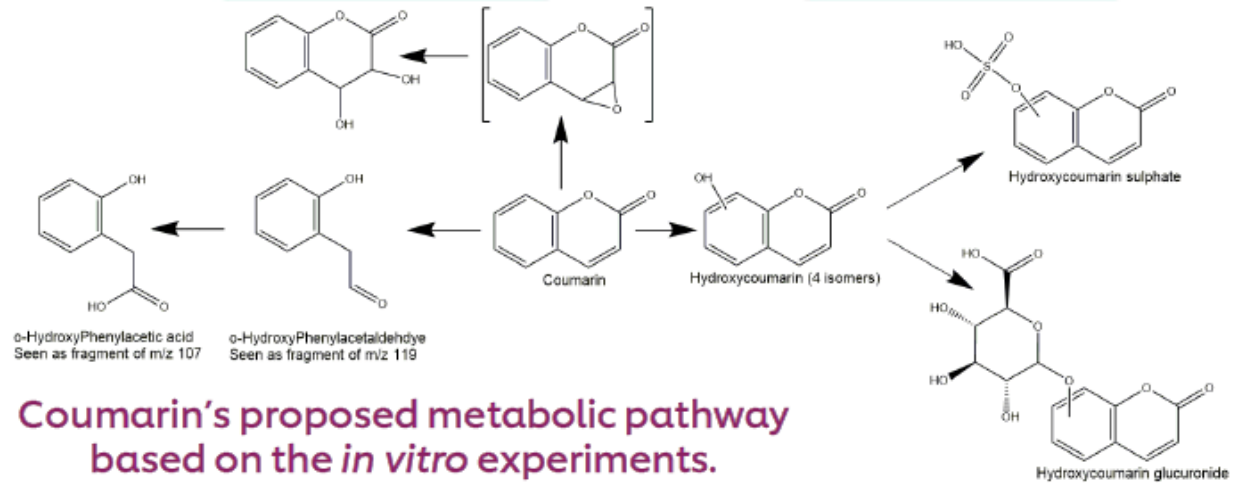
3D Models



Human *In vitro* metabolism



Cell stress & HTTr in 3D HepaRG models



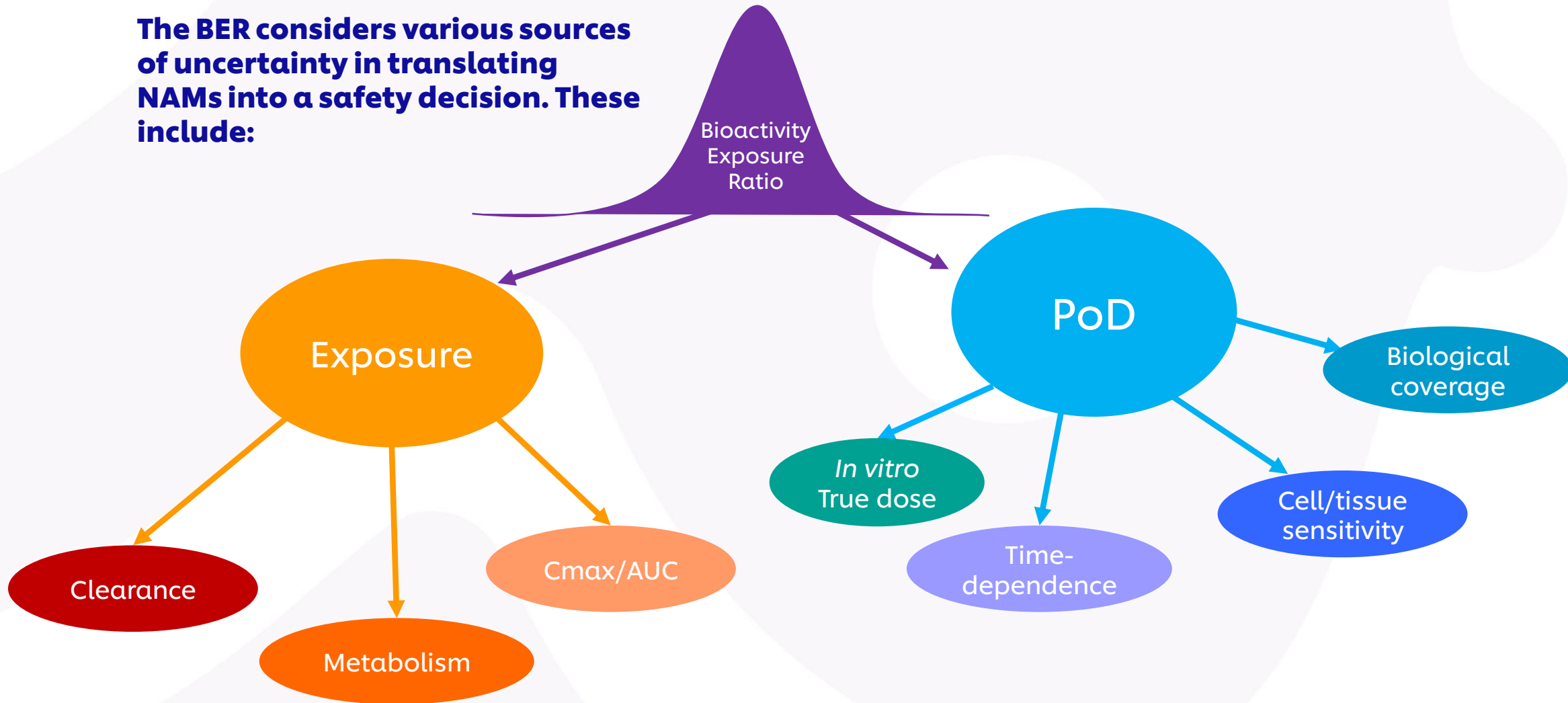
- Low bioactivity also found in a metabolic competent cell model (HepaRG 3D)
- PoDs range: 41-871  $\mu\text{M}$  – not very different from 2D cells





# Integrating Exposure and Bioactivity Data from NAMs to Make Safety Decisions

The BER considers various sources of uncertainty in translating NAMs into a safety decision. These include:



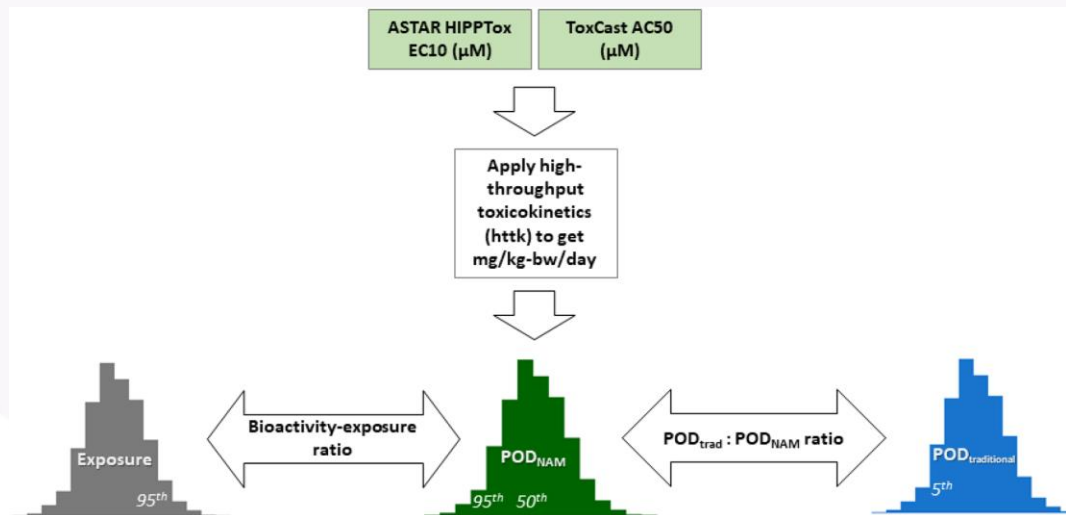
# How protective are the NAMs?

## Example from the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative



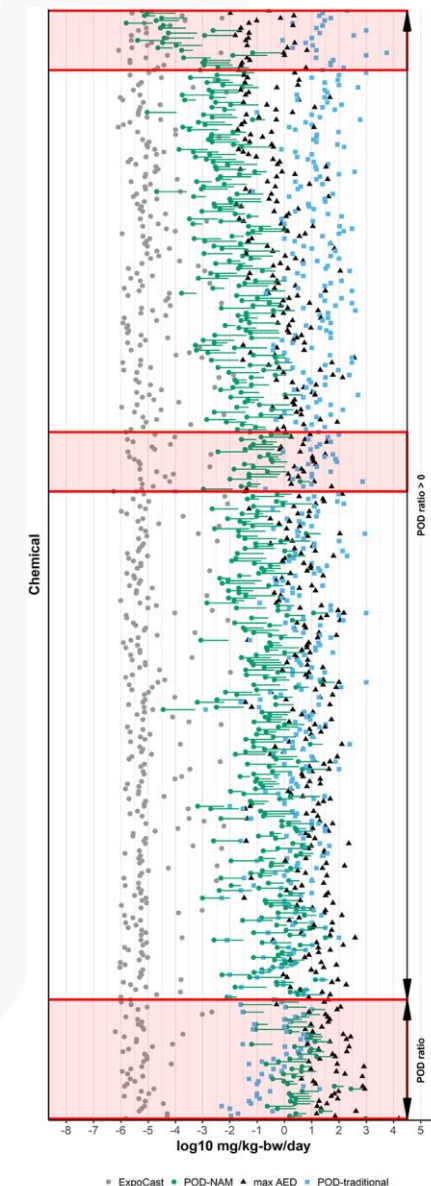
### Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

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



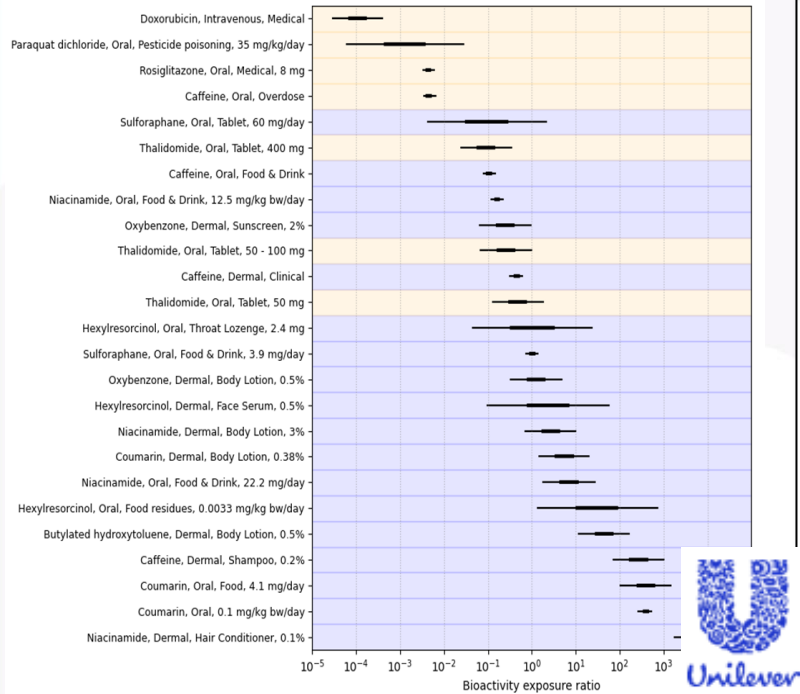
Of the 448 substances, 89% had a  $POD_{NAM,95}$  that was less than the traditional  $POD$  ( $POD_{traditional}$ ) value.

Bioactivity:exposure ratios (BERs), useful for identification of priority substances, demonstrated that high-throughput exposure predictions were greater than the  $POD_{NAM,95}$  for 11 substances.



# Examples of ongoing or completed case studies for NAM/NGRA based risk assessment or prioritisation

>85 scenarios  
Pilot + Full study



Benchmark BER against risk category for each exposure scenario

46 compounds

Science Approach Document

Bioactivity Exposure Ratio:  
Application in Priority Setting and Risk Assessment

Health Canada

March 2021

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

30 compounds

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 Testi  
No. 349

>22 compounds

EUTOXRISK  
EU-ToxRisk  
An Integrated European 'Flagship' Program  
Driving Mechanism-based Toxicity Testing and Risk Assessment  
for the 21<sup>st</sup> Century

Case Study 16 Reporting Template

Team: 2  
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Compound ID: CS\_16-02  
Compound Name: (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)iodoacetate; TEMPOL

Structure:

Other Identifiers: CAS ID 2226-96-2; CHE

Ab Initio Case Study Objectives

- Scientific Objectives:
  - Establish ability of NAM to explore a range of hypotheses for risk assessment
  - Ensure that a risk assessment for case study chemicals based on non-determined evidence is robust to a range of hypotheses for the mechanism of action
  - Identify address uncertainties within the risk assessment such that they can be fully resolved
  - Determine the extent to which the use of NAMs can be substantially justified in place of repeated toxicological testing
- People Objectives:
  - Establish risk assessment expertise in progress in diverse roles, that of whom are not currently conducting risk assessments in their day to day work
  - Supporting applying NAM data and methods to broader testing scenarios
  - Supporting testing from laboratory to in vivo to help complete risk assessment decisions



# Summary

- Exposure-led approach to determine protection through a BER (MoS)
- Focus on weight of evidence to show tools can be integrated to make a safety decision - requires diverse expertise
- Strength derived from a combination of targeted and broad unbiased tools – hypothesis led
- NAMs not standard - need to ensure robustness/quality of tools and include estimations of uncertainty to aid acceptance
- Utilise NAMs for further targeted follow where required to refine uncertainty e.g. metabolism
- Further evaluation, additional case studies internal/ in collaboration eg EPA, CosEU, EU-ToxRisk – as well as APCRA
- Dissemination required to progress assessment and build out confidence for broader stakeholder community on applicability domains/ remaining gaps



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