

# Embracing innovative toxicological science to transform regulatory assessments of chemical safety

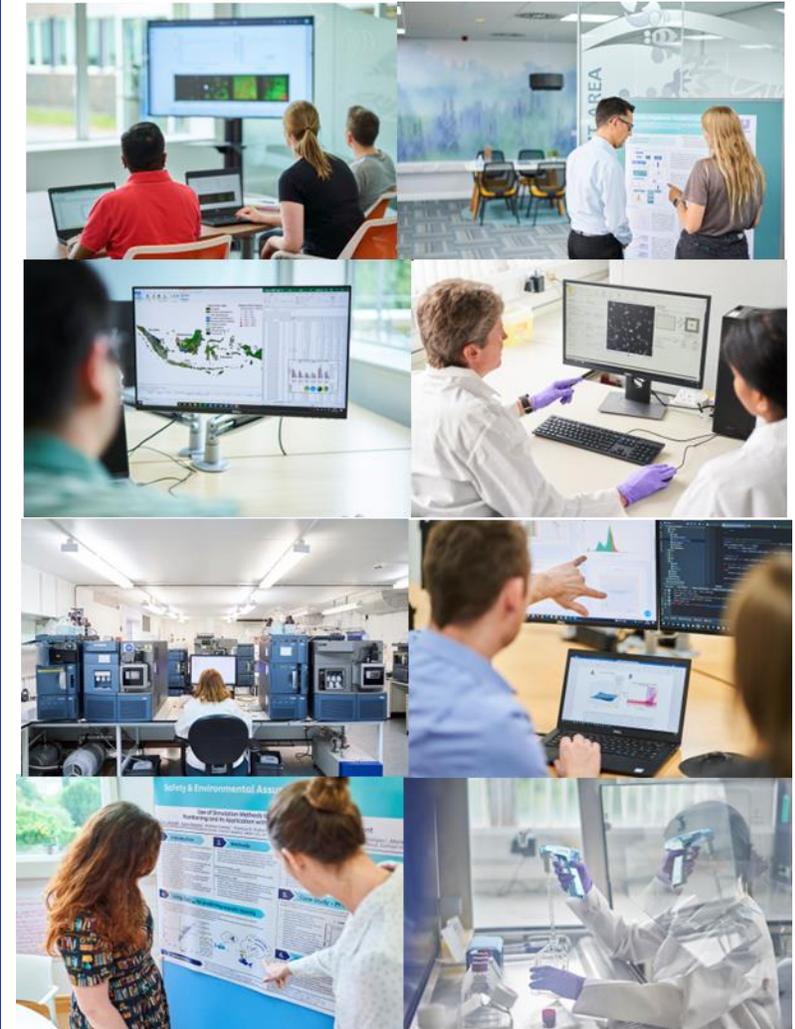
Dr Julia Fentem MBE FBTS

BTS Paton Prize Award Lecture – April 2024



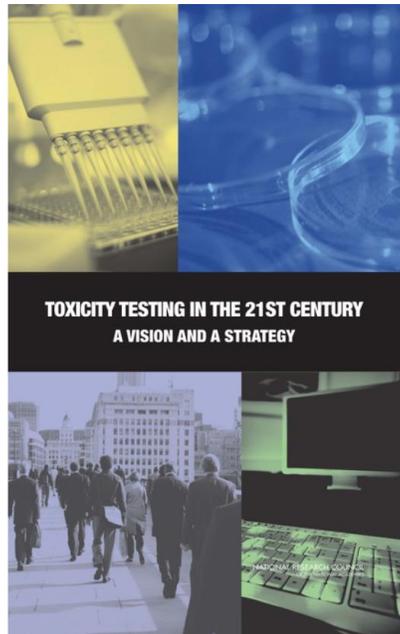
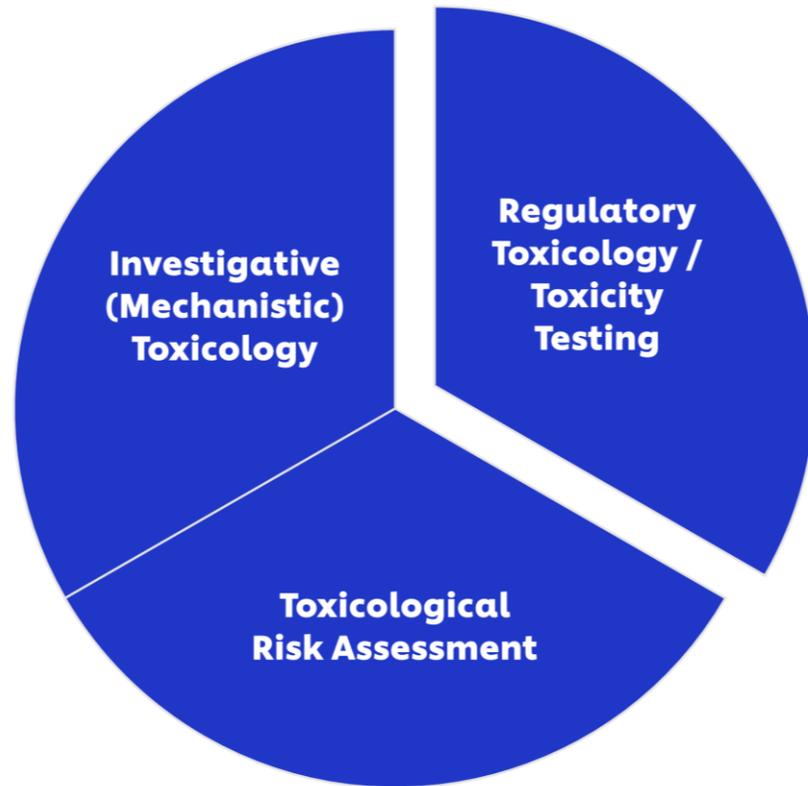
## Acknowledgement:

>80 toxicologists, biologists, chemists, computational modellers, data scientists & exposure / risk assessors in Unilever's Safety & Environmental Assurance Centre (SEAC)



# “Mind the Gap”: 21<sup>st</sup> century safety science, 20<sup>th</sup> century regulatory testing

**Data-driven toxicological safety decisions  
to protect people & the environment**



June 18, 2021, 9:01AM GMT+1

## Law—Not Science—Impedes Shift to Non-Animal Safety Testing



**Gary Marchant**

Sandra Day O'Connor College of Law

## Upholding the EU's Commitment to 'Animal Testing as a Last Resort' Under REACH Requires a Paradigm Shift in How We Assess Chemical Safety to Close the Gap Between Regulatory Testing and Modern Safety Science

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

Alternatives to Laboratory Animals  
2021, Vol. 49(4) 122–132  
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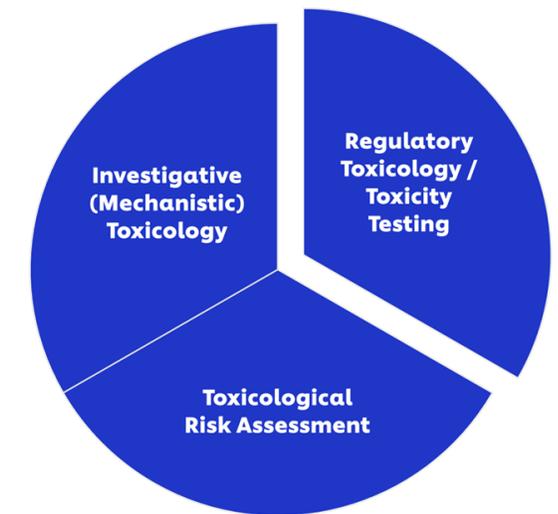
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DOI: 10.1177/02611929211040824  
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**Closing the gap requires investment in new regulatory science capability and use of modern scientific methods & new types of data for regulatory purposes**

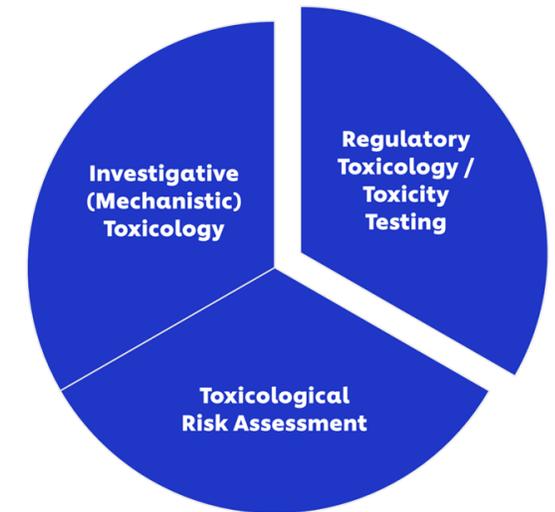
## Overview – toxicological risk assessment: more science, less art

- **Scientifically, is that the best we can do?**
  - A biochemist's first view of a chronic rodent toxicity study
- **Re-thinking consumer safety decision-making**
  - Responding to a ban on animal testing for cosmetics
- **A new scientific paradigm rooted in human biology**
  - Shaping 'next generation' risk assessment (NGRA) approaches
- **Advocating for regulatory change**
  - Applying innovative toxicological science in chemical safety dossiers

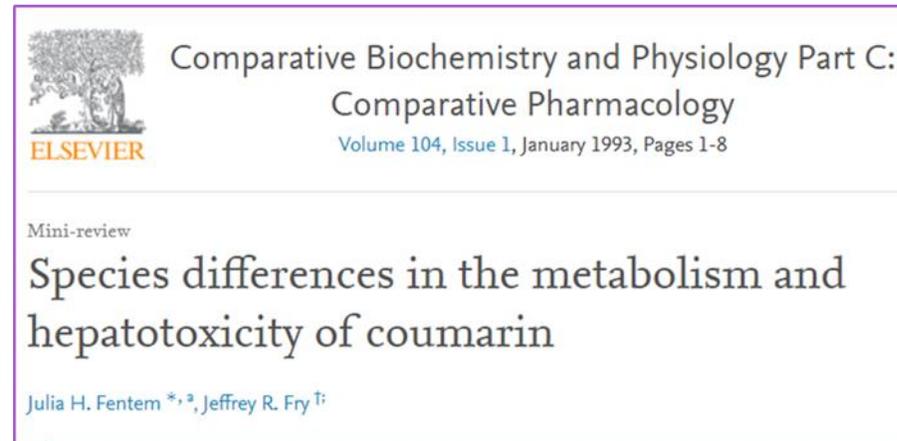
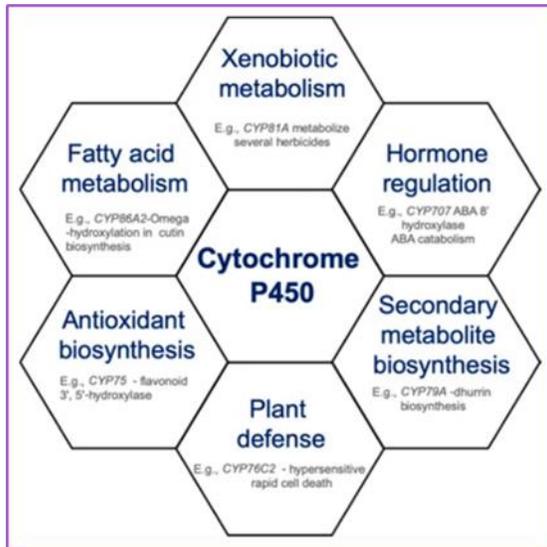


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# Cytochrome P450, metabolism-mediated toxicity & re-thinking risk assessment frameworks with our new safety science toolbox



## JOURNAL ARTICLE

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



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

*Toxicological Sciences*, Volume 176, Issue 1, July 2020, Pages 236–252,  
<https://doi.org/10.1093/toxsci/kfaa048>

**Published:** 10 April 2020



# MSc Toxicology - is this substance likely to cause reproductive or developmental effects in humans and at what exposure levels?

## Test conditions

Type of study	teratology segment II including rearing group
GLP	yes
Animal species	rat
Route of administration	oral
Method of administration	gavage
Dose levels (mg/kg bodyweight)	0, 0.7, 2.0, 6.0, 15.0
Days of treatment during pregnancy (TDP)	7-16 (evidence of mating = day 1)
Number of animals per group	21, 19, 17, 23 (C-section)

## Maternal toxicity

Dose (mg/kg)	Effect
0-15	↘ bw, TDP11-15 (females of rearing group only)

## Prenatal developmental toxicity, gestational parameters

Dose (mg/kg)	Effect	Mean % by Litter
15	↗ postimplantation loss	34.5 1.8 -

## Prenatal developmental toxicity, foetal growth parameters

Dose (mg/kg)	Effect	Change towards control %
15	↘ foetal wt	20

## Prenatal developmental toxicity, external effects

Dose (mg/kg)	Effects	Incidence of effects (%)					
		Foetal basis			Litter basis		
		Test	Cont.	Hist.	Test	Cont.	Hist.
15	cleft palate	60.9	0	<0.01	87.5	0	<0.01
	exencephaly	50.3	0	<0.01	75.0	0	<0.01
	spina bifida	3.1	0	<0.01	18.8	0	<0.01
	open eyes	16.8	0	<0.01	56.3	0	<0.01

Test = Treated animals; Cont. = Control; Hist. = Historical controls

## Prenatal developmental toxicity, skeletal effects

Dose (mg/kg)	Effects	Incidence of effects (%)					
		Foetal basis			Litter basis		
		Test	Cont.	Hist.	Test	Cont.	Hist.
6	occipital bone, incised and/or bipartite	4.6	0	0-0.2	18.2	0	0-1.2
	vertebral arches cervical, bipartite	8.3	4.2	0-25.0*	36.4	22.2	
	rib, supernumerary (14th)	41.7	6.3	0-29.3	90.9	33.3	
15	not examined						

Test = Treated animals; Cont. = Control; Hist. = Historical controls

\* includes split neural arches at cervical/ thoracic/ lumbar location

## Litters and foetuses examined

	Foetuses	
	Visceral	Skeletal
	99	96
	95	101
	87	84
	123	108
	-	-

Pups surviving weaning N (%)
83 (96.5)
90 (93.8)
89 (96.7)
57 (67.9)
0

- Species relevance?
- Dose extrapolation?
- Data reproducibility?
- Mechanistic understanding?
- Uncertainty factors?

*Guidance on Evaluation of  
Reproductive Toxicity Data*



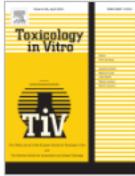
Monograph No. 31

# MSc Toxicology – developing new models & mechanistic insights



## Toxicology in Vitro

Volume 4, Issues 4–5, 1990, Pages 452-457



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Session 3

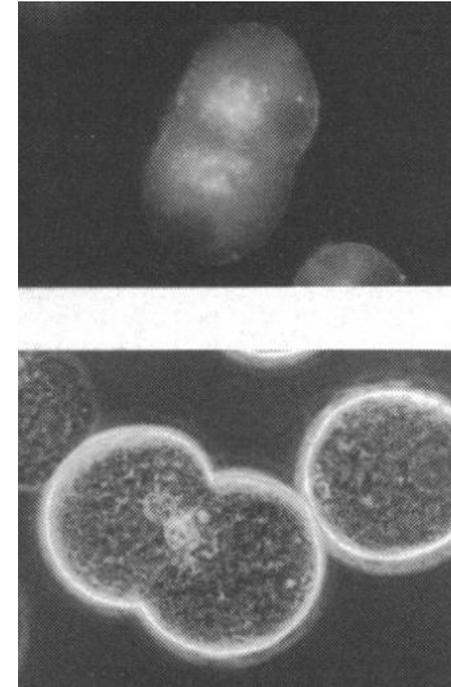
## Biliary excretion of fluorescent cholephiles in hepatocyte couplets: An *in vitro* model for hepatobiliary and hepatotoxicity studies

J.H. Fentem<sup>a\*</sup>, B. Foster<sup>a†</sup>, C.O. Mills<sup>‡</sup>, R. Coleman<sup>a</sup>, J.K. Chipman<sup>a</sup>

<sup>a</sup> Department of Biochemistry, University of Birmingham, UK  
<sup>‡</sup> Department of Medicine, University of Birmingham, UK



UNIVERSITY OF  
BIRMINGHAM



# PhD Biochemical Toxicology – metabolism & hepatotoxicity of coumarin



Comparative Study > Xenobiotica. 1991 Jul;21(7):895-904. doi: 10.3109/00498259109039529.

## Comparison of the effects of inducers of cytochrome P450 on Mongolian gerbil and rat hepatic microsomal monooxygenase activities

J H Fentem <sup>1</sup>, J R Fry

Affiliations

### Affiliation

<sup>1</sup> Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham, UK.

Comparative Study > Biochem Biophys Res Commun. 1991 Aug 30;179(1):197-203. doi: 10.1016/0006-291x(91)91354-f.

## O-hydroxyphenylacetaldehyde: a major novel metabolite of coumarin formed by rat, gerbil and human liver microsomes

J H Fentem <sup>1</sup>, J R Fry, D A Whiting

Affiliations

### Affiliation

<sup>1</sup> Department of Physiology & Pharmacology, University of Nottingham, U.K.

# Alternatives to animal testing for acute toxic effects of chemicals

- validation of *in vitro* tests for eye irritation, skin corrosion & skin irritation
- OECD test guidelines
- regulatory use for:
  - hazard identification & characterisation
  - classification & labelling

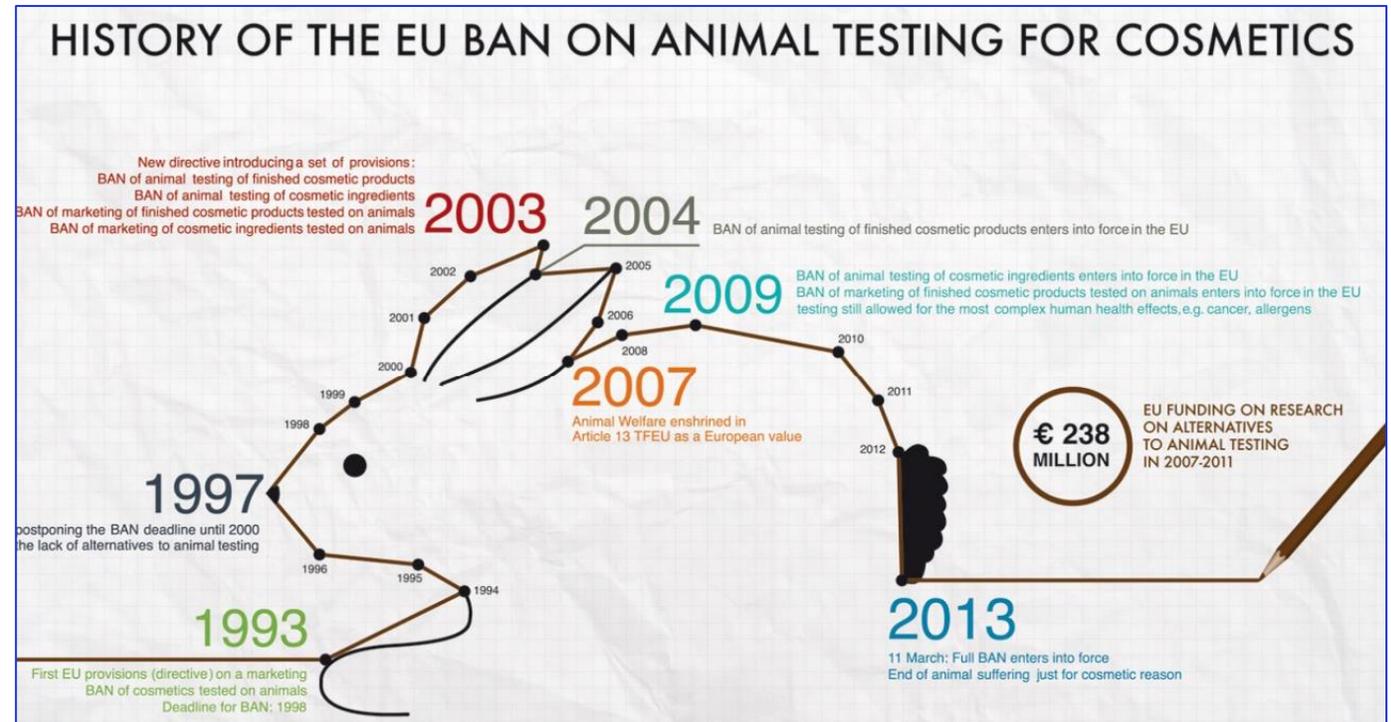


**How to use new or revised *in vitro* test methods to address Serious eye damage/Eye irritation**

(Revised in February 2018)

# Assuring safety of cosmetics ingredients & products without animal testing

- legislative bans on animal testing of cosmetics in 45 countries
- full EU ban implemented via 2013 Cosmetics Regulation (consumer safety)
- 2003 EU Directive implementing bans from 2009 (local effects) & 2013 (all toxicological endpoints) stimulated investment in non-animal approaches & accelerated use for safety assessment



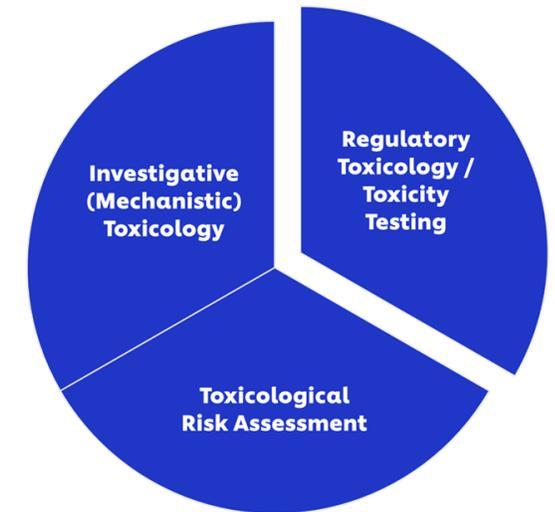
FACTSHEET | 11 March 2013

History of the EU ban on animal testing for cosmetics

[Ban on animal testing - European Commission \(europa.eu\)](http://europa.eu)

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# Unilever's "Assuring Safety without Animal Testing" research since 2004 re-thinking consumer safety decision-making

> [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<sup>1</sup>, Mark Chamberlain, Bart Sangster

Affiliations: [— collapse](#)

### Affiliation

<sup>1</sup> SEAC, Unilever Colworth Laboratory, Sharnbrook, Bedfordshire MK44 1LQ, UK.

### Safety assessment — future needs

- consumer safety decisions without animal testing
  - based on scientific risk assessment
  - improve relevant fundamental biological understanding
  - bring experimental biology/toxicology and clinical medicine closer together (in context of human health risk assessment)
  - improve *in vitro* models (tissue engineering)
  - apply omics/other new technologies as appropriate
  - develop *in silico* modelling tools
  - move to a computational “systems biology” approach

> [Altern Lab Anim.](#) 2006 Feb;34(1):11-8. doi: 10.1177/026119290603400116.

## Working together to respond to the challenges of EU policy to replace animal testing

Julia H Fentem<sup>1</sup>

# Developing new mechanistic understanding, a new toolbox & new exposure-driven safety risk assessment frameworks

Assuring safety without animal testing: Unilever's ongoing research programme to deliver novel ways to assure consumer safety.

Westmoreland C <sup>1</sup>, Carmichael P, Dent M, Fentem J, MacKay C, Maxwell G, Pease C, Reynolds F

[Author information](#) ▶

ALTEX, 01 Jan 2010, 27(3):61-65  
PMID: 21113564

*Assuring consumer safety without the generation of new animal data is currently a considerable challenge. However, through the application of new technologies and the further development of risk-based approaches for safety assessment, we remain confident it is ultimately achievable. For many complex, multi-organ consumer safety endpoints, the development, evaluation and application of new, non-animal approaches is hampered by a lack of biological understanding of the underlying mechanistic processes involved. The enormity of this scientific challenge should not be underestimated.*

*To tackle this challenge a substantial research programme was initiated by Unilever in 2004 to critically evaluate the feasibility of a new conceptual approach based upon the following key components:*

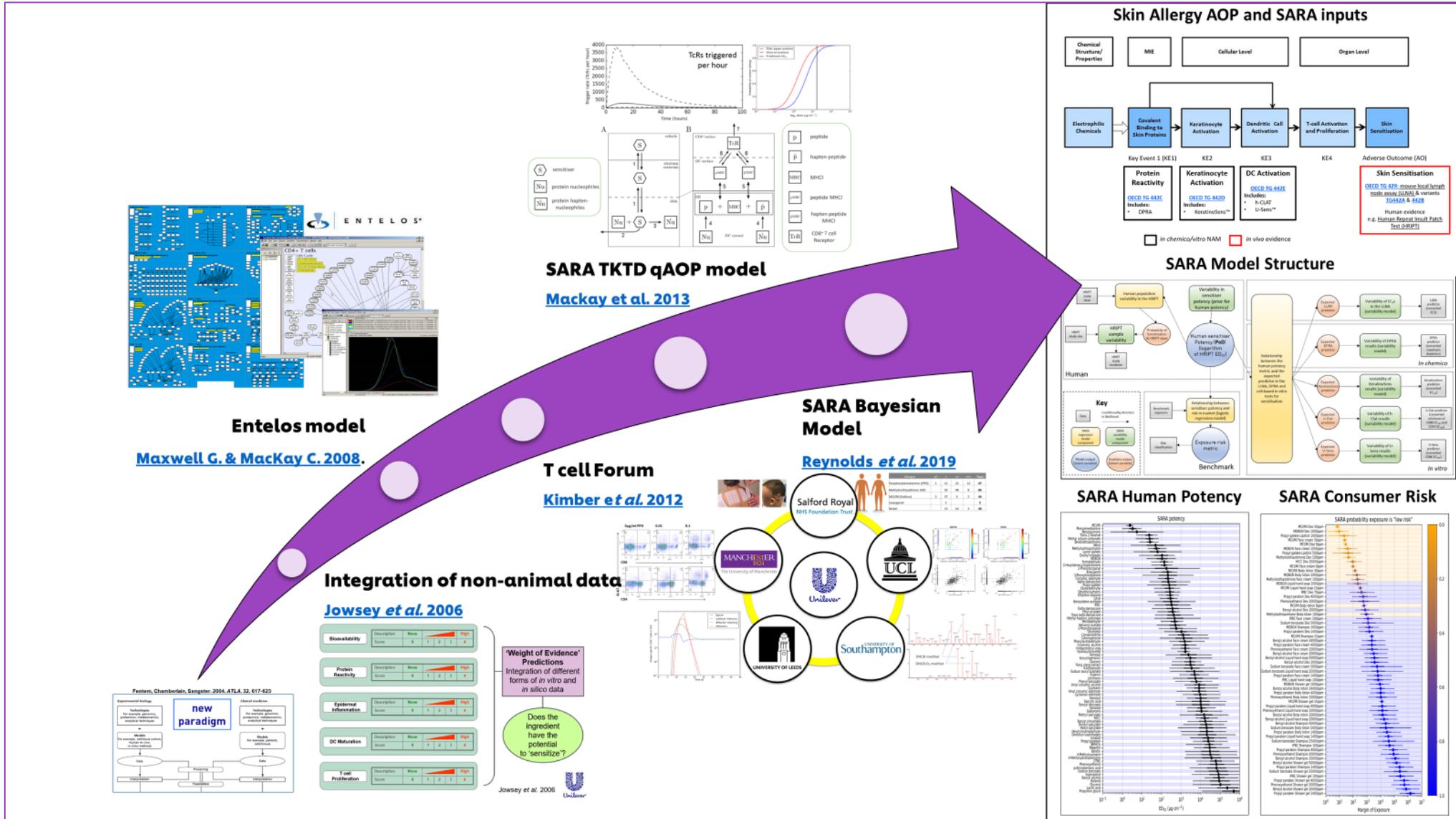
- 1. Developing new, exposure-driven risk assessment approaches*
- 2. Developing new biological (in vitro) and computer-based (in silico) predictive models*
- 3. Evaluating the applicability of new technologies for generating data (e.g. “omics”, informatics) and for integrating new types of data (e.g. systems approaches) for risk-based safety assessment*

*Our research efforts are focussed in the priority areas of skin allergy, cancer and general toxicity (including inhaled toxicity). In all of these areas, a long-term investment is essential to increase the scientific understanding of the underlying biology and molecular mechanisms that we believe will ultimately form a sound basis for novel risk assessment approaches.*

# Collaborating to modernise the scientific data & tools we use for making safety decisions – 20 years of research & evaluation



# Transforming our approach for Skin Allergy Risk Assessment (SARA)



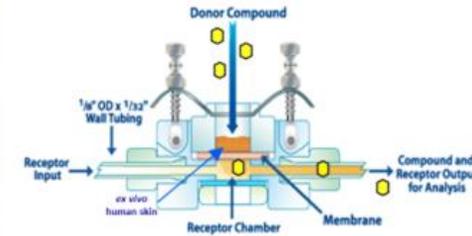
# Assessing consumer safety of cosmetics ingredients without new animal testing – maximising use of existing information & non-animal approaches

- All our risk assessments are exposure-led

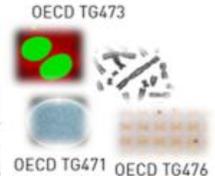
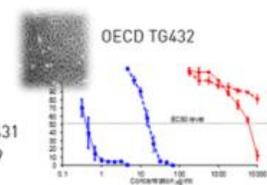
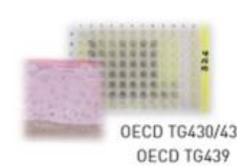
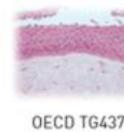


Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall et al., 2007, 2011).

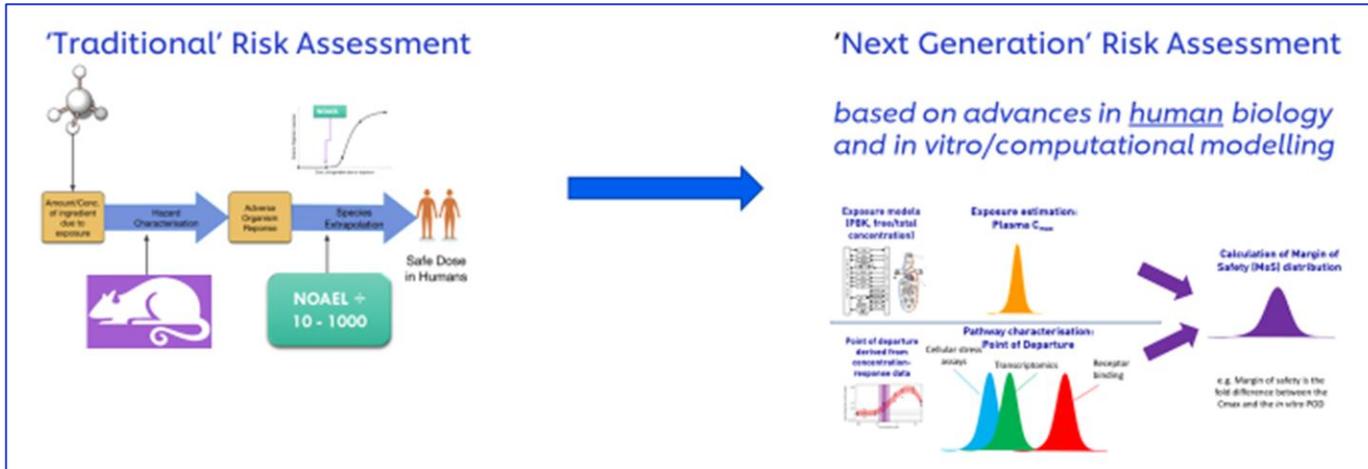
Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor <sup>1</sup>	Calculated daily exposure (µg)	Calculated relative daily exposure (µg/kg bw/d)
<b>Bathing, showering</b>					
Shower gel	18.67 g	279.20	0.01	0.29	2.79
Hand wash soap <sup>2</sup>	20.00 g	-	0.01	0.20 <sup>3</sup>	3.33
<b>Hair care</b>					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner <sup>4</sup>	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74



- Use all available safety data on the ingredient
  - clinical, epidemiological, animal (if dates permit), *in vitro*, etc.
- Exposure-based waiving approaches (e.g. toxicological threshold of concern)
- In silico* predictions
- History of safe use
- Read-across
- Use of existing OECD *in vitro* approaches
- Next Generation Risk Assessment (NGRA)**



# Embracing Next Generation Risk Assessment (NGRA) for assuring the consumer safety of cosmetics ingredients



NGRA is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing

“Risk assessment of cosmetics and their ingredients is shifting towards a strategic combination of NAMs and new technology with historical animal data, if available, to come to a Weight of Evidence (WoE) decision making approach.”

European Commission

Scientific Committee on Consumer Safety  
SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF  
COSMETIC INGREDIENTS AND THEIR SAFETY  
EVALUATION  
11<sup>TH</sup> REVISION

Scientific Committees  
on Consumer Safety  
on Health, Environmental and Emerging Risks

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

Scientific Committee on Consumer Safety (2021)



International Cooperation on Cosmetics Regulation (2018)

Contents lists available at ScienceDirect

**Computational Toxicology**

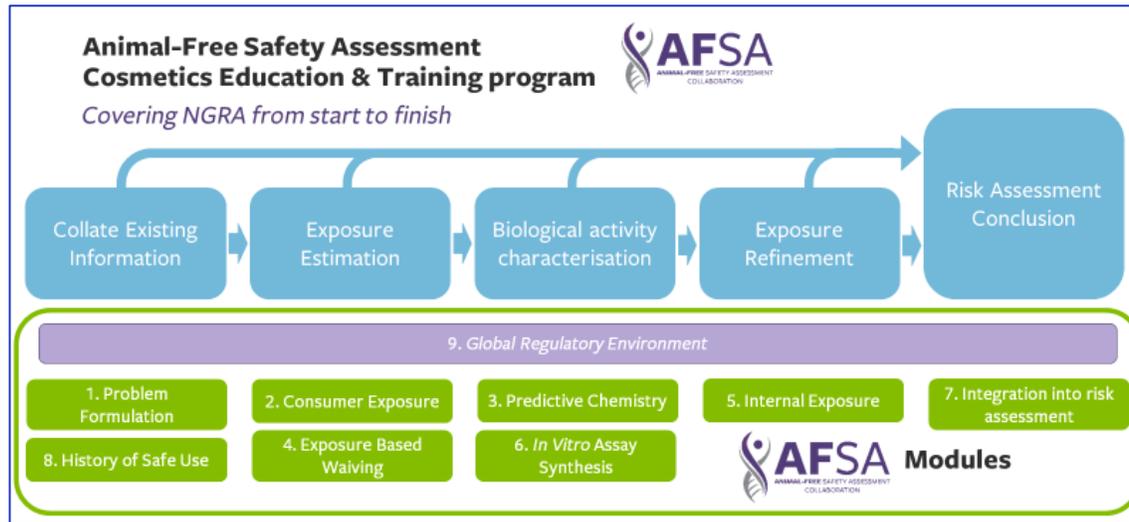
ELSEVIER journal homepage: [www.elsevier.com/locate/comtox](http://www.elsevier.com/locate/comtox)

Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

Matthew Dent<sup>a,\*</sup>, Renata Teixeira Amaral<sup>b</sup>, Pedro Amores Da Silva<sup>b</sup>, Jay Ansell<sup>c</sup>, Fanny Boislevé<sup>d</sup>, Masato Hatao<sup>e</sup>, Akihiko Hirose<sup>f</sup>, Yutaka Kasai<sup>g</sup>, Petra Kern<sup>h</sup>, Reinhard Kreiling<sup>i</sup>, Stanley Milstein<sup>j</sup>, Beta Montemayor<sup>k</sup>, Julcemara Oliveira<sup>l</sup>, Andrea Richarz<sup>m</sup>, Rob Taalman<sup>n</sup>, Eric Vaillancourt<sup>o</sup>, Rajeshwar Verma<sup>l</sup>, Nashira Vieira O'Reilly Cabral Posada<sup>l</sup>, Craig Weiss<sup>p</sup>, Hajime Kojima<sup>f</sup>



# Embedding use of new safety science for non-animal cosmetics assessments



### Animal-free Safety Assessment for Cosmetics

Click each thumbnail to learn more about the course components & access the modules

Master Class Overview (02)	Module 1: Problem Form... (01)	Module 2: Consumer Exp... (02)	Module 3: Predictive C... (03)
Module 4A: Exposure-b... (04)	Module 4B: Safety of ... (04)	Module 6 - Internal Ex... (06)	Module 8: Global Regul... (08)

## CTPA Practical Teaching on Risk Assessment of Cosmetics Using NAMs and NGRA

Would you like to become more confident in using Next Generation Risk Assessment (NGRA) and New Approach Methodologies (NAMs) for safety assessment?

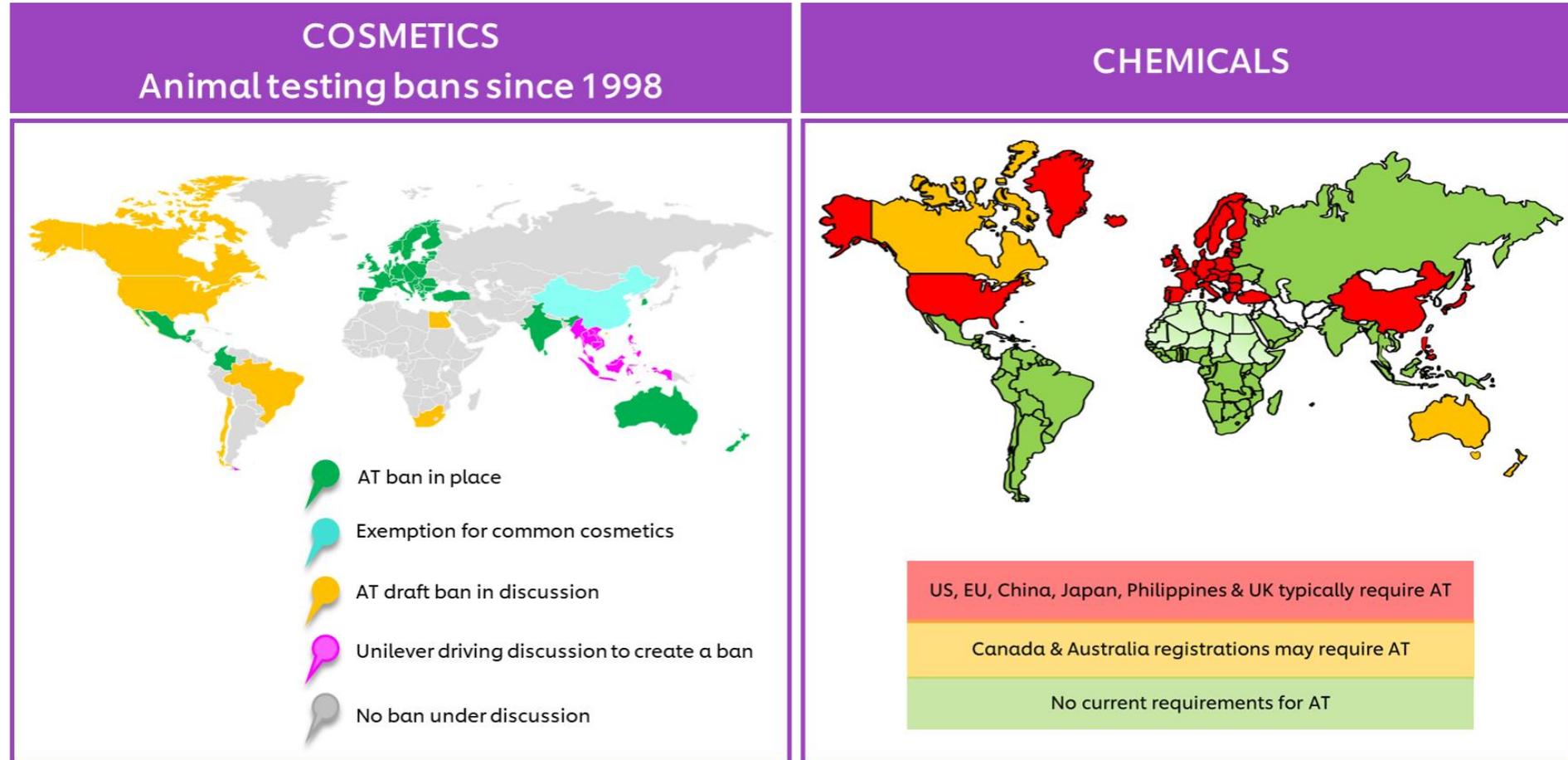
CTPA has been raising awareness and promoting the use of Next Generation Risk Assessment (NGRA) and New Approach Methodologies (NAMs) for safety assessment among industry and regulators. Now, CTPA is organising a **practical teaching day**, where attendees can put these methods in safety assessment into practice, thus increasing the experience and confidence of safety assessors in the cosmetics, and other chemicals sectors.

CTPA has teamed up with experts among its membership who are highly experienced in using NGRA and NAMs, in order to organise a practical workshop on integrating these methods into safety assessments. During the unique event, attendees will 'play' with NGRA/NAMs based data and examples to reach a safety assessment conclusion, whilst being assisted by experts. There will be plenty of opportunities to engage with the experts and ask questions on this topic, to overcome the challenges and barriers that you may be facing.



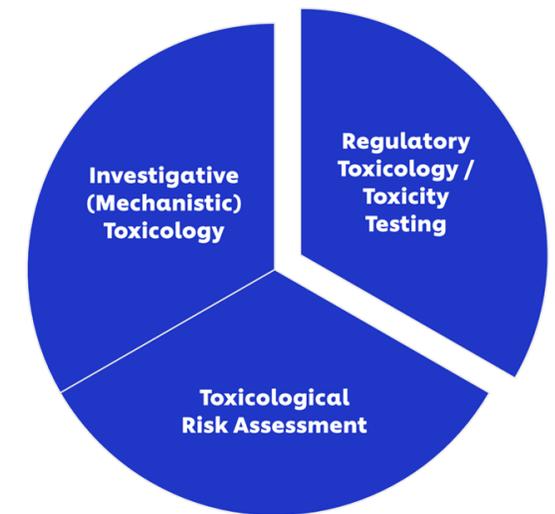
**ADVANCING ANIMAL-FREE SCIENCE FOR COSMETICS WORLDWIDE**

# Cosmetics regulations ban animal tests, Chemicals regulations require them

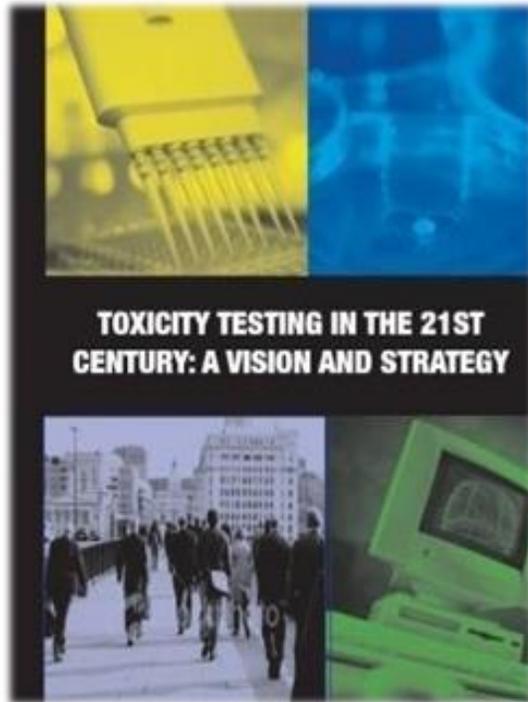


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# US National Academy of Sciences report in 2007 catalysed engagement of regulatory authorities with a new approach anchored in human biology



Review > [Toxicol Sci. 2009 Feb;107\(2\):324-30. doi: 10.1093/toxsci/kfn255. Epub 2008 Dec 12.](#)

## Toxicity testing in the 21st century: bringing the vision to life

Melvin E Andersen <sup>1</sup>, Daniel Krewski

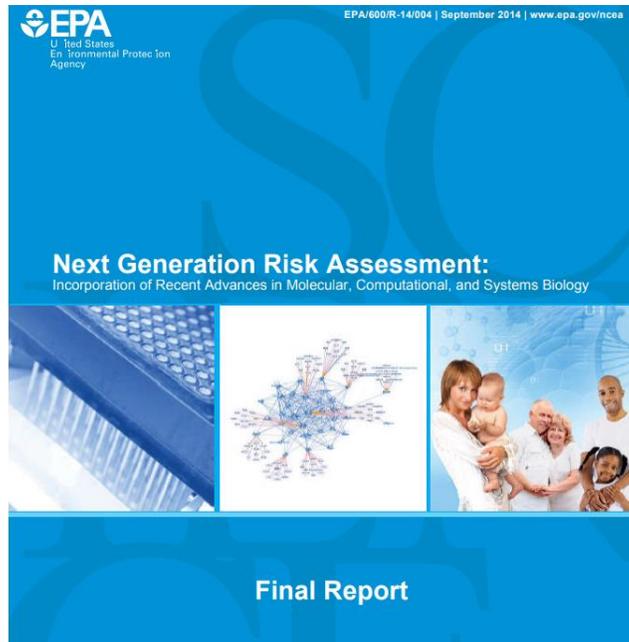
Affiliations + expand

PMID: 19074763 DOI: [10.1093/toxsci/kfn255](#)

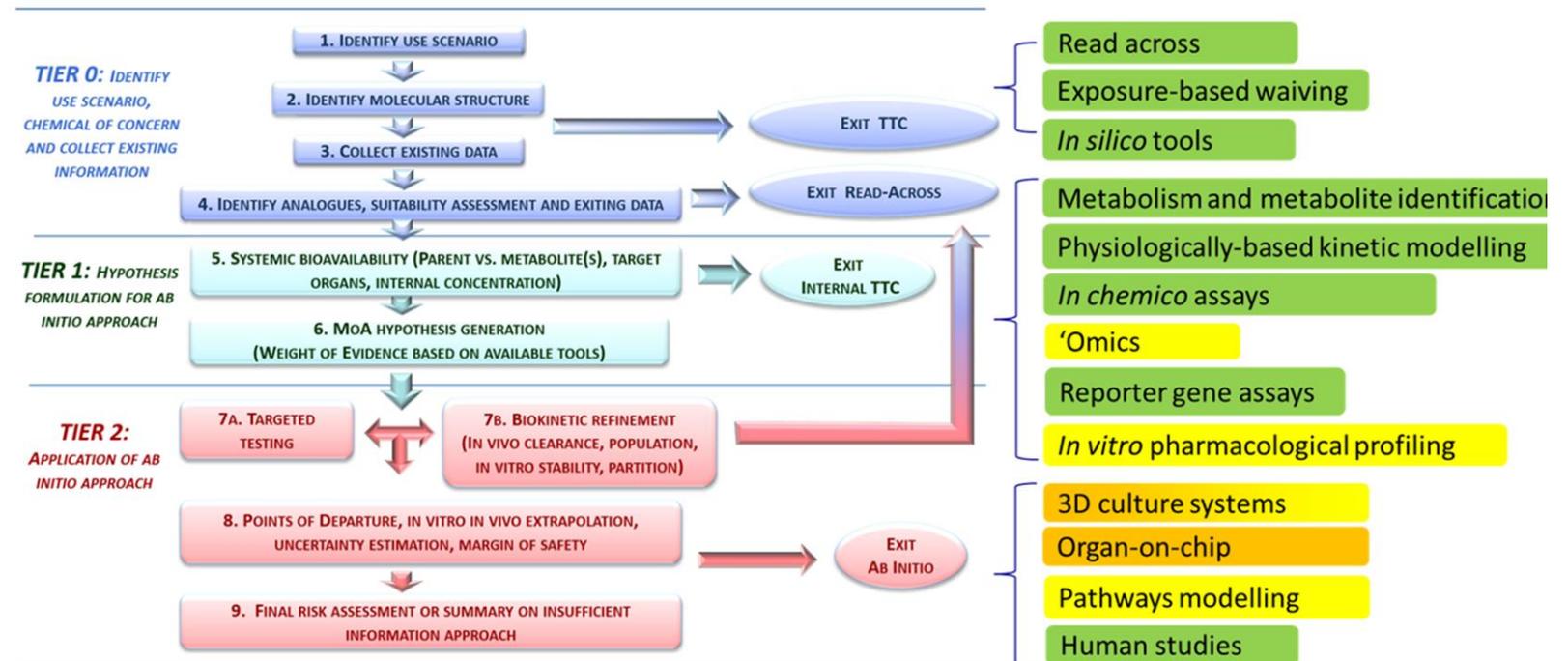
### Abstract

In 2007, the U.S. National Academy of Sciences released a report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*, that envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted in human cells or cell lines *in vitro* by evaluating cellular responses in a suite of toxicity pathway assays using high-throughput tests, that could be implemented with robotic assistance. Risk assessment based on results of these types of tests would shift towards the avoidance of significant perturbations of these pathways in exposed human populations. Dose-response modeling of perturbations of pathway function would be organized around computational systems biology models of the circuitry underlying each toxicity pathway. *In vitro* to *in vivo* extrapolations would rely on pharmacokinetic models to predict human blood and tissue concentrations under specific exposure conditions. All of the scientific tools needed to affect these changes in toxicity testing practices are either currently available or in an advanced state of development. A broad scientific discussion of this new vision for the future of toxicity testing is needed to motivate a departure from the traditional high dose animal-based toxicological tests, with its attendant challenges for dose and species extrapolation, towards a new approach more firmly grounded in human biology. The present paper, and invited commentaries on the report that will appear in *Toxicological Sciences* over the next year, are intended to initiate a dialog to identify challenges in implementing the vision and address obstacles to change.

# Next Generation Risk Assessment (NGRA) approaches for assuring safety



U.S. EPA. Next Generation Risk Assessment: Incorporation Of Recent Advances In Molecular, Computational, And Systems Biology (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-14/004, 2014



[Comput Toxicol](https://doi.org/10.1016/j.comtox.2017.10.001). 2017 Nov;4:31-44. doi: 10.1016/j.comtox.2017.10.001.

**Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods.**

Berggren E<sup>1</sup>, White A<sup>2</sup>, Quedraogo G<sup>3</sup>, Paini A<sup>1</sup>, Richarz AN<sup>1</sup>, Bois FY<sup>4</sup>, Exner T<sup>5</sup>, Leite S<sup>6</sup>, Grunsven LAV<sup>6</sup>, Worth A<sup>1</sup>, Mahony C<sup>7</sup>.

# Advancing NGRA scientific capabilities for chemical risk assessment

**Next Generation Risk Assessment is highly interdisciplinary**

**Risk assessment**

**Biology**

**Bioinformatics**

**Chemistry**

**Mathematical and statistical modelling**

## Unilever : U.S. EPA and Unilever Announce Major New Research Collaboration to Advance Non-Animal Approaches for Chemical Risk Assessment

09/08/2015 | 09:01am EDT



Research collaboration will develop ground-breaking scientific approaches to better assess the safety of chemicals found in some consumer products without using animal data



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

August 19, 2021

**Contact Information**

EPA Press Office ([press@epa.gov](mailto:press@epa.gov))

**WASHINGTON** – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), which are a promising alternative to conventional toxicity testing that are intended to reduce reliance on the use of animals.

EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

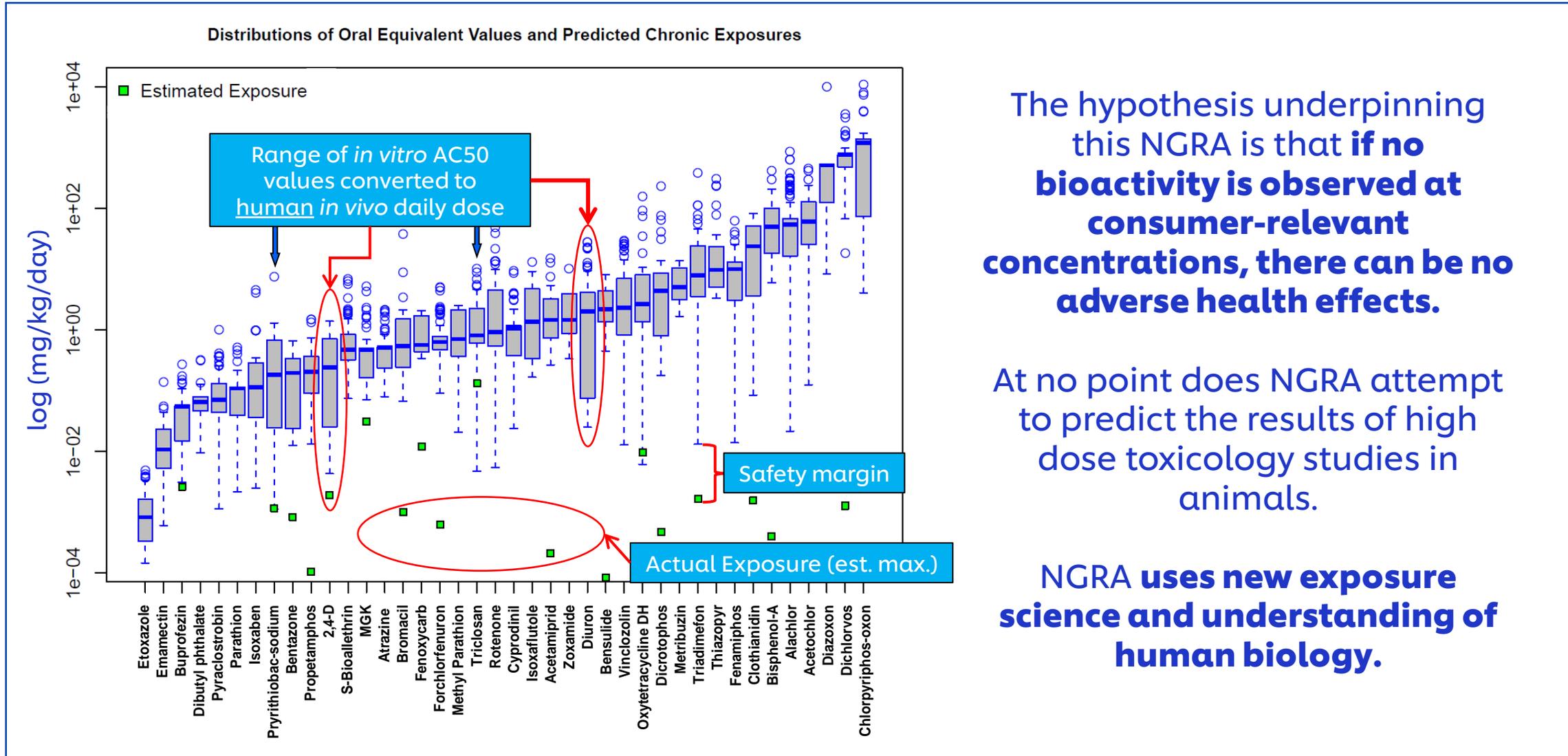
“EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing,” said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA’s Office of Research and Development**. “We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs.”



[Unilever, Safety & Environmental Assurance Centre \(SEAC\) – YouTube](#)  
US SoT March 2020 – NGRA concept & approach

[Unilever - Safety & Environmental Assurance Centre at Unilever Global IP Limited – YouTube](#)  
US SoT March 2022 – integrating NAMs in NGRA for consumer safety decisions

# NGRA: aim is protection of health not prediction of animal data



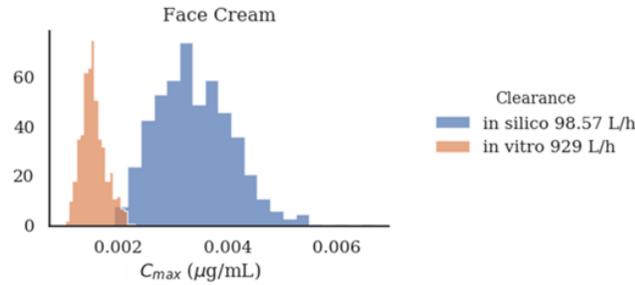
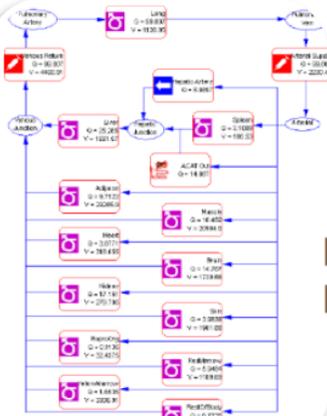
The hypothesis underpinning this NGRA is that **if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.**

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.

# Key tools in Unilever's NGRA approach for systemic effects

## 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 Bowen, Andrew J. Bowen, Jacques Hamon, Wolfgang Jarosimek, Arun Srihar, 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 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 amend their license and/or withdraw entirely.

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 ADIs in animal models or clinical studies, and 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 ADIs.

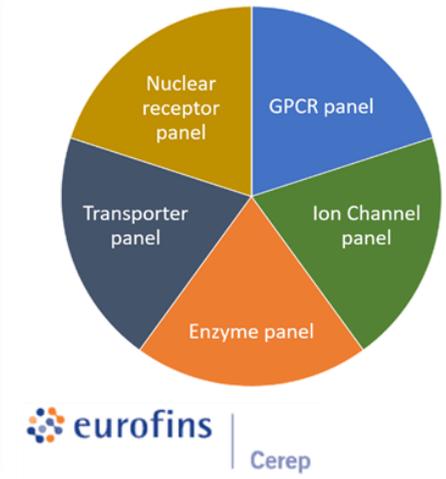
*In vitro* pharmacological profiling involves the screening of compounds against a broad range of target receptors, ion channels, enzymes and transporters that are diverse from the intended

safety testing of drug candidates and are designed to prevent serious ADIs from occurring in clinical studies.

The early *in vitro* pharmacology assay that is absolutely required by regulatory authorities is one that measures the effects of new chemical entities on the ion channel of hERG (hERG1) or heterologously expressed human voltage-gated potassium channel subfamily E1 member 2 (hKCNH2), also known as hERG2. 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 ADI 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 desirability of potential 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 state on the stage of the discovery process at which *in vitro* pharmacological profiling should occur. Nevertheless, a common goal for most pharmaceutical companies is to perform this testing early in drug discovery to reduce attrition and to facilitate better prediction of ADIs 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 best 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 describe drug candidates and to

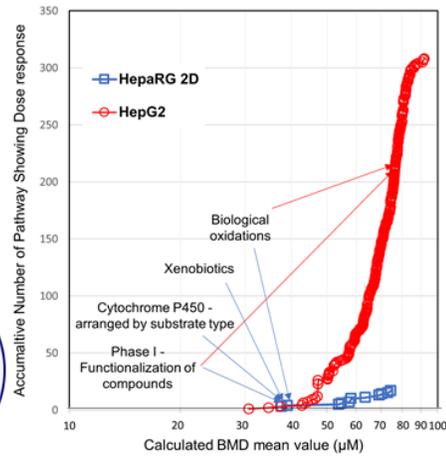


## Transcriptomics

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



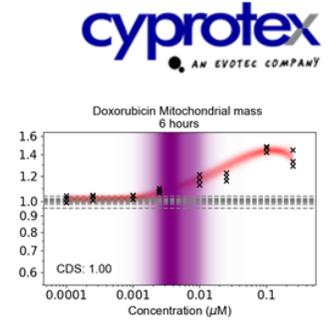
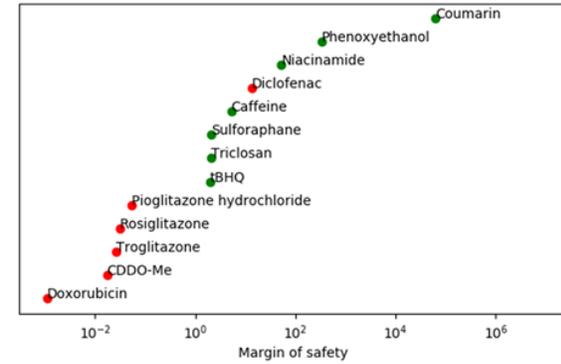
## BMDexpress 2



## Cellular Stress Pathways

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

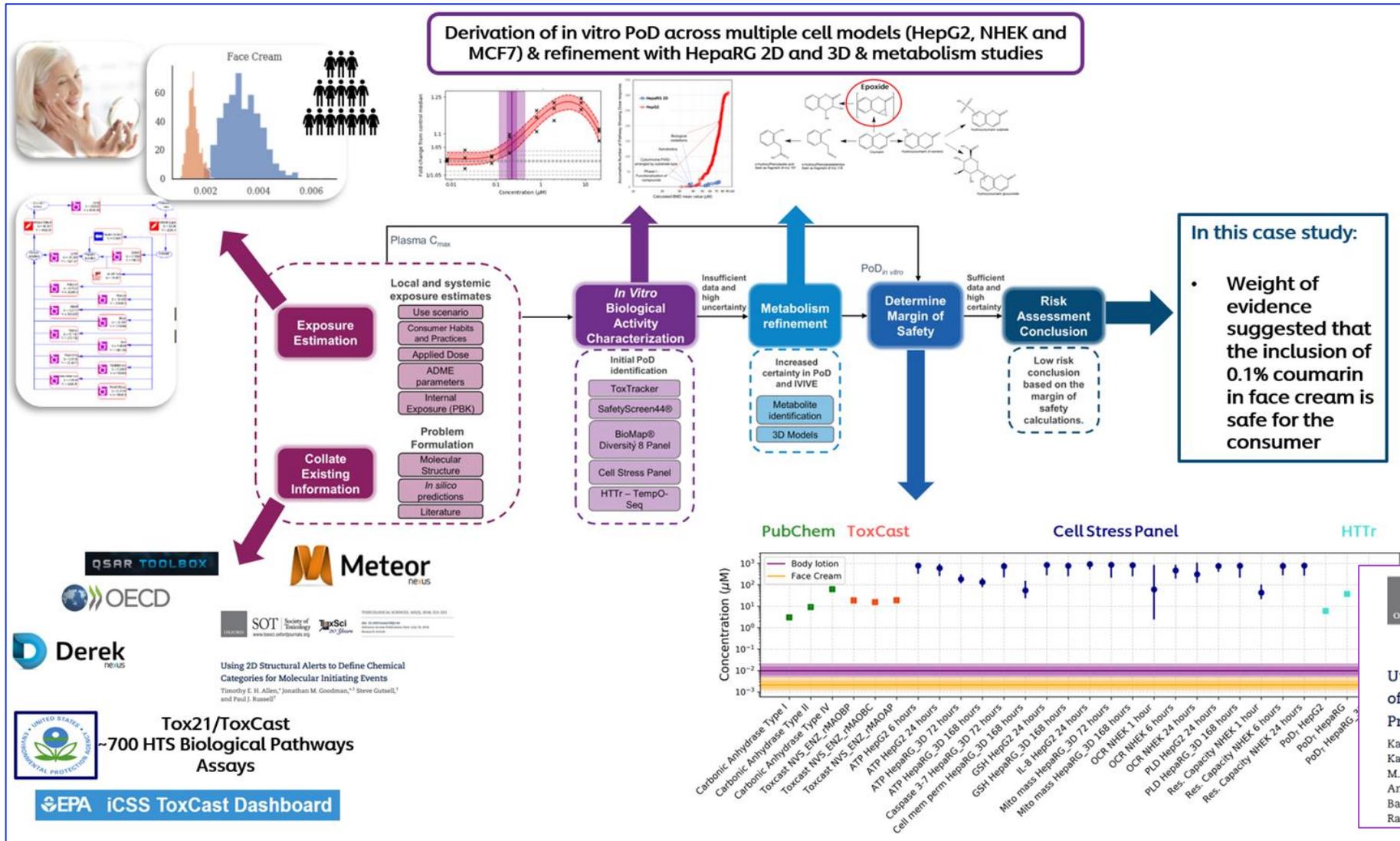
- Exposure scenario adopted for chemical is 'low risk'** (from consumer goods perspective)
- Niacinamide (food, cosmetics)
  - Caffeine (beverages, cosmetics)
  - Phenoxyethanol (cosmetics)
  - Sulfuraphane (food)
  - BHQ (antioxidant)
  - Triclosan (antimicrobial)
- Exposure scenario adopted for chemical 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 frameworks developed to enable data integration & interpretation



Not a prescriptive set of tools, but **driven by the safety assessment**

**Exposure** tools to inform level of Systemic Exposure

**Bioactivity** tools to provide Points of Departure: **Bioactivity-Exposure Ratio**

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tr-x Spotlight

TOKICOLOGICAL SCIENCES, 173(1), 2020, 202-225  
doi: 10.1093/toxsci/kfz011  
Advance Access Publication Date: September 16, 2019  
Research Article

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

Katie Paul Friedman, 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, Steven Foster, Kathleen Raffaele, Tina Bahadori, Maureen R. Gwinn, Jason Lambert, Maurice Whelan, Mike Rasenberg, Tara Barton-Maclaren, and Russell S. Thomas

Hatherell *et al* (2020) Toxicological Sciences, **176**, 11-33

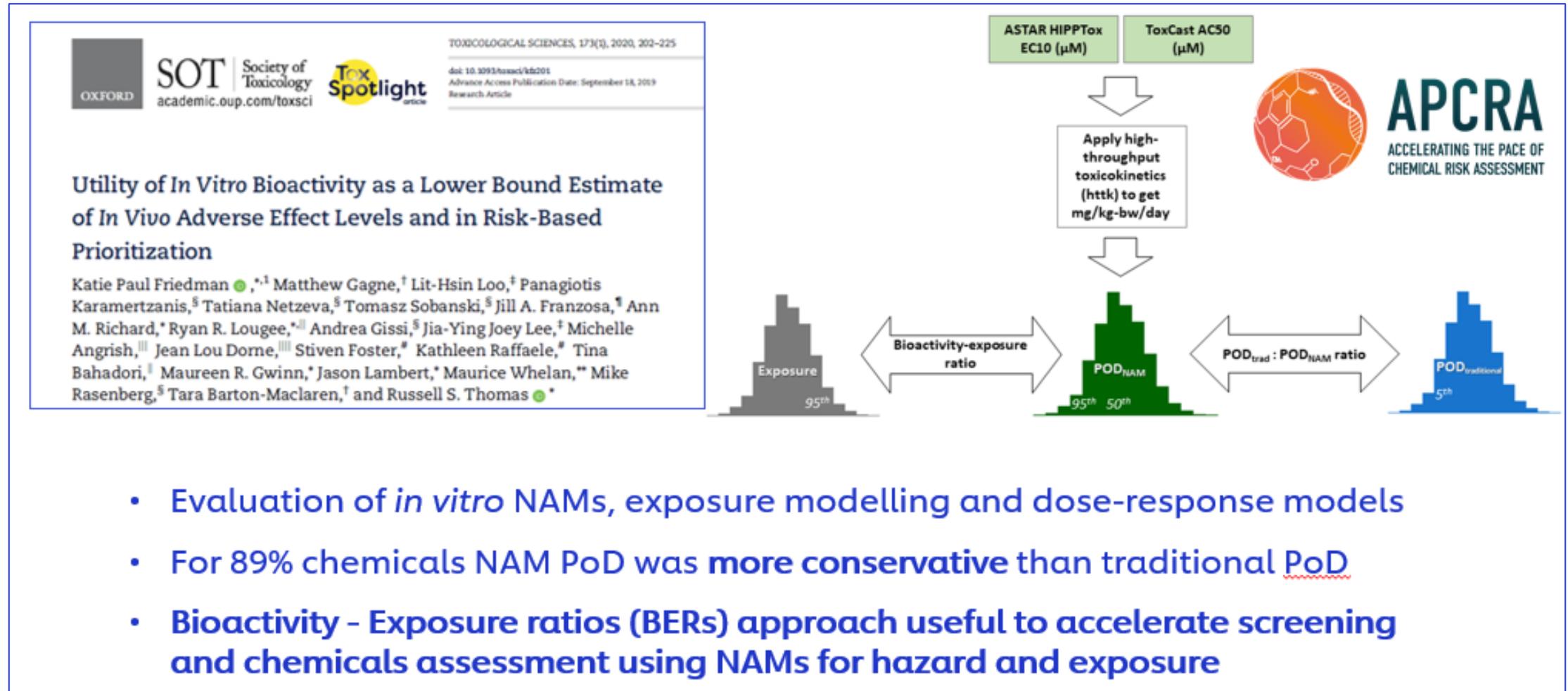
Li *et al* (2022) Toxicol. Appl. Pharmacol., **442** 115992

Moxon *et al* (2020) Toxicology in Vitro, **63** 104746



# Interpreting non-animal data for assessing chemical safety

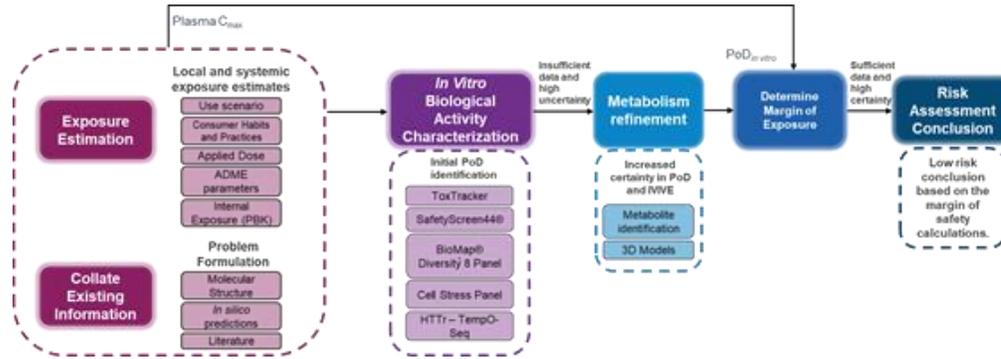
## Bioactivity – Exposure Ratio (BER) approach



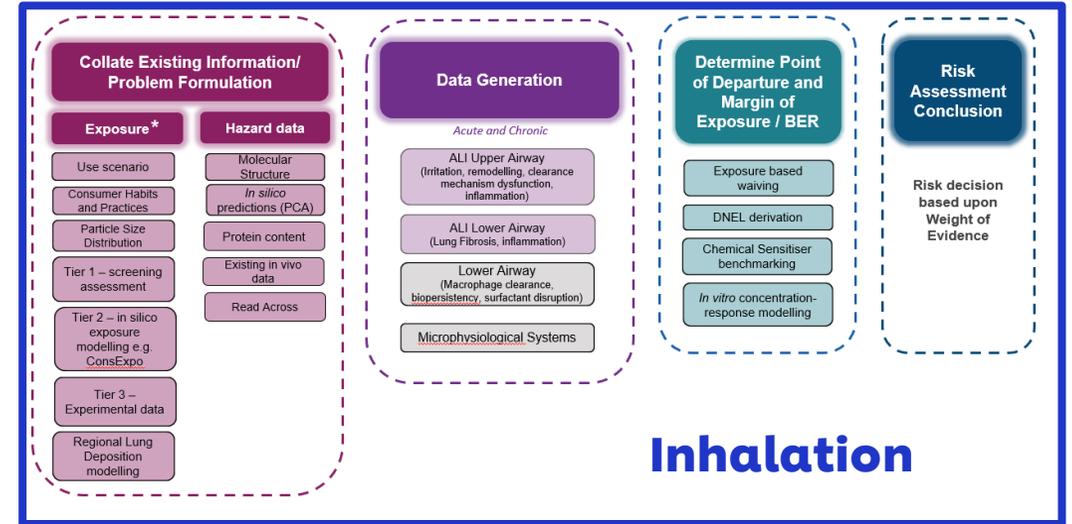
NAM = New Approach Method | Non-Animal Method

# Unilever NGRA frameworks for using non-animal data for consumer safety decisions

## Systemic

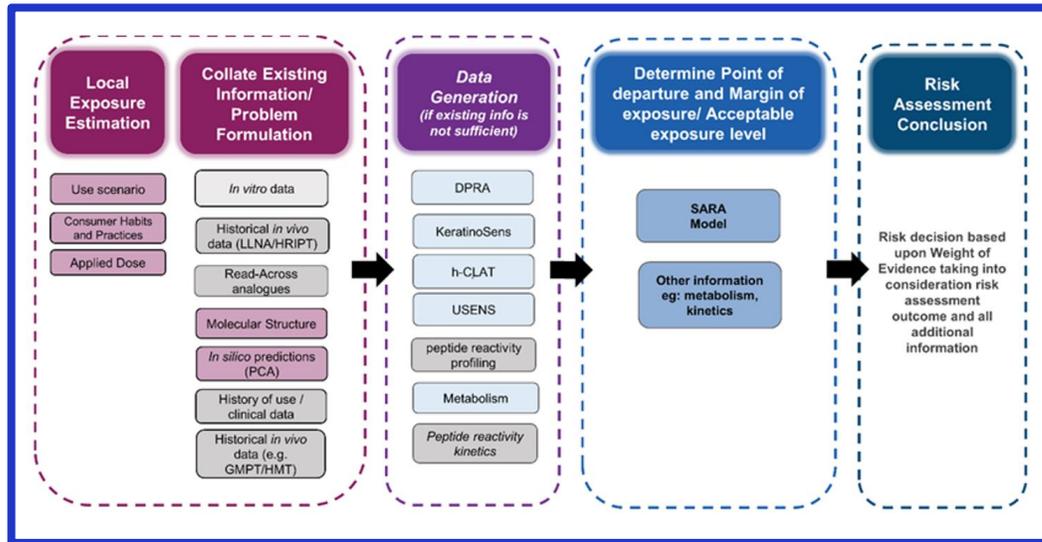


Baltazar et al (2020) *Toxicol Sci*, **176**, 236-252



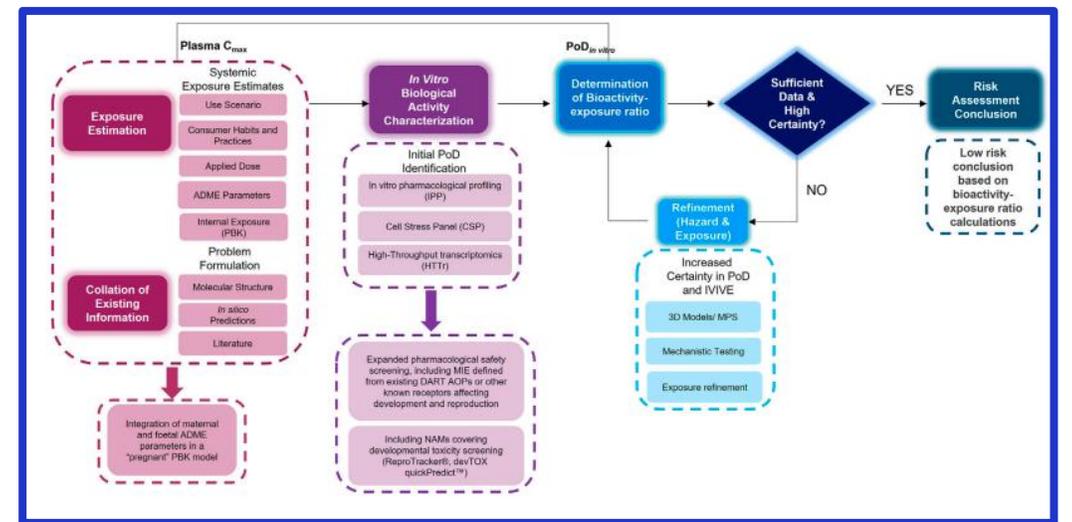
## Inhalation

## Skin Allergy



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

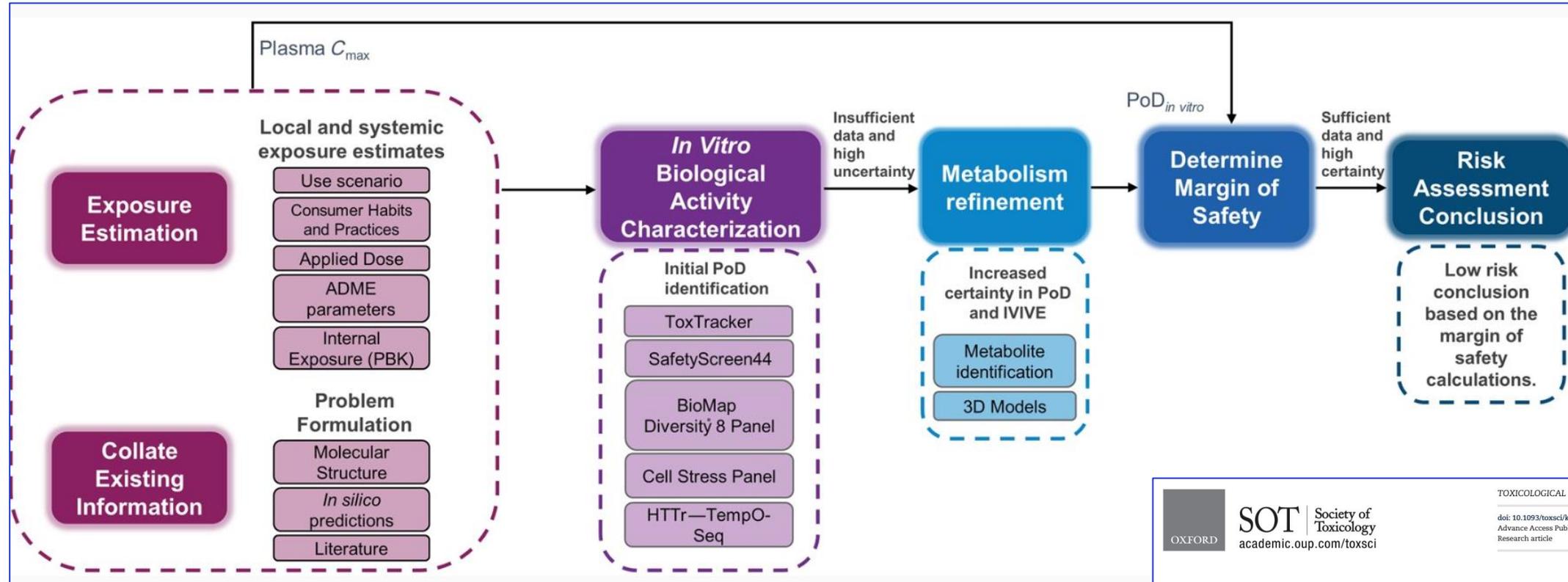
## Developmental & Reproductive (DART)



Rajagopal et al (2022) *Frontiers in Toxicology*, **4**, 838466

# NGRA framework for systemic exposure: case study – coumarin (1)

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



Next-Generation Risk Assessment case study workflow for 0.1% coumarin in consumer products. Initial steps involved collating existing data, generating *in silico* predictions, and problem formulation. In parallel, applied and systemic consumer exposure estimates were calculated based on the use scenario, habits and practices information, and chemical parameters. A battery of *in vitro* assays was then conducted to characterize the cellular response to coumarin. From these data, point of departure (PoD) values with associated uncertainties were determined, however, the lack of metabolic capacity of the cell line models used, and the potential toxicity of reactive metabolites led to the generation of additional data (metabolism refinement). All PoDs were compared with exposure estimates (plasma  $C_{max}$ ) to calculate a margin of safety, which was used for the risk assessment decision. Abbreviations: HTTr, high-throughput transcriptomics; IVIVE, *in vitro* to *in vivo* extrapolation.

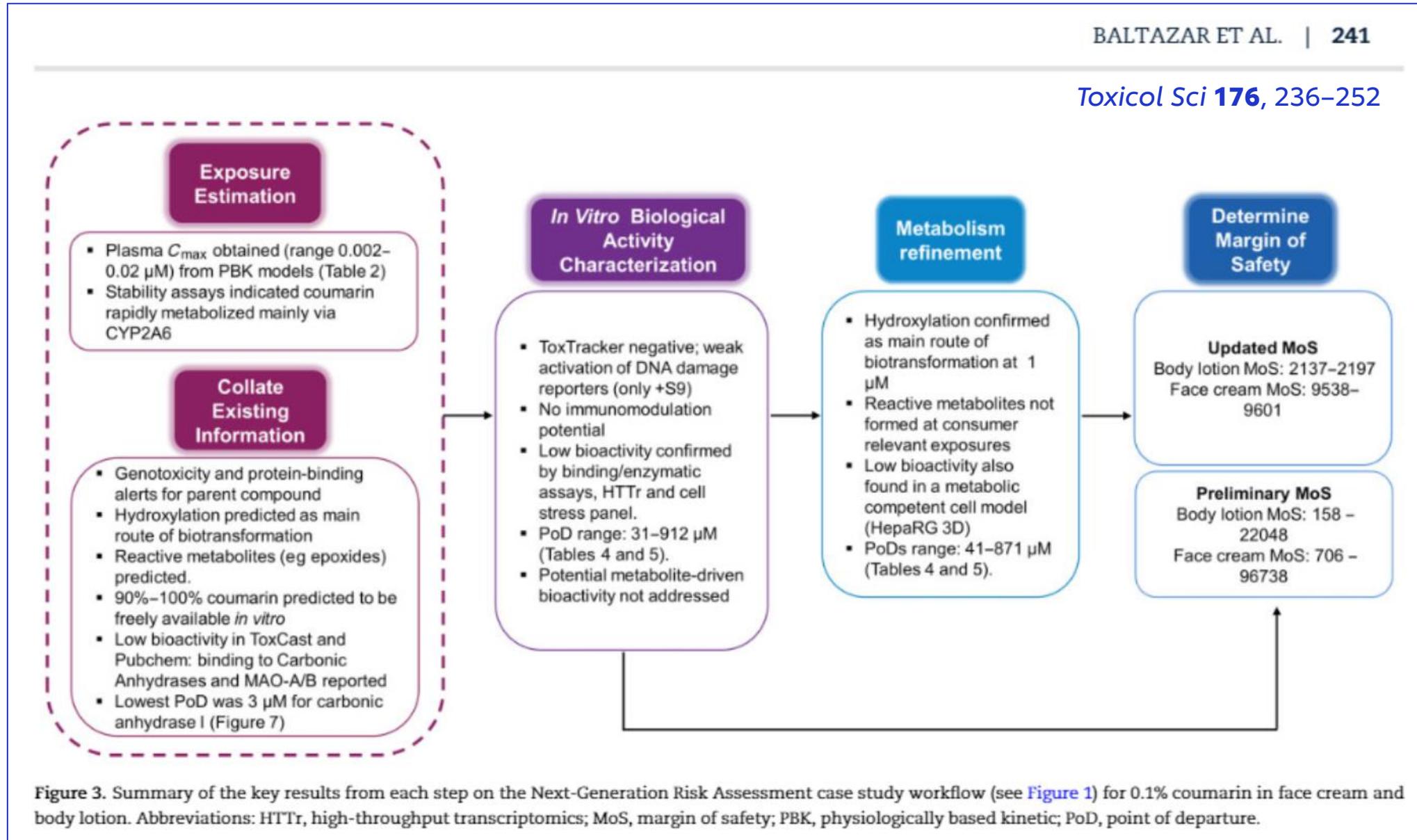
OXFORD SOT Society of Toxicology academic.oup.com/toxsci  
 TOXICOLOGICAL SCIENCES, 176(1), 2020, 236–252  
 doi: 10.1093/toxsci/kaa048  
 Advance Access Publication Date: April 10, 2020  
 Research article

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

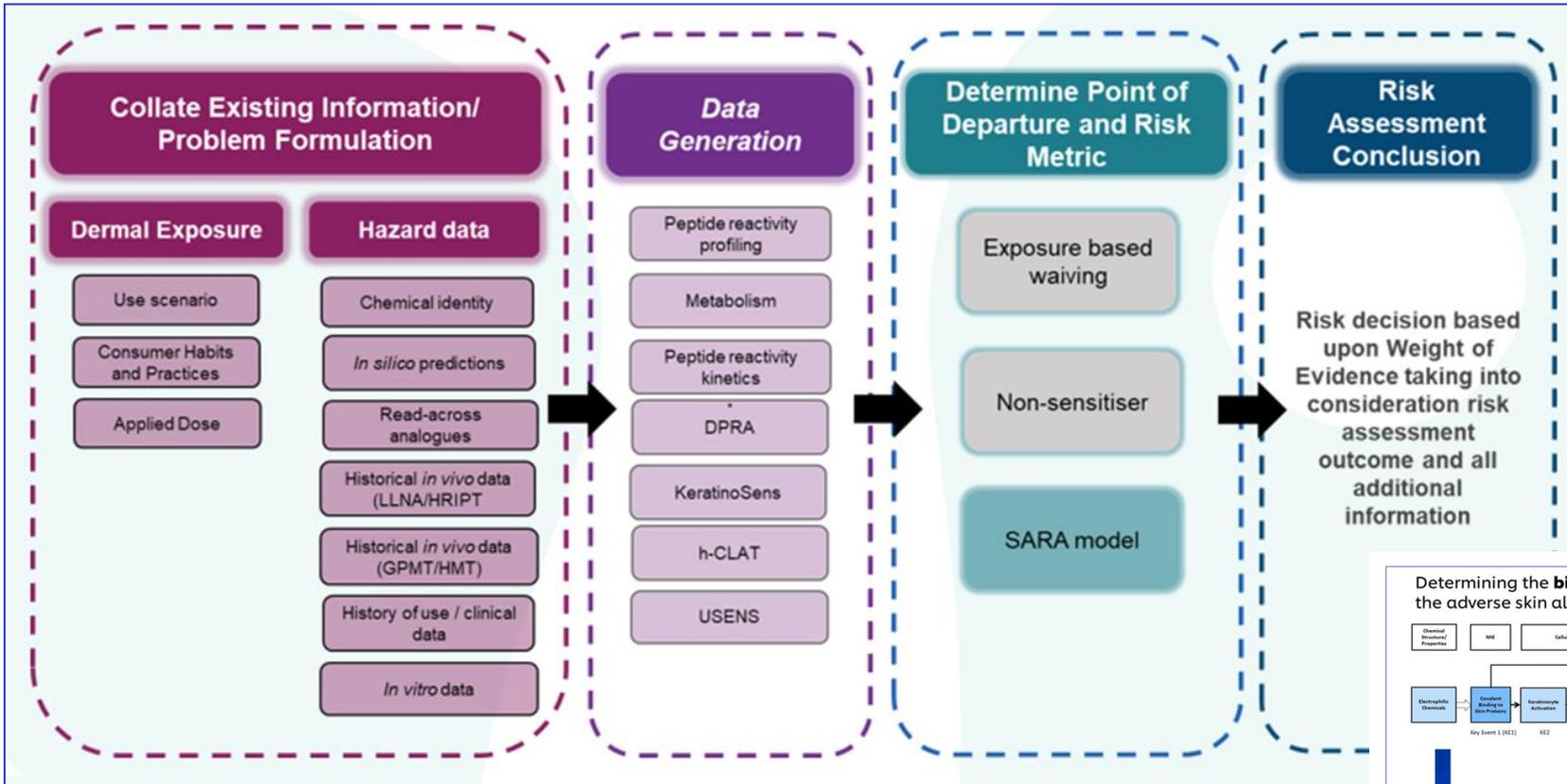
Maria T. Baltazar,<sup>1</sup> Sophie Cable, Paul L. Carmichael, Richard Cubberley, Tom Cull, Mona Delagrangre, Matthew P. Dent, Sarah Hatherell, Jade Houghton, Predrag Kukic, Hequn Li, Mi-Young Lee, Sophie Malcomber, Alistair M. Middleton, Thomas E. Moxon, Alexis V. Nathanail, Beate Nicol, Ruth Pendlington,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

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

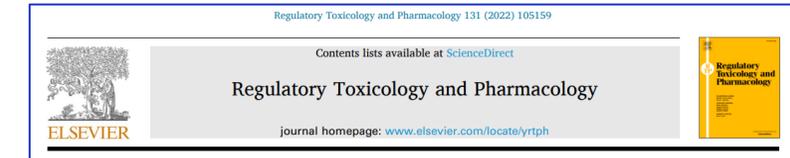
# NGRA framework for systemic exposure: case study – coumarin (2)



# Unilever NGRA framework for skin allergy



A hypothetical skin sensitisation next generation risk assessment for coumarin in cosmetic products  
 G. Reynolds<sup>\*</sup>, J. Reynolds, N. Gilmour, R. Cubberley, S. Spriggs, A. Aptula, K. Przybylak, S. Windebank, G. Maxwell, M.T. Baltazar<sup>\*\*</sup>  
 Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK



Next generation risk assessment for skin allergy: Decision making using new approach methodologies  
 N. Gilmour<sup>\*</sup>, J. Reynolds, K. Przybylak, M. Aleksic, N. Aptula, M.T. Baltazar, R. Cubberley, R. Rajagopal, G. Reynolds, S. Spriggs, C. Thorpe, S. Windebank, G. Maxwell  
 Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, UK

Determining the **biological pathway** behind the adverse skin allergy reaction ...

Unilever's **SARA Model** – developed as a computational approach to integrate information from the historical data and various cell-based experiments ...

SARA Model published and collaboration with US Gov. group (NICEATM) to adapt the model for **regulatory use**.

Developing a **cell-based** experiments to measure activation of different parts of the biological pathway ...

Developing a **risk assessment framework** ...

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

Gilmour *et al* (2022) *Reg Tox Pharmacol*, 131, June 2022, 105159



# Building confidence in the application of new tools & data

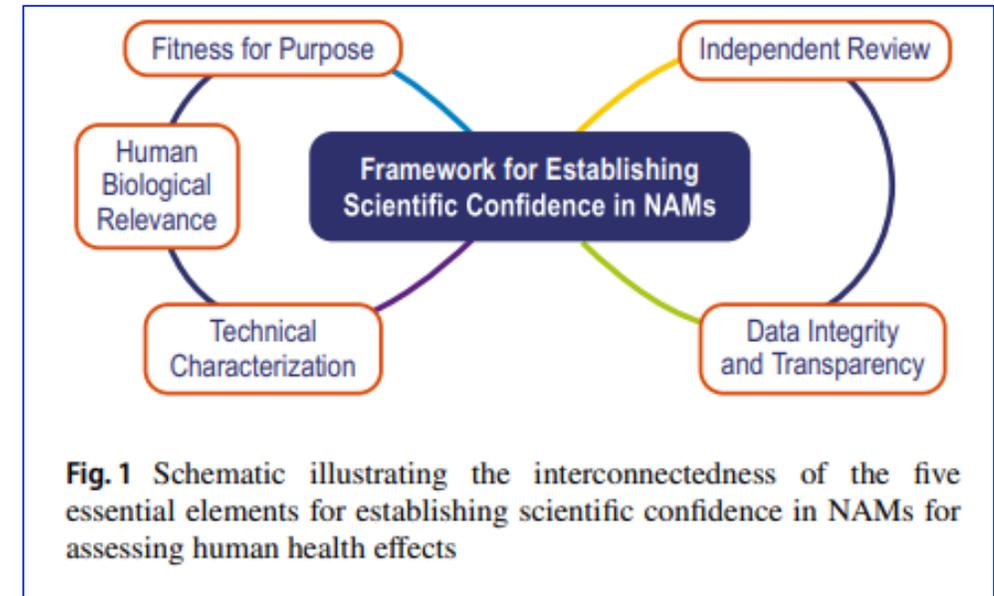
Archives of Toxicology (2022) 96:2865–2879  
<https://doi.org/10.1007/s00204-022-03365-4>

REVIEW ARTICLE

## A framework for establishing scientific confidence in new approach methodologies

Anna J. van der Zalm<sup>1</sup>  · João Barroso<sup>2</sup> · Patience Browne<sup>3</sup> · Warren Casey<sup>4</sup> · John Gordon<sup>5</sup> · Tala R. Henry<sup>6</sup> · Nicole C. Kleinstreuer<sup>7</sup> · Anna B. Lowit<sup>6</sup> · Monique Perron<sup>8</sup> · Amy J. Clippinger<sup>1</sup>

Received: 17 May 2022 / Accepted: 11 August 2022 / Published online: 20 August 2022  
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**Fig. 1** Schematic illustrating the interconnectedness of the five essential elements for establishing scientific confidence in NAMs for assessing human health effects

# Evaluating the new non-animal toolbox for systemic safety assessments

JOURNAL ARTICLE FEATURED

## Are Non-animal Systemic Safety Assessments Protective? A Toolbox and Workflow

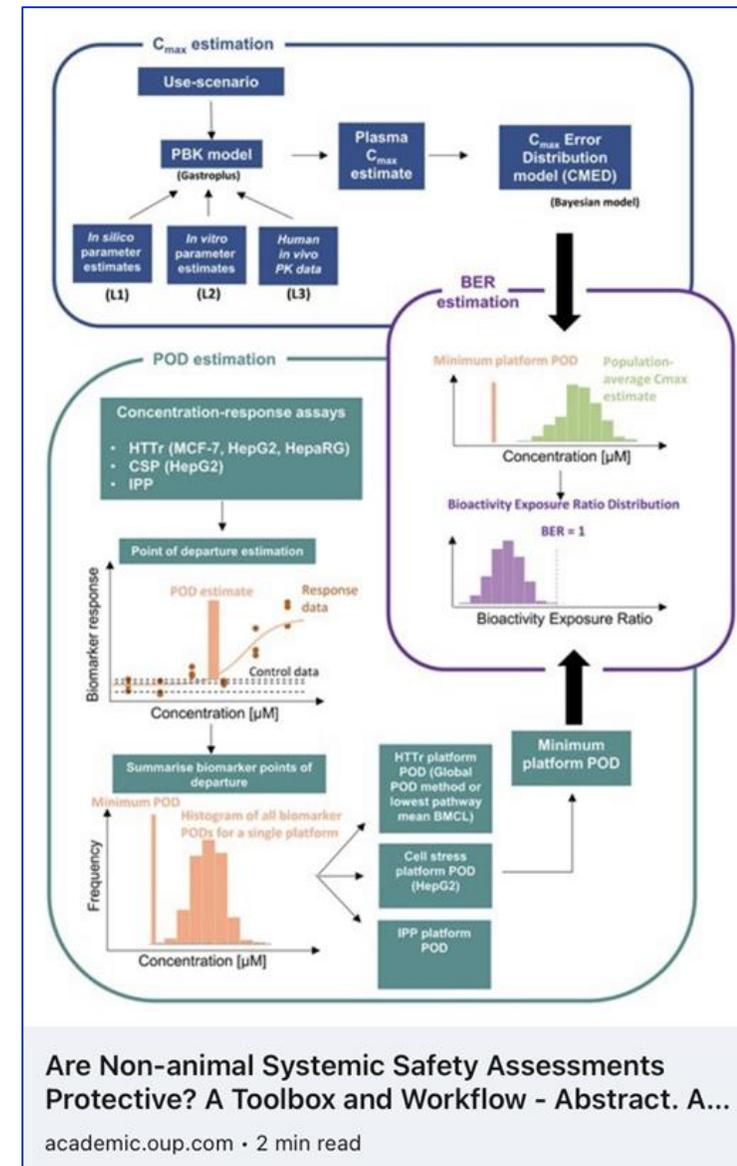
Alistair M Middleton ✉, Joe Reynolds, Sophie Cable, Maria Teresa Baltazar, Hequn Li, Samantha Bevan, Paul L Carmichael, Matthew Philip Dent, Sarah Hatherell, Jade Houghton, Predrag Kukic, Mark Liddell, Sophie Malcomber, Beate Nicol, Benjamin Park, Hiral Patel, Sharon Scott, Chris Sparham, Paul Walker, Andrew White

*Toxicological Sciences*, Volume 189, Issue 1, September 2022, Pages 124–147,

<https://doi.org/10.1093/toxsci/kfac068>

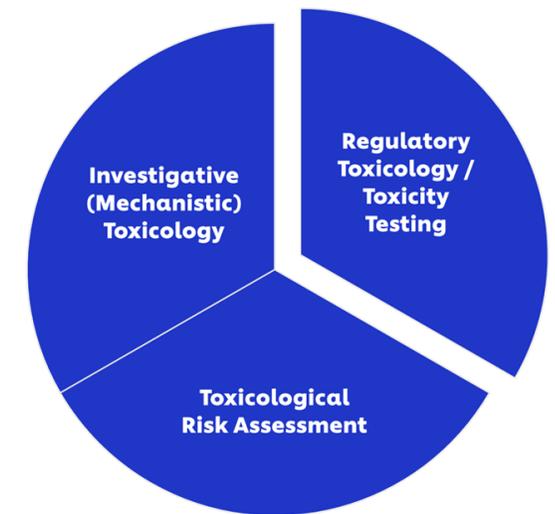
Published: 13 July 2022

**Assessing the protectiveness and utility of a NAM-based approach to safety decision-making**  
Sophie Cable *et al.*

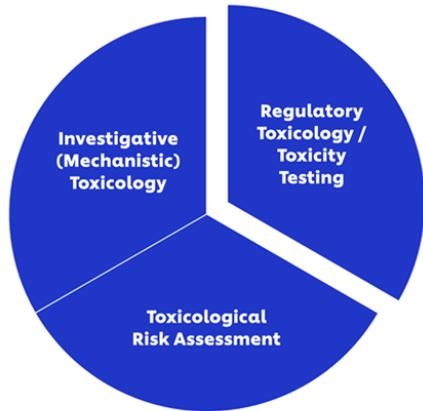


## Overview – toxicological risk assessment: more science, less art

- **Scientifically, is that the best we can do?**
  - A biochemist's first view of a chronic rodent toxicity study
- **Re-thinking consumer safety decision-making**
  - Responding to a ban on animal testing for cosmetics
- **A new scientific paradigm rooted in human biology**
  - Shaping 'next generation' risk assessment (NGRA) approaches
- **Advocating for regulatory change**
  - Applying innovative toxicological science in chemical safety dossiers



# Advocating for regulatory change – modernisation of chemical safety assessment approaches & application of innovative toxicological science



- use of modern scientific methods & new types of data for regulatory purposes
- investment in new regulatory science capability

## Upholding the EU’s Commitment to ‘Animal Testing as a Last Resort’ Under REACH Requires a Paradigm Shift in How We Assess Chemical Safety to Close the Gap Between Regulatory Testing and Modern Safety Science

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

Alternatives to Laboratory Animals  
 2021, Vol. 49(4) 122–132  
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 DOI: 10.1177/02611929211040824  
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### Unilever: EU needs ‘paradigm shift’ in chemical safety assessment methods

By Kacey Culliney

23-Sep-2021 - Last updated on 23-Sep-2021 at 14:59 GMT

Cosmetics  
design-europe.com

THE LONG READ: IN CONVERSATION WITH UNILEVER SAFETY & ENVIRONMENTAL ASSURANCE CENTRE (SEAC) EXECUTIVES

The future of animal-free chemical testing? There’s a ‘big frustration’ in the scientific community, say Unilever execs

By Kacey Culliney   
 20-Oct-2021 - Last updated on 20-Oct-2021 at 09:54 GMT



Non-animal methods (NAMs) have to be fast prioritised in EU chemicals testing under REACH and much can be learned from the US Environmental Protection Agency [Getty Images]

RELATED TAGS: Animal testing; Animal testing alternatives; non-animal testing methods; REACH; Chemicals; Regulation; next-generation safety assessments; Unilever; safety assessment

A complete shift in the safety assessment of chemicals will be necessary if the EU is to uphold its ‘animal testing as a last resort’ policy under the European Chemicals Agency’s REACH regulation – a critical aspect to maintaining the wider cosmetics animal testing ban, say Unilever execs.

# Regulatory assessments of chemical safety – use of new tools & data

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ECHA > Legislation > REACH > Alternatives to animal testing under REACH

**REACH**

- Understanding REACH
- Substance Identification
- Registration
- Evaluation
- Authorisation
- Restriction
- Communication in the supply chain
- Candidate List substances in articles
- Legislation
- Alternatives to animal testing under REACH
- Enforcement

## Alternatives to animal testing under REACH

Chemicals can cause cancer; affect the immune, respiratory, endocrine, reproductive or cardiovascular systems; weaken human resilience and the capacity to respond to vaccines; and increase vulnerability to diseases.

The European Parliament and Council adopted chemicals legislation to protect people and the environment from such harm and to promote alternative test methods.

In practice, this means companies must test their chemicals for safety – by using alternative methods or – as a last resort – testing on animals. Animal tests are only permitted if there is no alternative way to gather the safety information.

The law requires companies to use alternative methods whenever possible – so companies should only ever test on animals as a last resort.

EU REACH legislation has been in place since June 2007. It was introduced to protect people & the environment from harm and to promote alternative test methods.

Science & technology have advanced hugely and chemicals regulations need to catch up → framework for using best scientific data for safety decisions.

Archives of Toxicology (2022) 96:743–766  
https://doi.org/10.1007/s00204-021-03215-9

**REGULATORY TOXICOLOGY**

**ecefoc**

## A framework for chemical safety assessment incorporating new approach methodologies within REACH

Nicholas Ball<sup>1</sup> · Remi Bars<sup>2</sup> · Philip A. Botham<sup>3</sup> · Andreea Cuciureanu<sup>4</sup> · Mark T. D. Cronin<sup>5</sup> · John E. Doe<sup>5</sup> · Tatsiana Dudzina<sup>6</sup> · Timothy W. Gant<sup>7</sup> · Marcel Leist<sup>8</sup> · Bennard van Ravenzwaay<sup>9</sup>

**Regulatory Toxicology and Pharmacology**  
Available online 11 September 2022, 105261  
In Press, Journal Pre-proof

**ELSEVIER**

**epaa**  
The European Partnership for Alternative Approaches to Animal Testing

## Use of New Approach Methodologies (NAMs) in regulatory decisions for chemical safety: Report from an EPAA Deep Dive Workshop

Carl Westmoreland<sup>a</sup>, Hans J. Bender<sup>b</sup>, John E. Doe<sup>c</sup>, Miriam N. Jacobs<sup>d</sup>, George E.N. Kass<sup>e</sup>, Federica Madia<sup>f</sup>, Catherine Mahony<sup>g</sup>, Irene Manou<sup>h</sup>, Gavin Maxwell<sup>a</sup>, Pilar Prieto<sup>f</sup>, Rob Roggeband<sup>i</sup>, Tomasz Sobanski<sup>j</sup>, Katrin Schütte<sup>k</sup>, Andrew P. Worth<sup>f</sup>, Zvonimir Zvonar<sup>h</sup>, Mark T.D. Cronin<sup>c</sup>

**ALTEX, accepted manuscript published July 4, 2022**  
doi:10.14573/altex.2204281

Food for Thought ...

## Ready for Regulatory Use: NAMs and NGRA for Chemical Safety Assurance

Paul L. Carmichael<sup>1,2</sup>, Maria T. Baltazar<sup>1</sup>, Sophie Cable<sup>1</sup>, Stella Cochrane<sup>1</sup>, Matthew Dent<sup>1</sup>, Hequn Li<sup>1</sup>, Alistair Middleton<sup>1</sup>, Iris Müller<sup>1</sup>, Georgia Reynolds<sup>1</sup>, Carl Westmoreland<sup>1</sup> and Andrew White<sup>1</sup>

<sup>1</sup>Safety & Environmental Assurance Centre (SEAC), Unilever, Sharnbrook, Bedfordshire, UK; <sup>2</sup>Toxicology, Wageningen University & Research, Wageningen, The Netherlands



# Protecting workers by applying NGRA and non-animal approaches

### Exposure Estimation

The worst-case levels of exposure of workers to SI in several factory environments were estimated using factory-specific data and occupational exposure models including CHESAR and ART. These exposure values were then used to estimate worst-case levels of systemic exposure to SI following occupational exposure using Physiologically Based Kinetic (PBK) modelling [5]. Experimental ADME data from NAMs were also generated on SI for this PBK modelling.

**Worker Exposure Data**



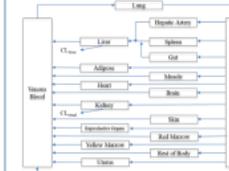
ART  
chesar

**Data Generation**

*In vitro* data on SI:

- Dermal absorption
- Blood to plasma ratio
- Plasma protein binding
- Metabolic stability

**PBK Modelling**

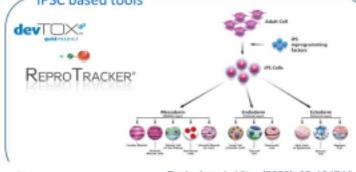


G+

### In Vitro Biological Activity Characterisation

The bioactivity of SI was assessed in a battery of NAMs relevant to systemic [6], reproductive, and developmental toxicity [7]. Concentration-response curves were derived for 40 cell stress markers and High Throughput Transcriptomics was conducted in HepG2, HepaRG and MCF7 cells. Pharmacological profiling of SI against 73 targets was conducted as well as specific assays relating to developmental toxicity (Reprotracker, devTOX<sup>®</sup>).

**IPSC based tools**



Toxicology in Vitro (2020), 63, 1047-46

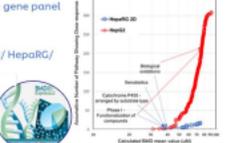
**In vitro Pharmacological Profiling**



PERSPECTIVES

**High-throughput Transcriptomics (HTTr)**

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

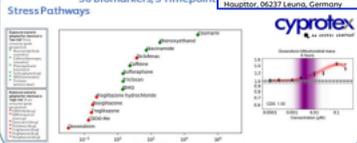


BMDexpress 2 and BIFROST

Comp Tox (2020) 16: 100138  
Toxicol Sci (2020) 176, 236–252

**Cell Stress Panel (CSP)**

36 Biomarkers; 3 Timepoints



Toxicol Sci (2020), 176, 11–33

### Bioactivity: Exposure Ratio (BER)

The use of ERM as independent consultants throughout this work ensured appropriate protection of individual companies' confidential business information

**C<sub>max</sub> estimation**

Use Scenario

Dermal exposure

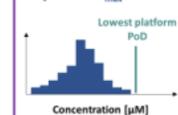
Inhalation exposure

PBK population model

Predicted C<sub>max</sub>

**BER estimation**

Population C<sub>max</sub> estimate



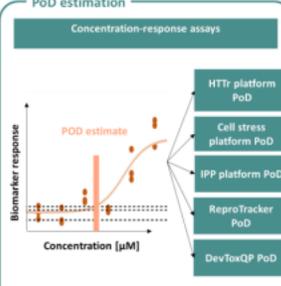
Lowest platform PoD

BER-1 = systemic bioactivity leading to adverse effects can be ruled out

BER-1 = systemic bioactivity leading to adverse effects cannot be ruled out

**PoD estimation**

Concentration-response assays



HTTr platform PoD

Cell stress platform PoD

IPP platform PoD

ReproTracker PoD

DevToxQP PoD

Lowest platform PoD

### Results

- The PBK modelling indicated a worst-case plasma C<sub>max</sub> of 0.80 µM across the factory environments studied
- Points of Departure (PoDs) for SI in the *in vitro* assays ranged from 104–5044 µM.

	Cell Stress Panel	IPP	HTTr (MCF7)	HTTr (HepG2)	HTTr (HepRG)	DevTox Quickpredict	Reprotracker
PoD (µM)	5044	>100	104	1728	829	>1000	>1000
			(BIFROST PoD)				

- The lowest PoD of 104 µM was compared with the highest, worst case C<sub>max</sub> across all simulations (0.80 µM representing the 95th percentile pregnant female population simulation) covering the entire life cycle of SI, resulting in the most conservative BER for SI of 130.









## An exposure-led approach to worker safety assessment of sodium 2- hydroxyethane sulphonate using New Approach Methodologies

Carl Westmoreland<sup>1</sup>, Catherine Breffa<sup>2</sup>, Caroline Chaine<sup>3</sup>, Susann Fayyaz<sup>2</sup>, Fabian Grimm<sup>2</sup>, Steve Gutsell<sup>1</sup>, Reiko Kiwamoto<sup>4</sup>, Mung Sook Lee<sup>2</sup>, Colin Smith<sup>5</sup>, Willemien Wieland<sup>6</sup>, Adam Wood<sup>1</sup> and Tristan Zellmann<sup>6</sup>

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<https://seac.unilever.com/files/c52d0ce8-0fbd-44a4-867b-fa4f7c1260d4/si-poster-for-wc12-final.pdf>

## Next Generation Risk Assessment for Occupational Chemical Safety – a Real World Example

Adam Wood *et al.*

Symposium 1 – *In silico* paths to chemical safety assessment

# Regulatory modernisation – starting the transition with new pre-regulatory frameworks & roadmaps for phasing-in new approaches

Government of Canada / Gouvernement du Canada

## REGULATORY USE OF BIOACTIVITY-EXPOSURE RATIOS FOR PRIORITY-SETTING AND CHEMICAL RISK ASSESSMENT

Humane Society International  
Webinar on Risk Assessment  
July 13, 2022

Canada.ca | Health | Product safety | Chemical safety | Chemical substances | Chemical substances fact sheets and frequently asked questions

### Use of new approach methods (NAMs) in risk assessment

Fact sheet series: Topics in risk assessment of substances under the *Canadian Environmental Protection Act, 1999* (CEPA 1999)

Tara Barton-Maclaren, PhD, Health Canada

## Notice of intent on the development of a strategy to guide the replacement, reduction, or refinement of vertebrate animal testing under the Canadian Environmental Protection Act, 1999 (CEPA)

CEPA, HC and ECCC continue to work on the establishment of frameworks and alternative approaches into prioritization and risk assessments. These scientific advances align with the work of a growing number of regulatory authorities, including those in the United States, Australia, and the European Union, where an emphasis is being placed on modern approaches to replace, reduce, or refine the use of vertebrate animals in toxicity testing wherever possible. This includes the development of strategies and research programs to accelerate development and implementation of NAMs for regulatory decision-making.

European Commission

Business, Economy, Euro

Internal Market, Industry, Entrepreneurship and SMEs

Home | Single market and standards | Industry | Entrepreneurship and SMEs | Access to finance | Sectors | Tools and databases

Home > Presentations from the Workshop on the Commission roadmap towards phasing out animal testing for chemical safety assessments

## Presentations from the Workshop on the Commission roadmap towards phasing out animal testing for chemical safety assessments

These presentations were given as part of the Commission's workshop that was held in Brussels as a 2-day hybrid event from 11 - 12 December 2023.

Towards an animal-free regulatory system for industrial chemicals

31 May - 1 June  
Helsinki

ECHA  
EUROPEAN CHEMICALS AGENCY

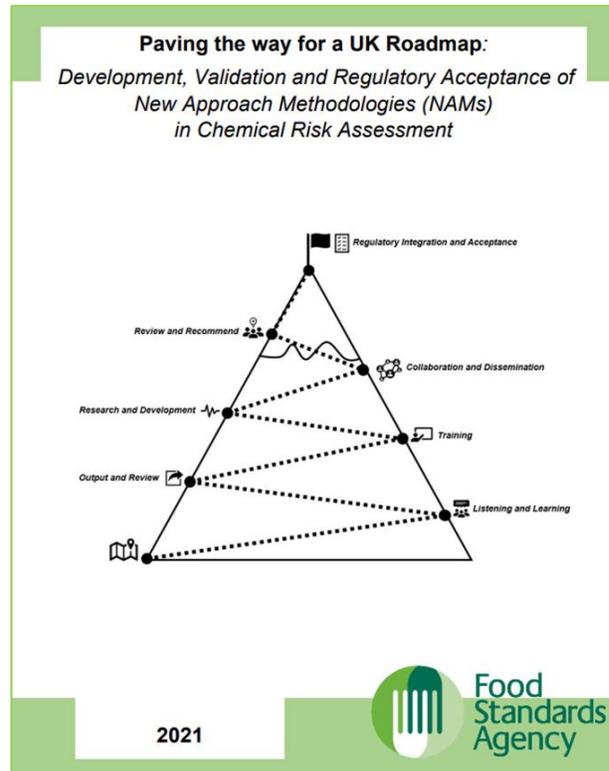


## *Towards an animal-free regulatory system for industrial chemicals*

### ECHA New Approach Methodologies Workshop background paper

The NAMs workshop "Towards an animal free regulatory system for industrial chemicals" will provide the space for collecting feedback and commitments from all stakeholders on how to accelerate the transition to a regulatory system with no or minimal reliance on animal testing.

# Enabling application of modern safety science for regulatory purposes in UK

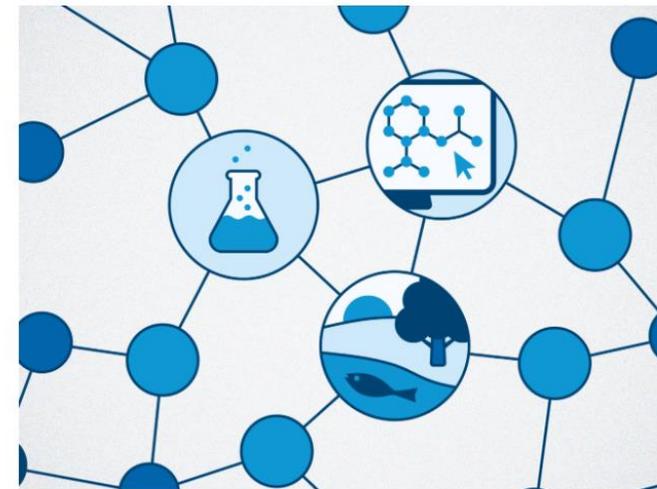


Overall objectives of the roadmap are to:

- identify latest available NAMs for optimal risk assessment
- learn from other regulatory agencies and beyond
- validate through case studies
- build confidence in NAMs in the regulatory setting
- develop skills and training
- implement and integrate NAMs in the regulatory setting

## NAMs Network launch event

Tue, Apr 30 2024, 9:30 - 17:00



The NAMs Network is open to stakeholders from all sectors and at all career levels. The purpose of the Network is to encourage and support conversations and collaborations across sectors in new approach methodologies.



Pioneering Better Science

- Session 1: Welcome and overview of the NAMs landscape.
  - Invited presentations from Ruth Roberts (Birmingham University, Apconix) and Carl Westmoreland (Unilever).
- Session 2: Taking NAMs from development to application.
- Session 3: CRACK IT as a mechanism to accelerate the development and uptake of NAMs.
- Session 4: Working together to accelerate the adoption of NAMs.
- Session 5: Changing the way we think about safety assessment.
  - Invited presentation from Camilla Alexander-White (MKTox).

# Joining forces in advocating for regulatory application of innovative toxicological science to “Close the Gap”



National Centre  
for the Replacement  
Refinement & Reduction  
of Animals in Research



## Workshop report: Opportunities for the UK to develop world-leading chemicals regulation

Workshop: 11 May 2023  
Report published: 23 October 2023

Dr Natalie Burden, NC3Rs  
Dr Carl Westmoreland, Unilever  
Dr Andrew Scott, Unilever  
Professor Ian Kimber, University of Manchester



National Centre  
for the Replacement  
Refinement & Reduction  
of Animals in Research



## Vision for a Modern Science-Based Approach to UK Chemicals Regulation

### UK Chemicals Regulations: Time for change

1. As the result of exit from the European Union, the UK Government has a unique opportunity to modernise the UK's approach to assuring the safety of chemicals (including industrial chemicals, pesticides and biocides). The Government can now make important changes to domestic regulations to improve the scientific quality and relevance of chemical safety assessment to protect human health and the environment.
2. Embracing a modernised approach to UK chemicals regulation that embeds the latest science and technology into an agile system will yield significant benefits. These include scientific, business and economic advantages as well as reducing the reliance on animal-based testing methods and developing a more sustainable approach to safety assessment. The purpose of this short position paper is to share a vision for a science-based approach to chemicals regulation which positions the UK as a world-leader within global markets. The paper focuses on what can be achieved now and why change is important, rather than mapping out the hurdles that must be negotiated to deliver the vision.

# A biochemist's view today: good progress in applying innovative toxicological science; much more to do in strengthening regulatory science & its application

1987

Safety, Environmental & Regulatory Science (SERS) | Unilever

### MSc Toxicology - is this substance likely to cause reproductive or developmental effects in humans and at what exposure levels?

Test conditions		Prenatal developmental toxicity, skeletal effects	
Type of study	toxicology segment II including rearing group	Dose (mg/kg)	Effects
GCP	yes	0	0.02
Animal species	rat	0.2	0.2
Route of administration	oral	0.5	0.5
Method of administration	gavage	1	1
Dose levels (mg/kg bodyweight)	0, 0.2, 2.0, 6.0, 15.0	2	2
Days of treatment during pregnancy (TDI)	7-16 (incidence of malting - day 1)	3	3
Number of animals per group	21, 19, 17, 23 (C-section)	4	4
	8	5	5

Species relevance?  
Dose extrapolation?  
Data reproducibility?  
Mechanistic understanding?  
Uncertainty factors?

Guidance on Evaluation of Reproductive Toxicity Data  
ecetoc  
Monograph No. 31

1991

Toxicology, 71 (1992) 129-136  
Elsevier Scientific Publishers Ireland Ltd.

### Species differences in the hepatotoxicity of coumarin: A comparison of rat and Mongolian gerbil

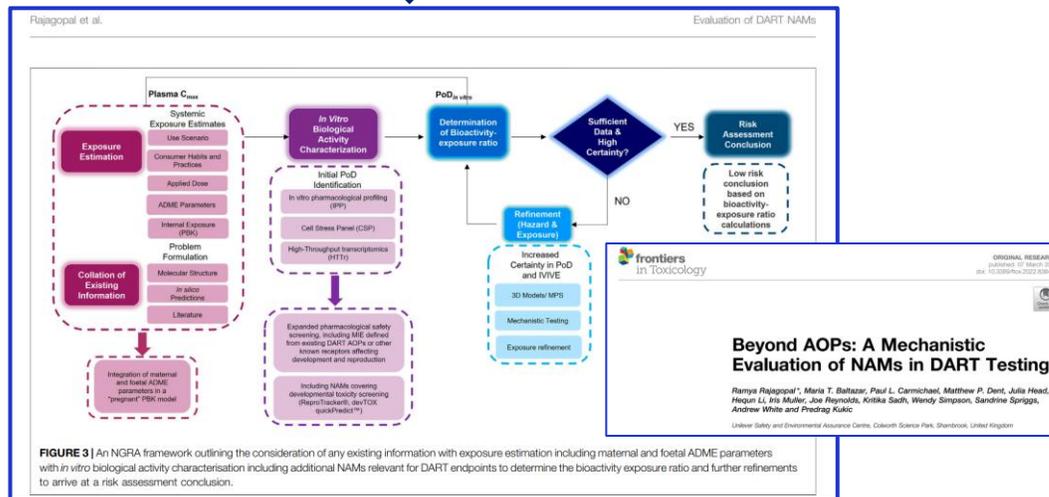
Julia H. Fentem<sup>a</sup>, Jeffrey R. Fry<sup>a</sup> and Norman W. Thomas<sup>b</sup>

Departments of <sup>a</sup>Physiology and Pharmacology and <sup>b</sup>Human Morphology, Medical School, Queen's Medical Centre, Nottingham NG7 2UH (U.K.)

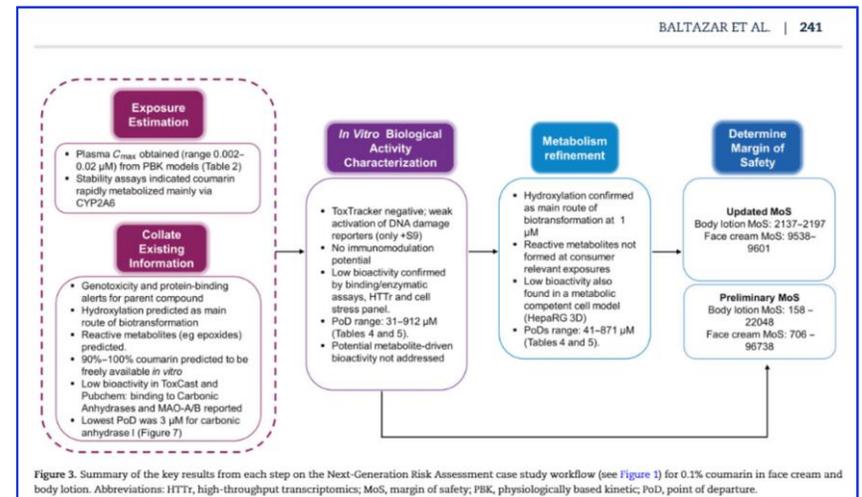
(Received July 3rd, 1991; accepted October 23rd, 1991)

2022

Application of an integrated approach using NAMs for DART  
NGRA  
Katy Wilson et al.



2020



# Thank You ...

- Unilever's safety scientists in SEAC (Safety & Environmental Assurance Centre)
- External scientific collaborators – academia, companies and governmental & NGO leads
- Kevin Chipman & Jeffrey Fry
- Phil Botham
- Carl Westmoreland
- BTS Executive Committee

website link: [Safety & Environmental Sciences | Unilever](#)

## Safety & Environmental Science

Unilever's Safety and Environmental Assurance Centre (SEAC)

“  
Advances in science and technology mean that we can generate much more relevant safety data to protect people and the environment using modern non-animal approaches.  
”

### Our Science

#### Safety Without Animal Testing

Unilever is committed to ending animal testing globally. We use the latest non-animal safety science, not animals, to assure the safety of our products and the ingredients in them.

#### Environmental Sustainability Science

Unilever's ambition is to be the global leader in sustainable business. We have been using Life Cycle Assessment (LCA) approaches for many years to assess the environmental impacts of our products.

#### Case Studies

Real-life and hypothetical case studies to demonstrate how our leading-edge safety and environmental sustainability science capabilities are applied.

### Partnerships & Collaborations

We are proud to be working closely with leading scientific authorities around the world, including academic and government scientists.

[Learn more about Partnerships & Collaborations](#)