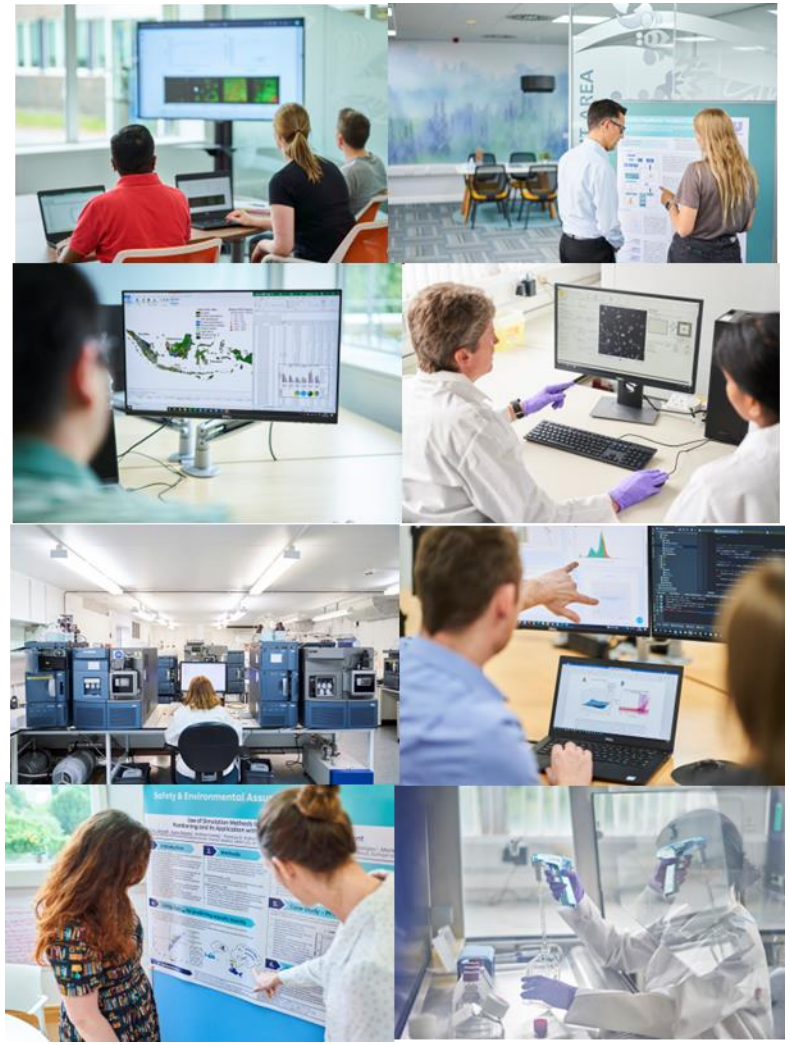
Embracing innovative toxicological science to transform regulatory assessments of chemical safety

Dr Julia Fentem MBE FBTS

BTS Paton Prize Award Lecture – April 2024

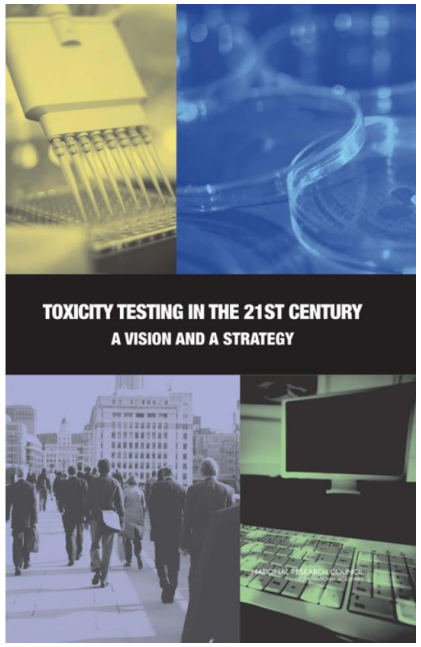
Acknowledgement:
>80 toxicologists, biologists, chemists, computational modellers, data scientists & exposure / risk assessors in Unilever's Safety & Environmental Assurance Centre (SEAC)



Unilever

"Mind the Gap": 21st century safety science, 20th century regulatory testing

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



June 18, 2021, 9:01 AM 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

Alternatives to Laboratory Animals
2021, Vol. 49(4) 122–132

DOI: 10.1177/02611929211040824
journals.sagepub.com/home/atl
SAGE

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

Closing the gap requires investment in new regulatory science capability and use of modern scientific methods & new types of data for regulatory purposes

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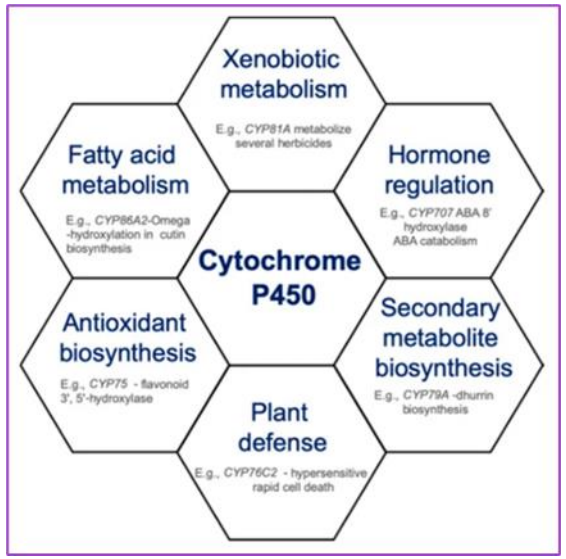
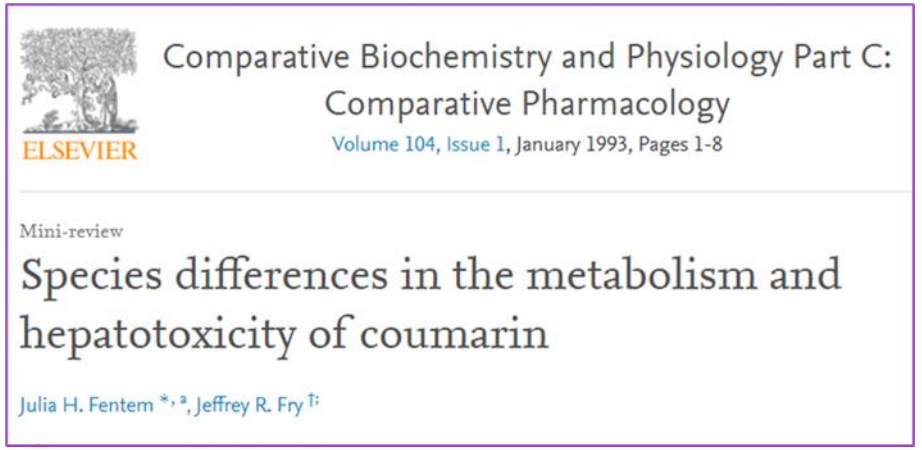
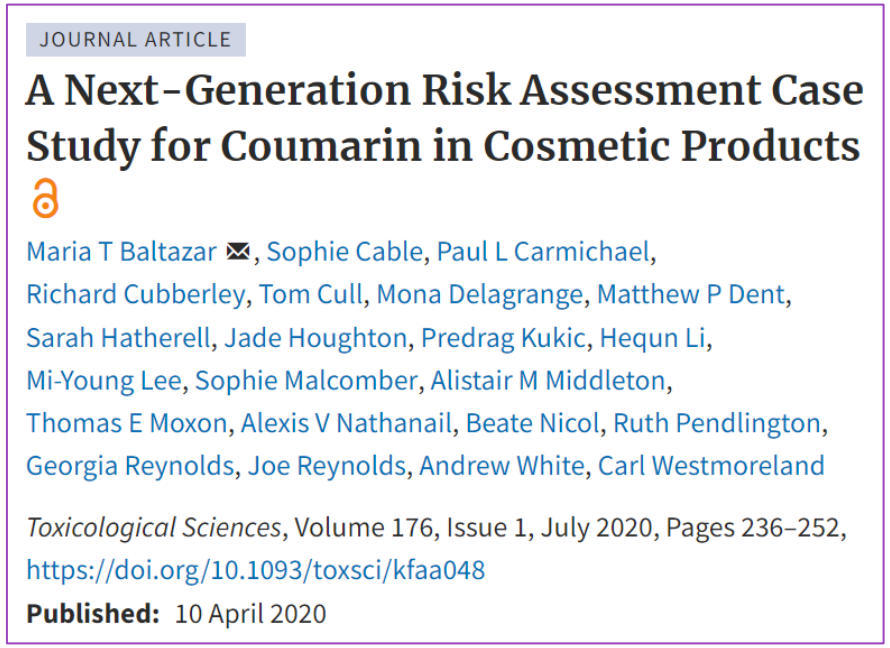
Cytochrome P450, metabolism-mediated toxicity & re-thinking risk assessment frameworks with our new safety science toolbox







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UNIVERSITY OF BIRMINGHAM

QUEEN'S MEDICAL CENTRE
UNIVERSITY OF NOTTINGHAM
MEDICAL SCHOOL

SEAC SAFETY & ENVIRONMENTAL ASSURANCE CENTRE
Scientific Excellence And Collaboration

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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)
	8,

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

ecetoc

Monograph No. 31

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MSc Toxicology – developing new models & mechanistic insights

ELSEVIER

Toxicology in Vitro

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

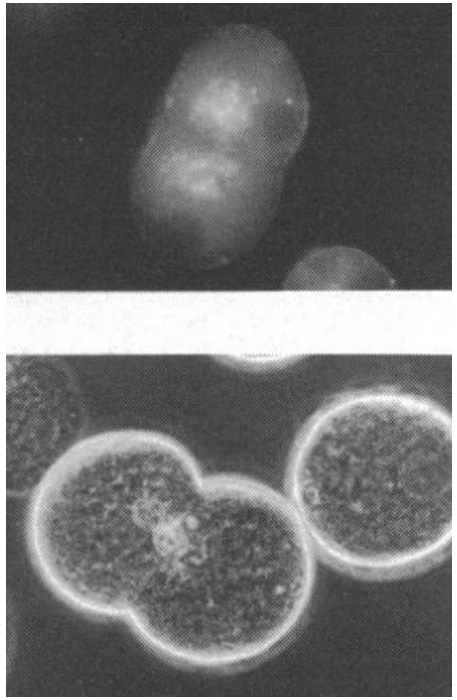
Session 3

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

J.H. Fentem [a] *, B. Foster [a] †, C.O. Mills [‡], R. Coleman [a], J.K. Chipman [a]

[a] Department of Biochemistry, University of Birmingham, UK

[‡] Department of Medicine, University of Birmingham, UK



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PhD Biochemical Toxicology – metabolism & hepatotoxicity of coumarin

The University of Nottingham

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 [1], J R Fry

Affiliations – collapse

Affiliation

1 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 [1], J R Fry, D A Whiting

Affiliations – collapse

Affiliation

1 Department of Physiology & Pharmacology, University of Nottingham, U.K.

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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

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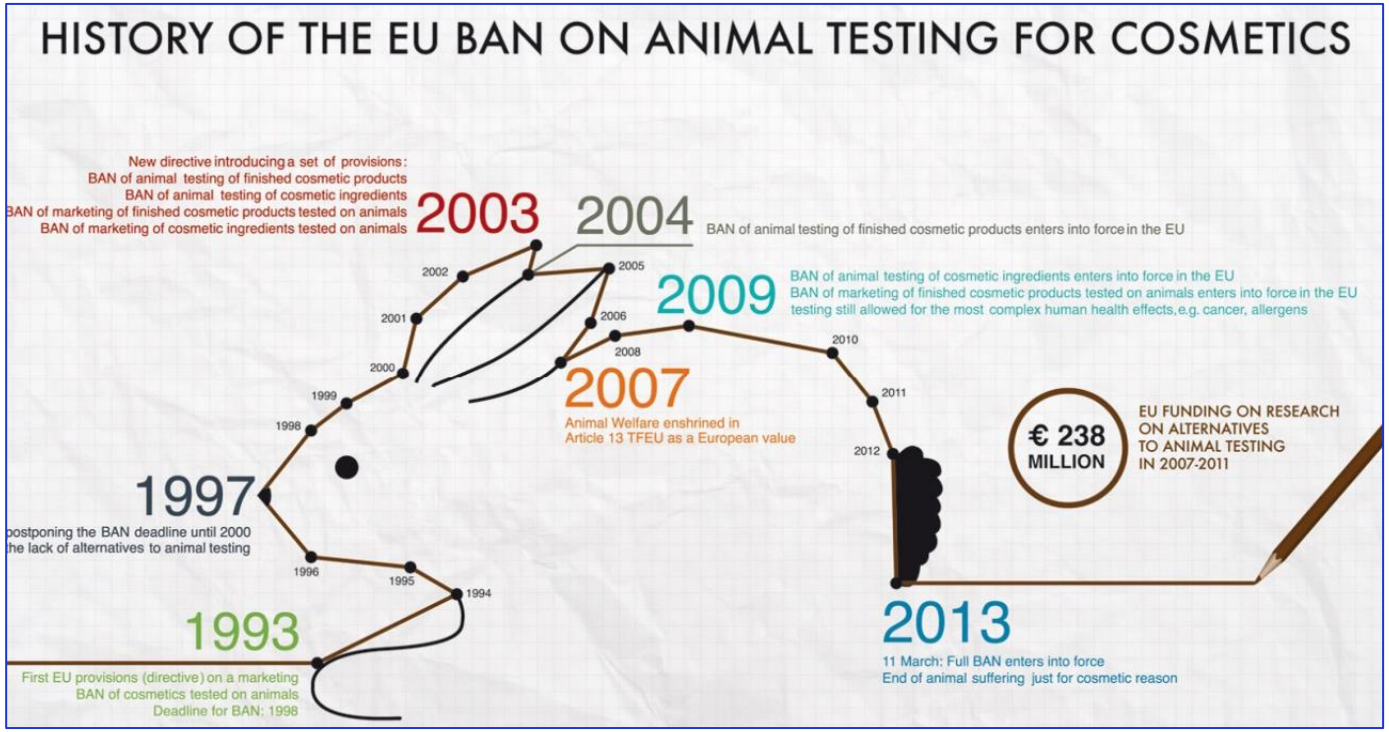
Assuring safety of cosmetics ingredients & products without animal testing

- 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)]

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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 [1], Mark Chamberlain, Bart Sangster

Affiliations – collapse

Affiliation

1 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 [1]

Unilever

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 [1], 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.

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

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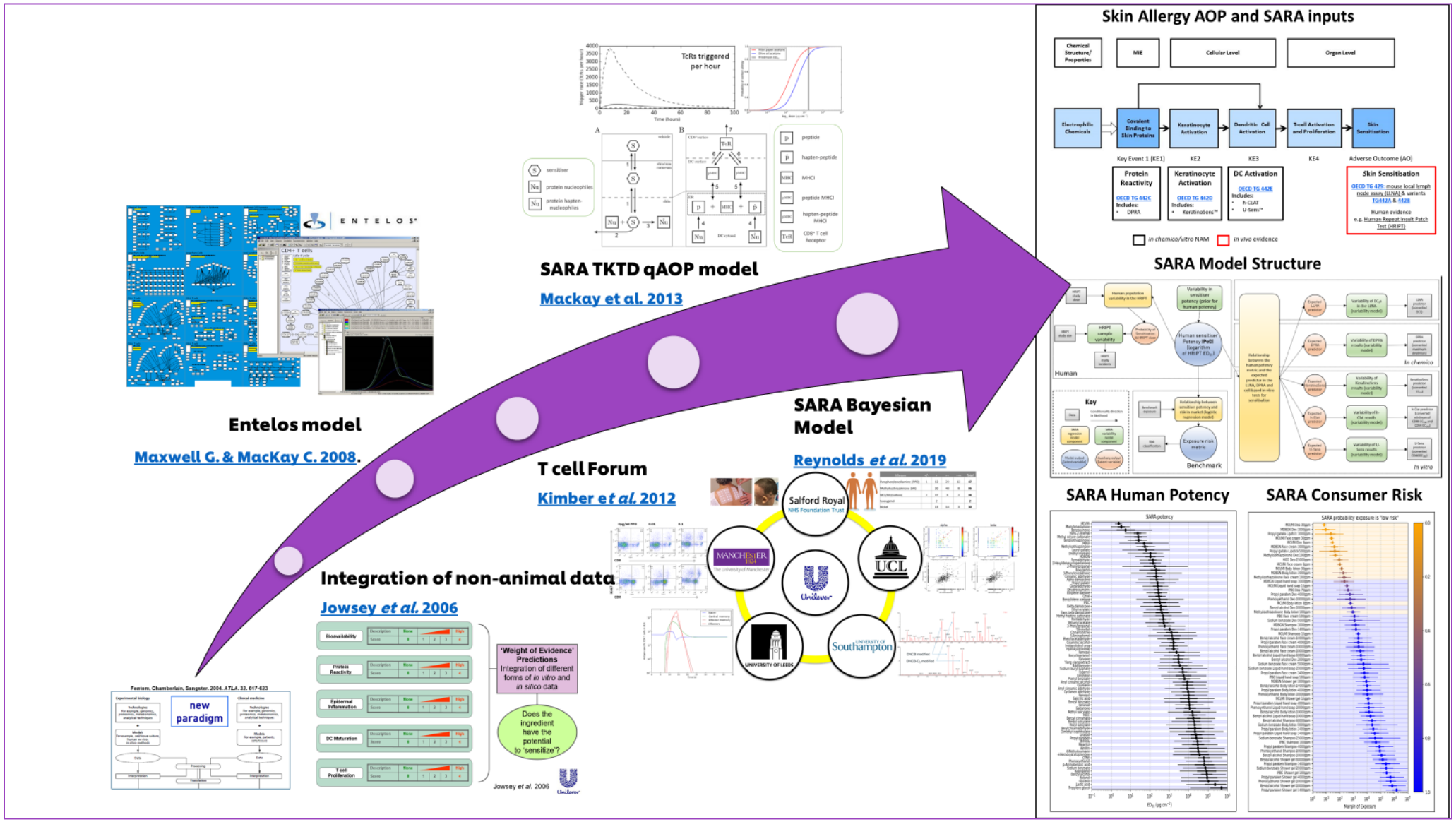
Transforming our approach for Skin Allergy Risk Assessment (SARA)



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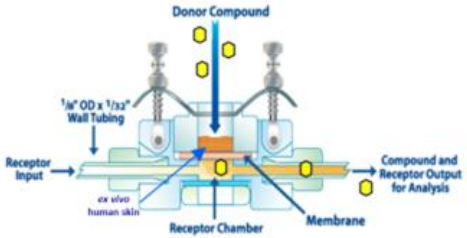
Assessing consumer safety of cosmetics ingredients without new animal testing – maximising use of existing information & non-animal approaches

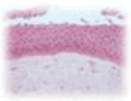
- All our risk assessments are exposure-led

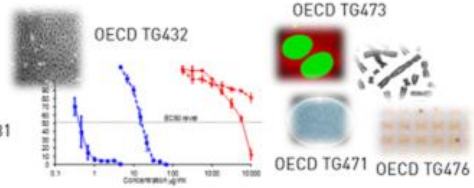
Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall et al., 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor	Calculated daily exposure (g/d)	Calculated relative daily exposure (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67 g	279.20	0.01	0.19	2.79
Hand wash soap	20.00 g	-	0.01	0.20	3.33
Hair care					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74

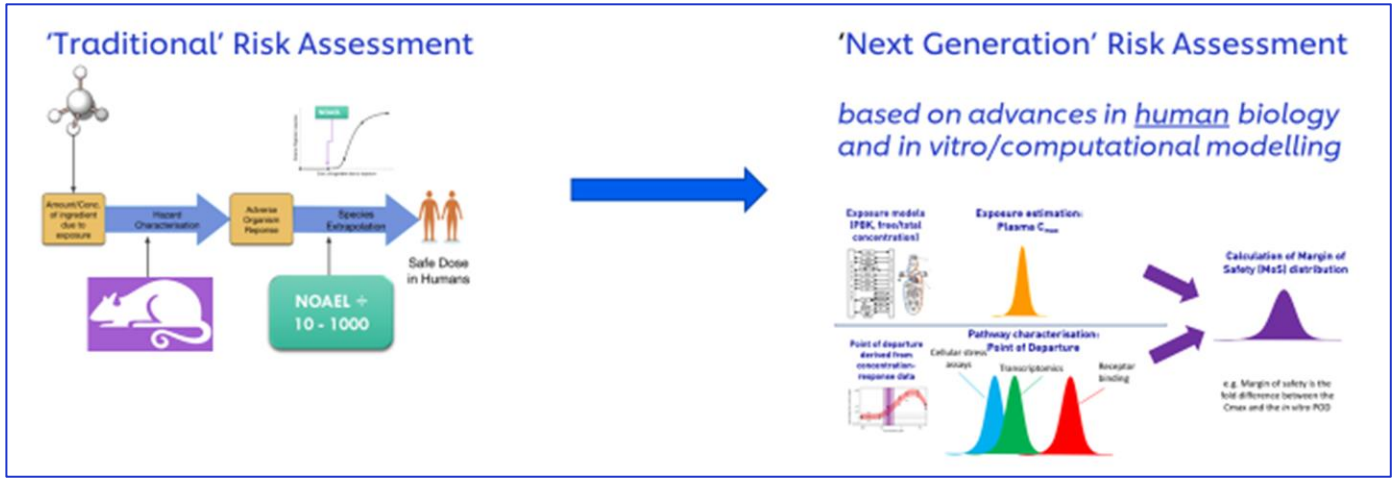


- Use all available safety data on the ingredient
  - clinical, epidemiological, animal (if dates permit), *in vitro*, etc.
- Exposure-based waiving approaches (e.g. toxicological threshold of concern)
- *In silico* predictions
- History of safe use
- Read-across
- Use of existing OECD *in vitro* approaches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



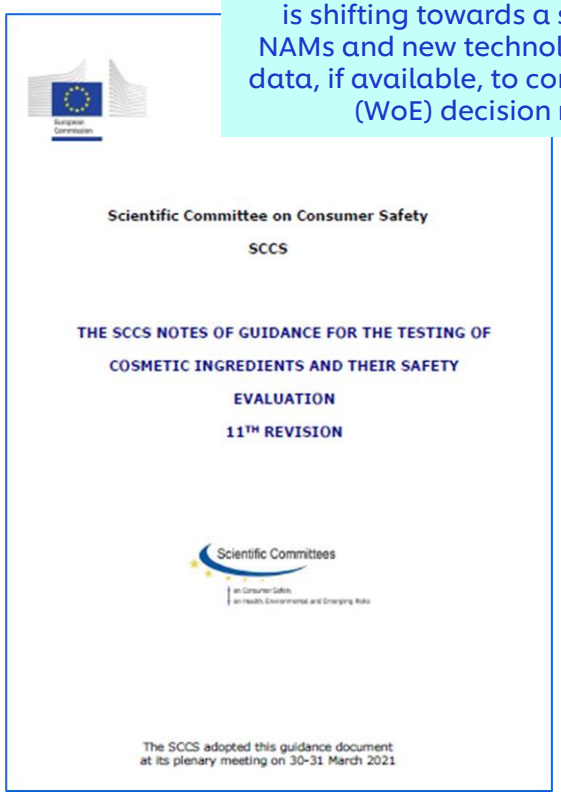


Embracing Next Generation Risk Assessment (NGRA) for assuring the consumer safety of cosmetics ingredients



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."



Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION

11TH REVISION

Scientific Committees

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

Scientific Committee on Consumer Safety (2021)

ICCR International Cooperation on Cosmetics Regulation

International Cooperation on Cosmetics Regulation (2018)

Contents lists available at ScienceDirect

Computational Toxicology

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

ELSEVIER

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

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

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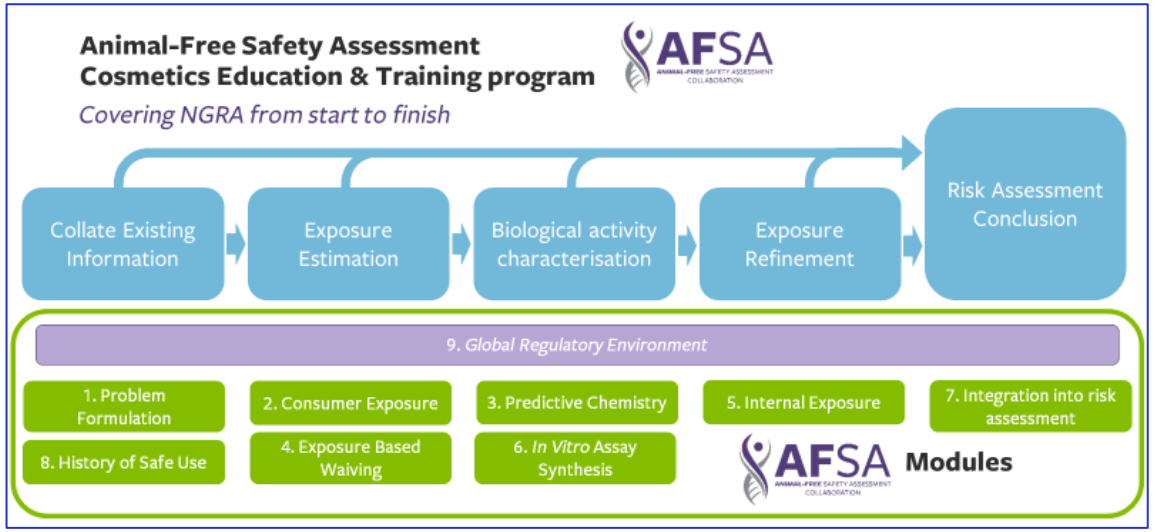
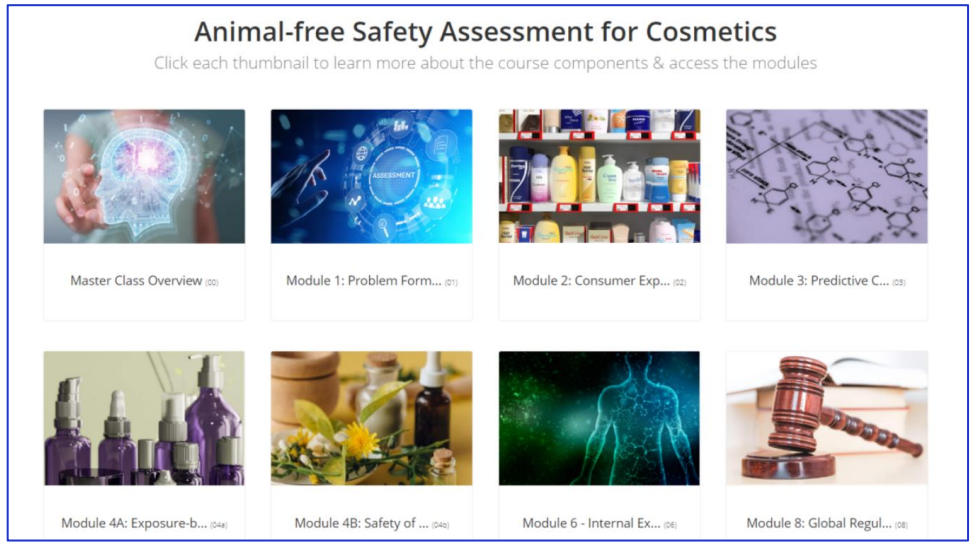
Embedding use of new safety science for non-animal cosmetics assessments





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

ctpa

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.

ICCS INTERNATIONAL COLLABORATION ON COSMETICS SAFETY

ADVANCING ANIMAL-FREE SCIENCE FOR COSMETICS WORLDWIDE

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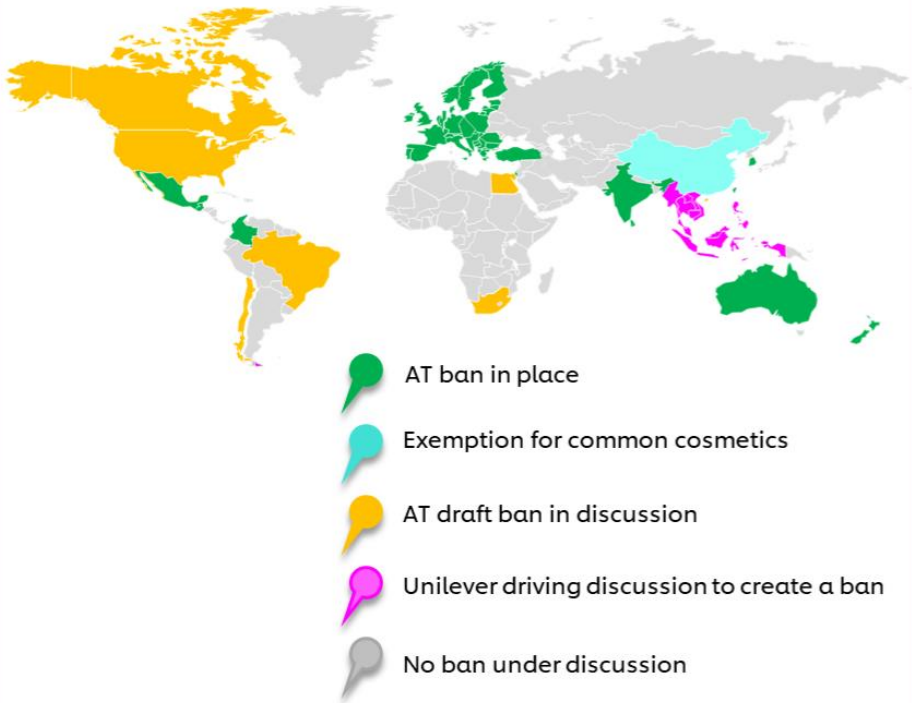
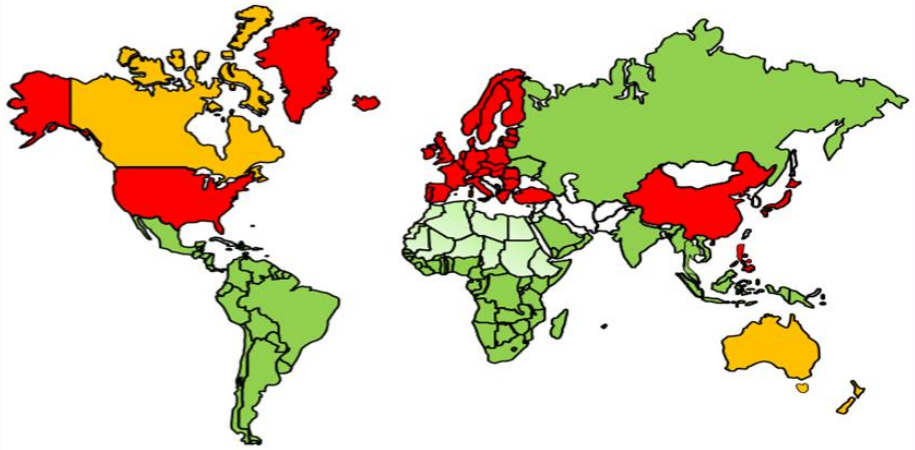
Cosmetics regulations ban animal tests, Chemicals regulations require them

COSMETICS
Animal testing bans since 1998



CHEMICALS



US, EU, China, Japan, Philippines & UK typically require AT

Canada & Australia registrations may require AT

No current requirements for AT

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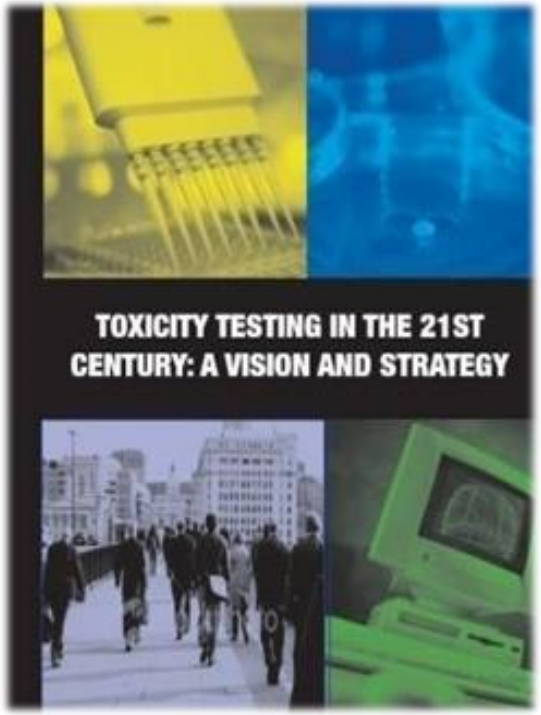
US National Academy of Sciences report in 2007 catalysed engagement of regulatory authorities with a new approach anchored in human biology



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 [1], 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.

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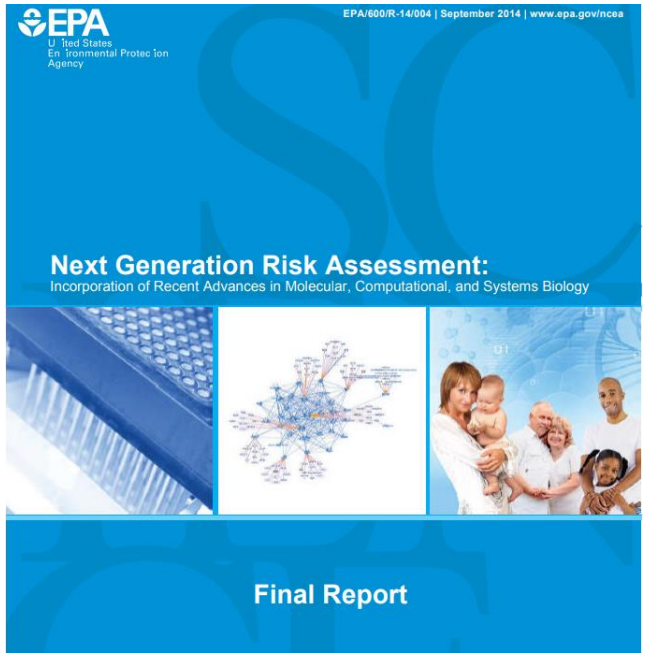
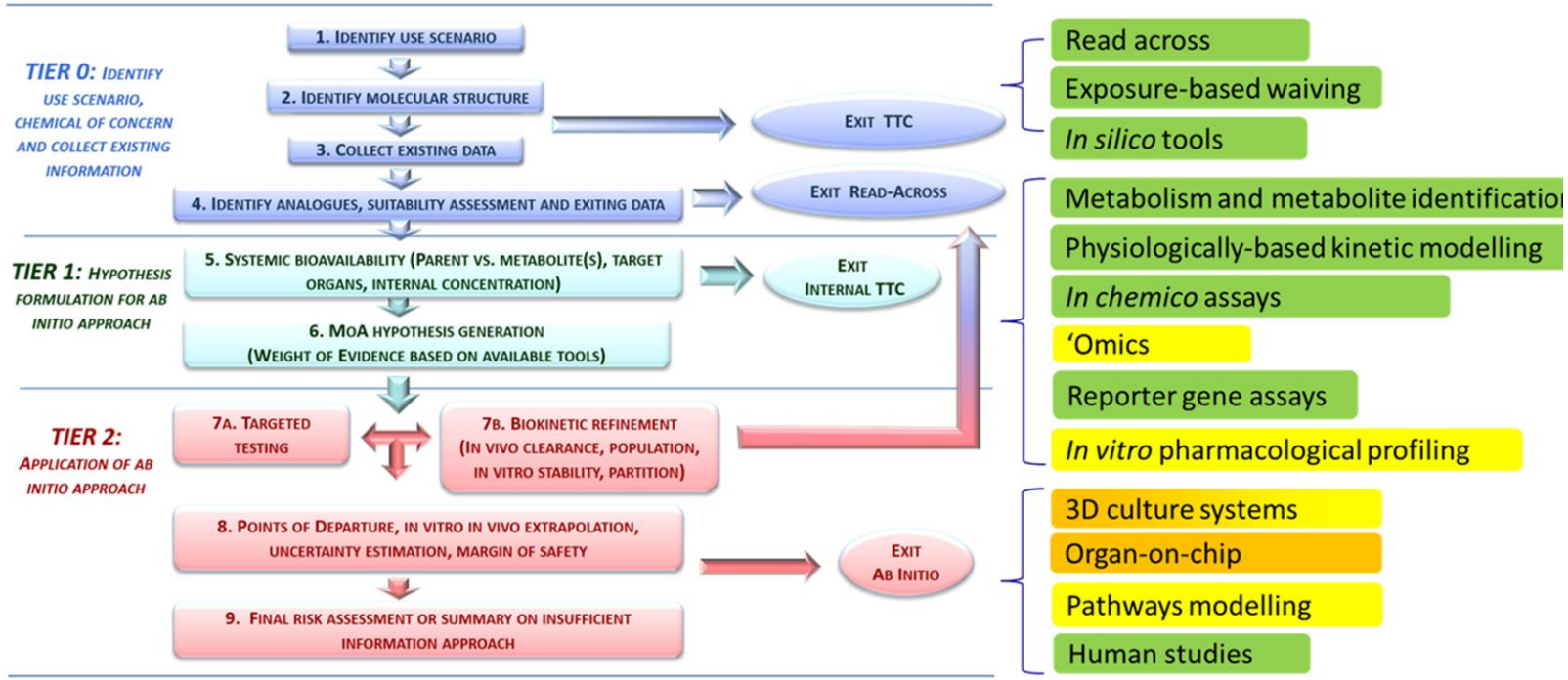
Next Generation Risk Assessment (NGRA) approaches for assuring safety



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

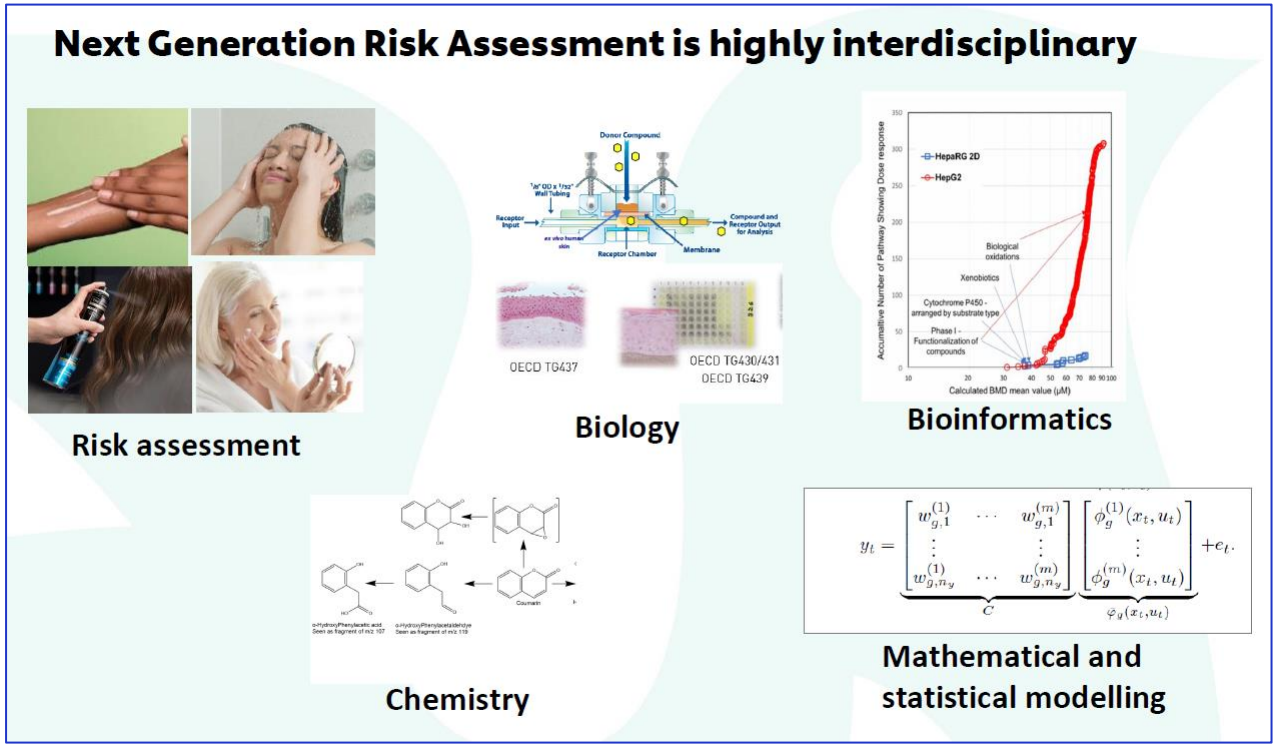


Comput Toxicol. 2017 Nov;4:31-44. doi: 10.1016/j.comtox.2017.10.001.

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

Berggren E[1], White A[2], Ouedraogo G[3], Paini A[1], Richarz AN[1], Bois FY[4], Exner T[5], Leite S[6], Grunsven LAV[6], Worth A[1], Mahony C[7].

Advancing NGRA scientific capabilities for chemical risk assessment



[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

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

EPA United States Environmental Protection Agency

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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)

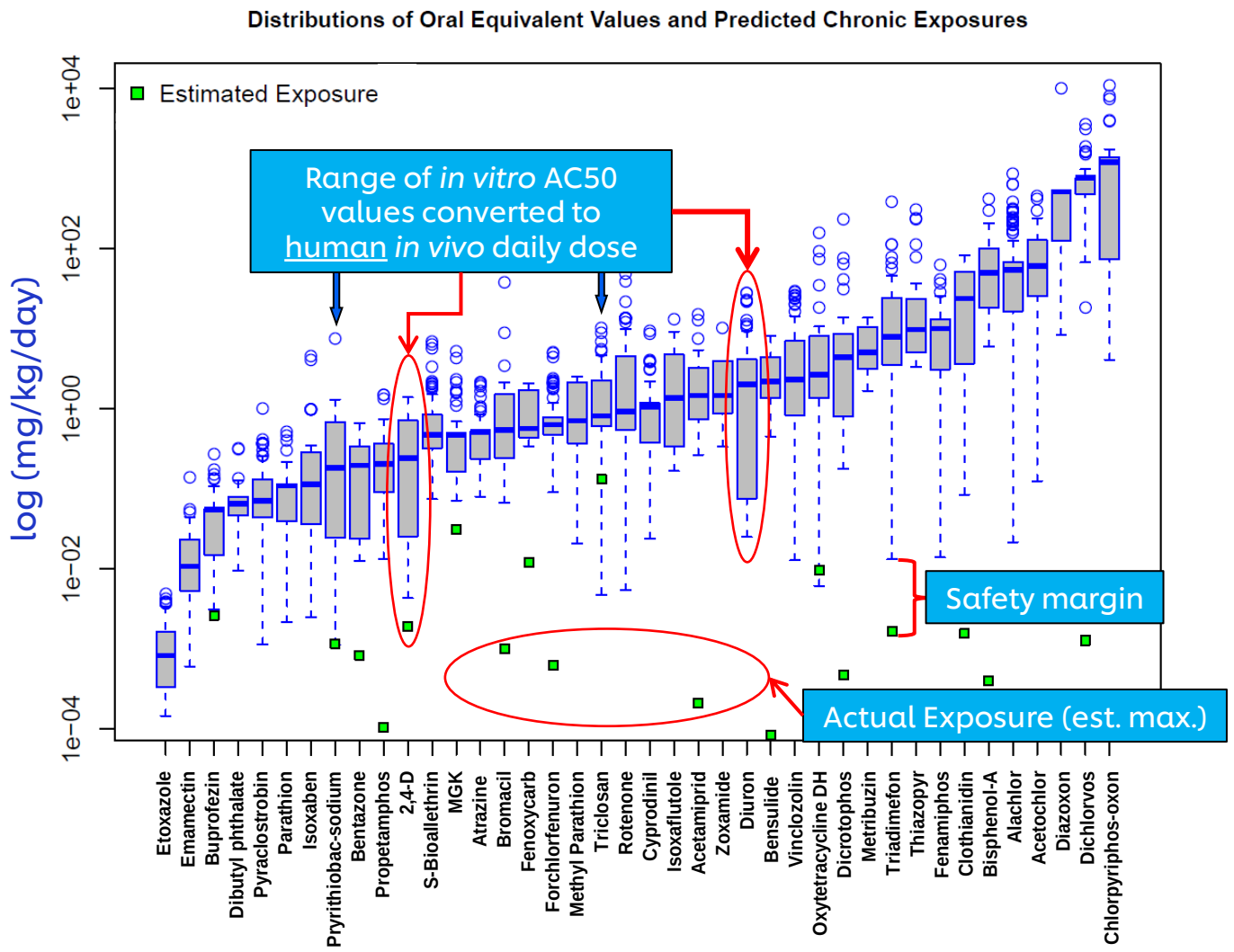
WASHINGTON – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), 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

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.**

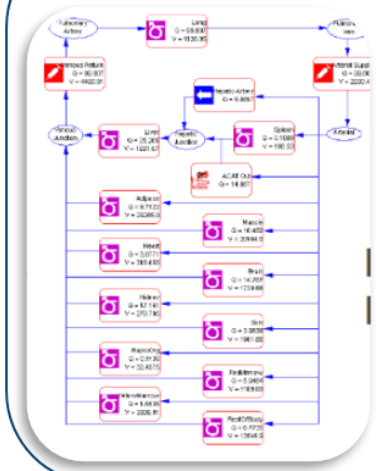
At no point does NGRA attempt to predict the results of high dose toxicology studies in animals.

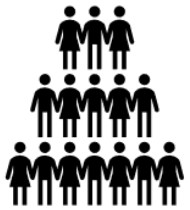
NGRA **uses new exposure science and understanding of human biology.**

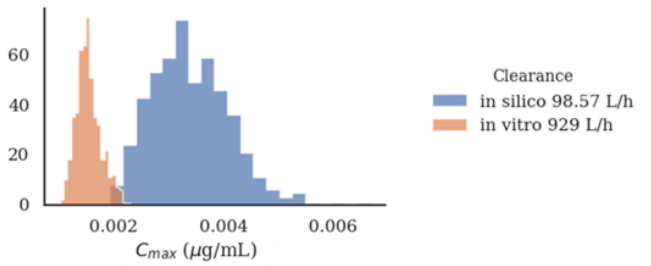
Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

Key tools in Unilever's NGRA approach for systemic effects

PBK Modelling







Toxicology in Vitro (2020), **63**, 104746

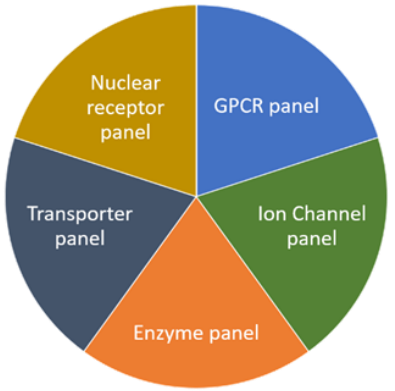
In vitro pharmacological profiling


PERSPECTIVES

A GUIDE TO DRUG DISCOVERY — OPINION

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling

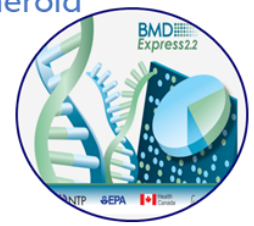
Joanne Bowes, Andrew J. Brown, Jacques Hamon, Wolfgang Jarolimek, Arun Sridhar, Gareth Waldron and Steven Whitebread



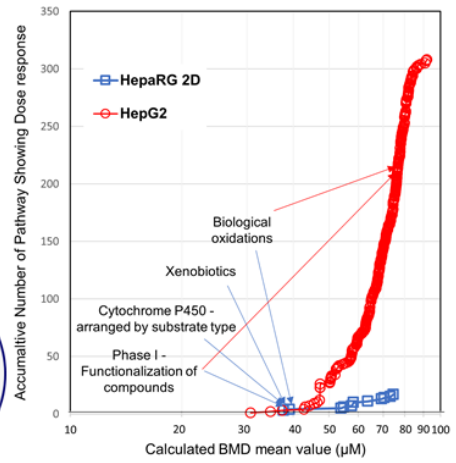
eurofins | Cerep

Transcriptomics

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

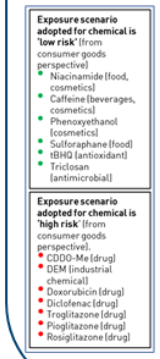


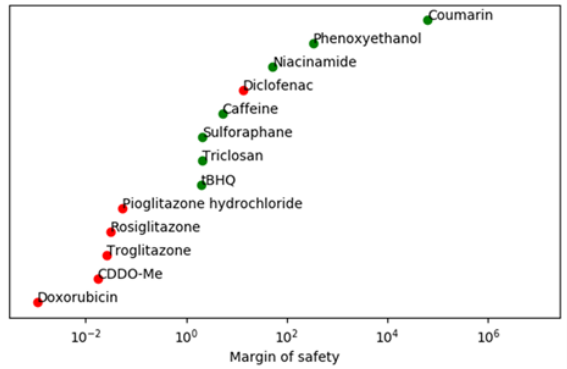
BMDexpress 2



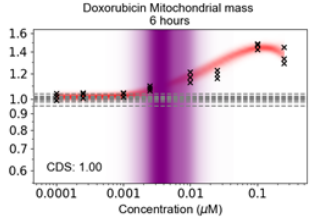
Cellular Stress Pathways

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





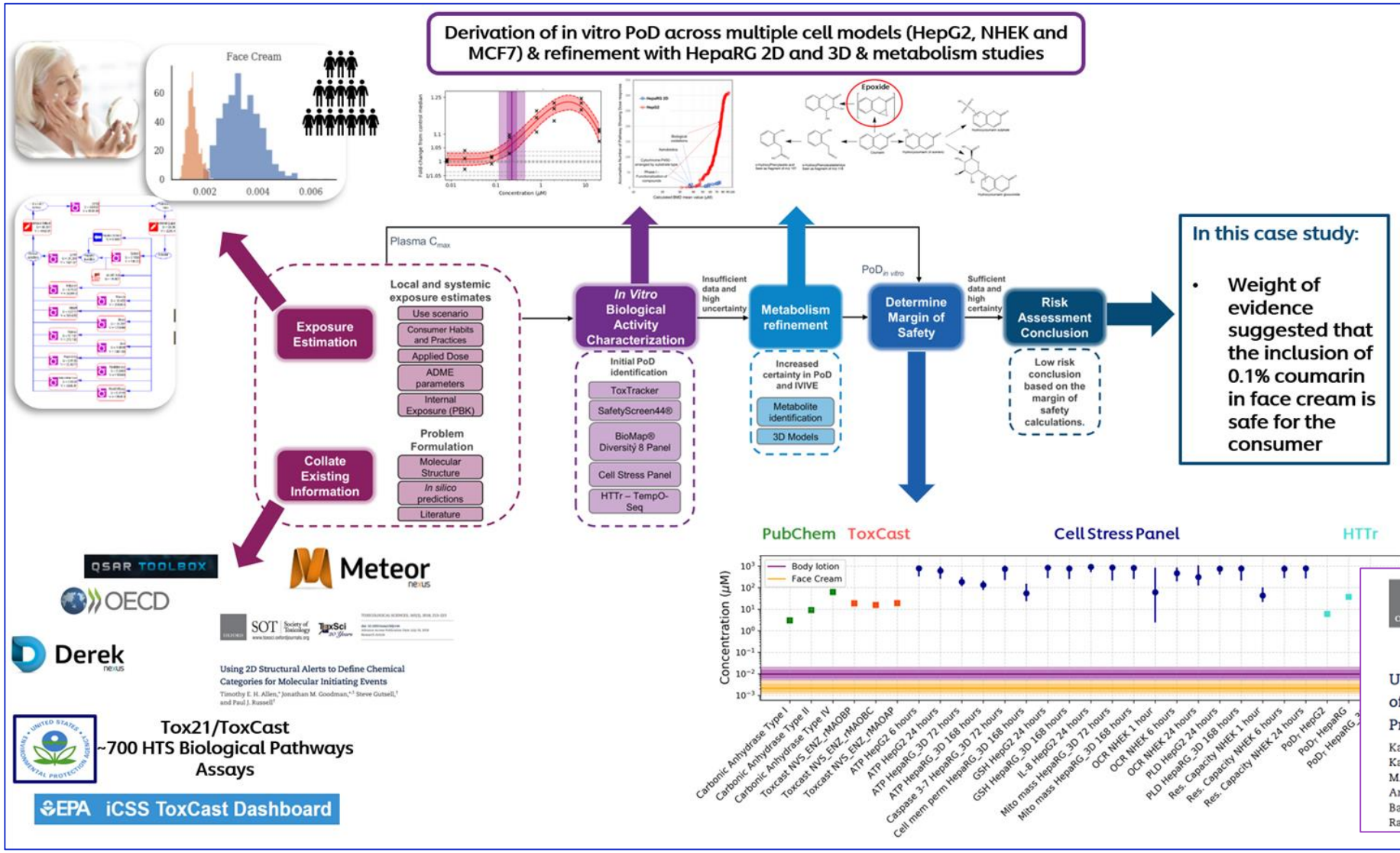
cyprotex AN EVOTEC COMPANY



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

Unilever

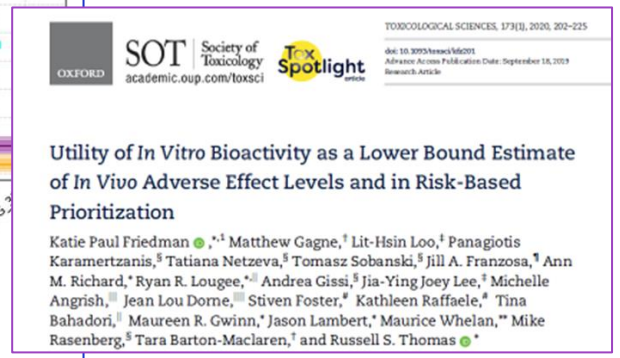
NGRA frameworks developed to enable data integration & interpretation



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

Exposure tools to inform level of Systemic Exposure

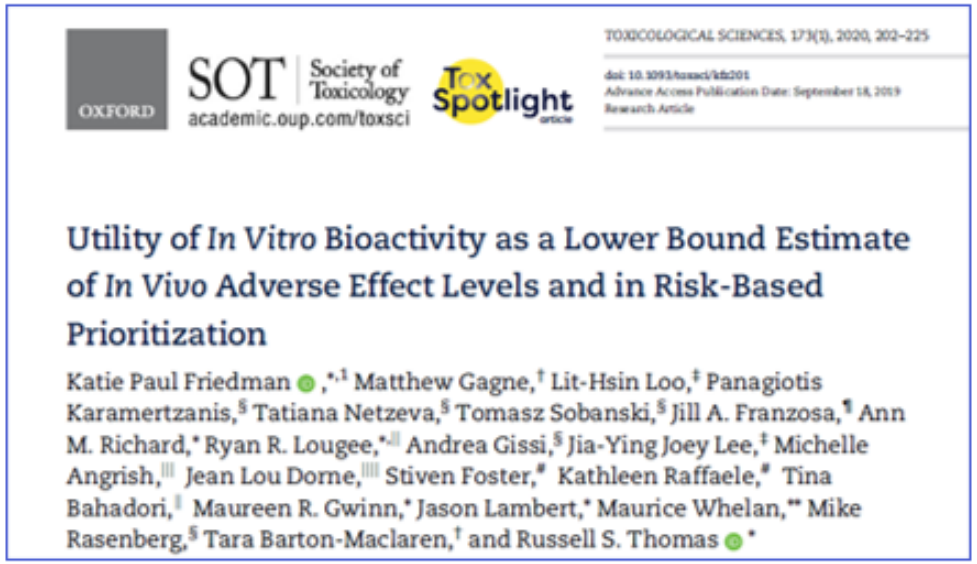
Bioactivity tools to provide Points of Departure: ***Bioactivity - Exposure Ratio***



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

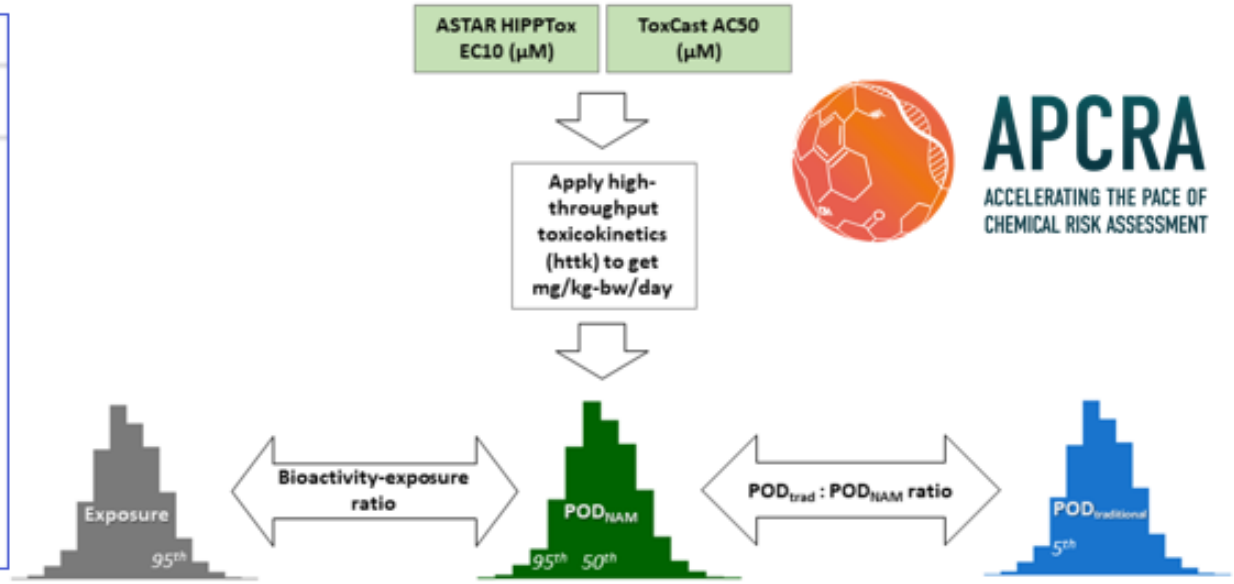
Unilever

Interpreting non-animal data for assessing chemical safety
Bioactivity – Exposure Ratio (BER) approach


OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article
TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 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,*,1 Matthew Gagne,† Lit-Hsin Loo,‡ Panagiotis Karamertzanis,§ Tatiana Netzeva,§ Tomasz Sobanski,§ Jill A. Franzosa,¶ Ann M. Richard,* Ryan R. Lougee,*,|| Andrea Gissi,§ Jia-Ying Joey Lee,‡ Michelle Angrish,|| Jean Lou Dorne,|| Stiven Foster,# Kathleen Raffaele,# Tina Bahadori,|| Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,§ Tara Barton-Maclaren,† and Russell S. Thomas*



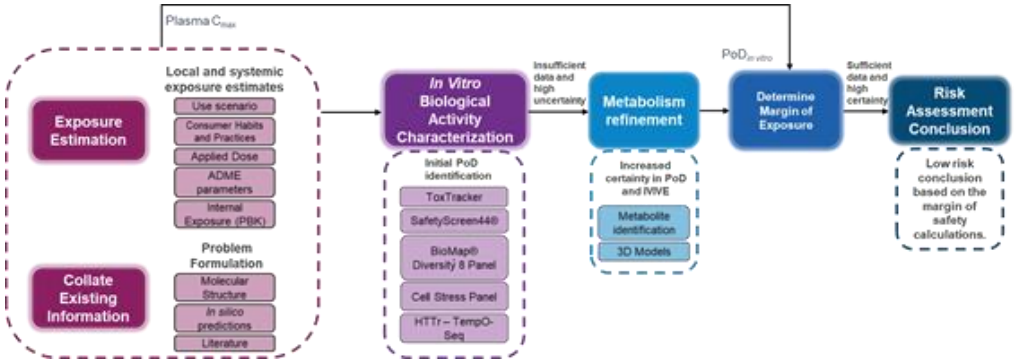
- Evaluation of *in vitro* NAMs, exposure modelling and dose-response models
- For 89% chemicals NAM PoD was **more conservative** than traditional PoD
- **Bioactivity - Exposure ratios (BERs) approach useful to accelerate screening and chemicals assessment using NAMs for hazard and exposure**

NAM = New Approach Method | Non-Animal Method

Unilever

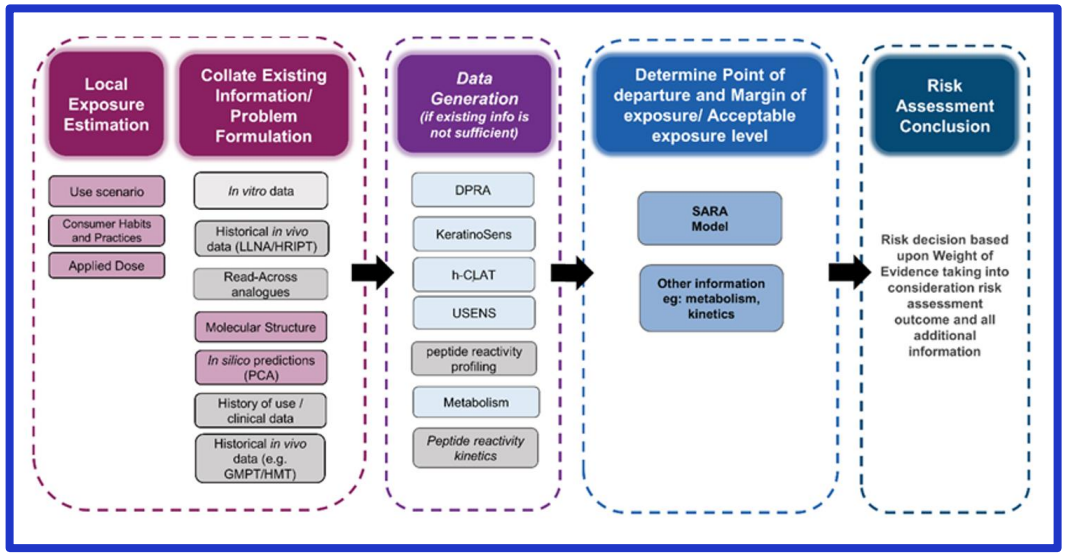
Unilever NGRA frameworks for using non-animal data for consumer safety decisions

Systemic



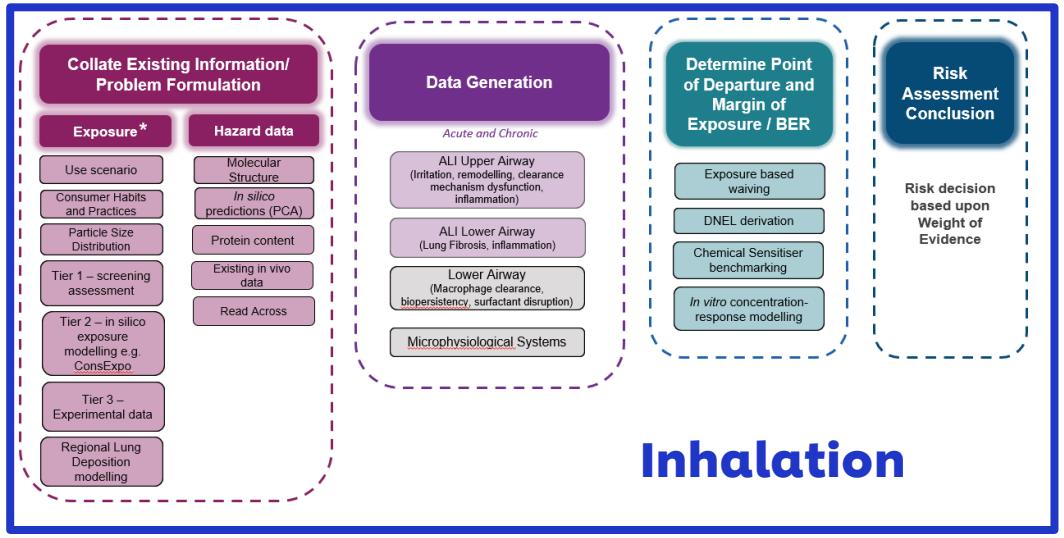
Baltazar et al (2020) *Toxicol Sci*, **176**, 236-252

Skin Allergy

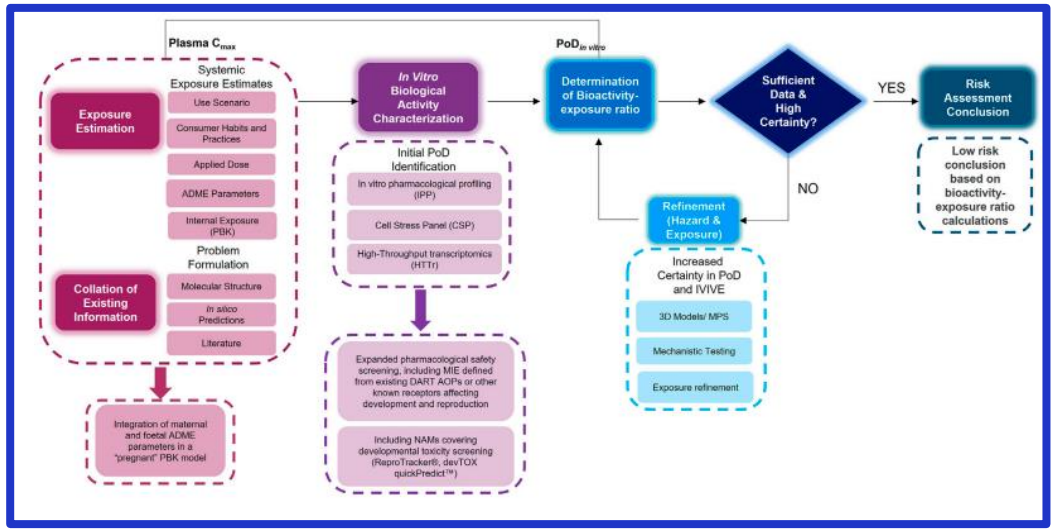


Reynolds et al (2021) *Reg Tox Pharmacol*, **127**, 105075

Inhalation



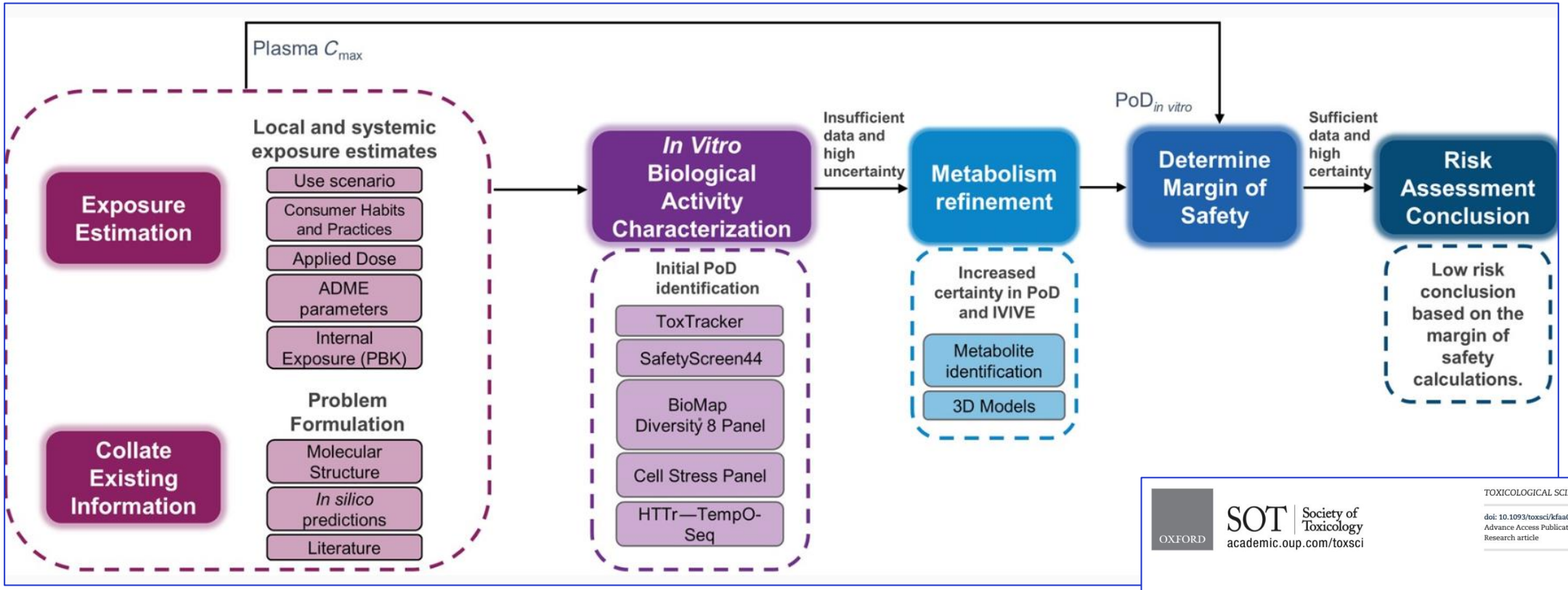
Developmental & Reproductive (DART)



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/kfaa048
Advance Access Publication Date: April 10, 2020
Research article

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

Maria T. Baltazar,[1] 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, and Carl Westmoreland

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

Unilever

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

Toxicol Sci **176**, 236–252

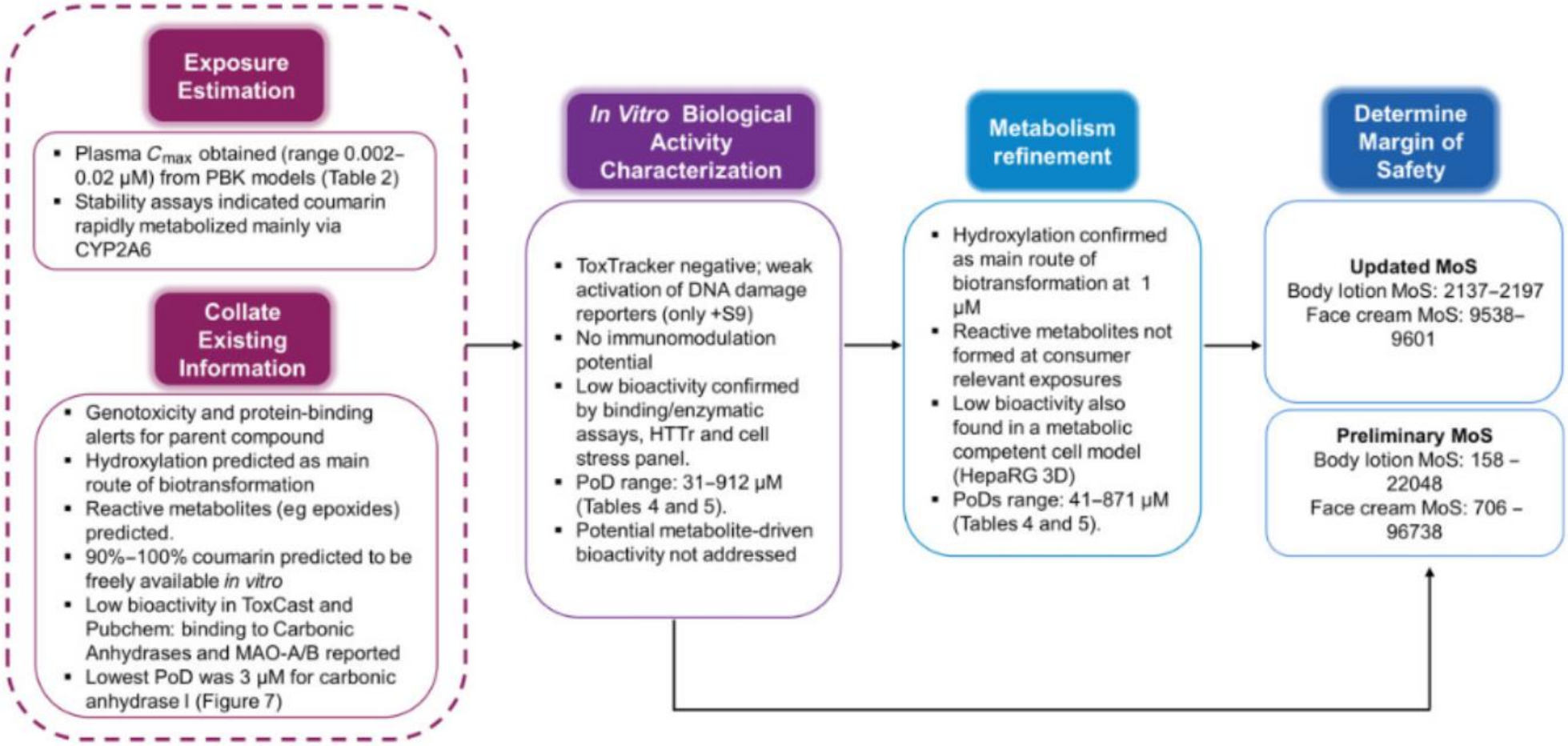
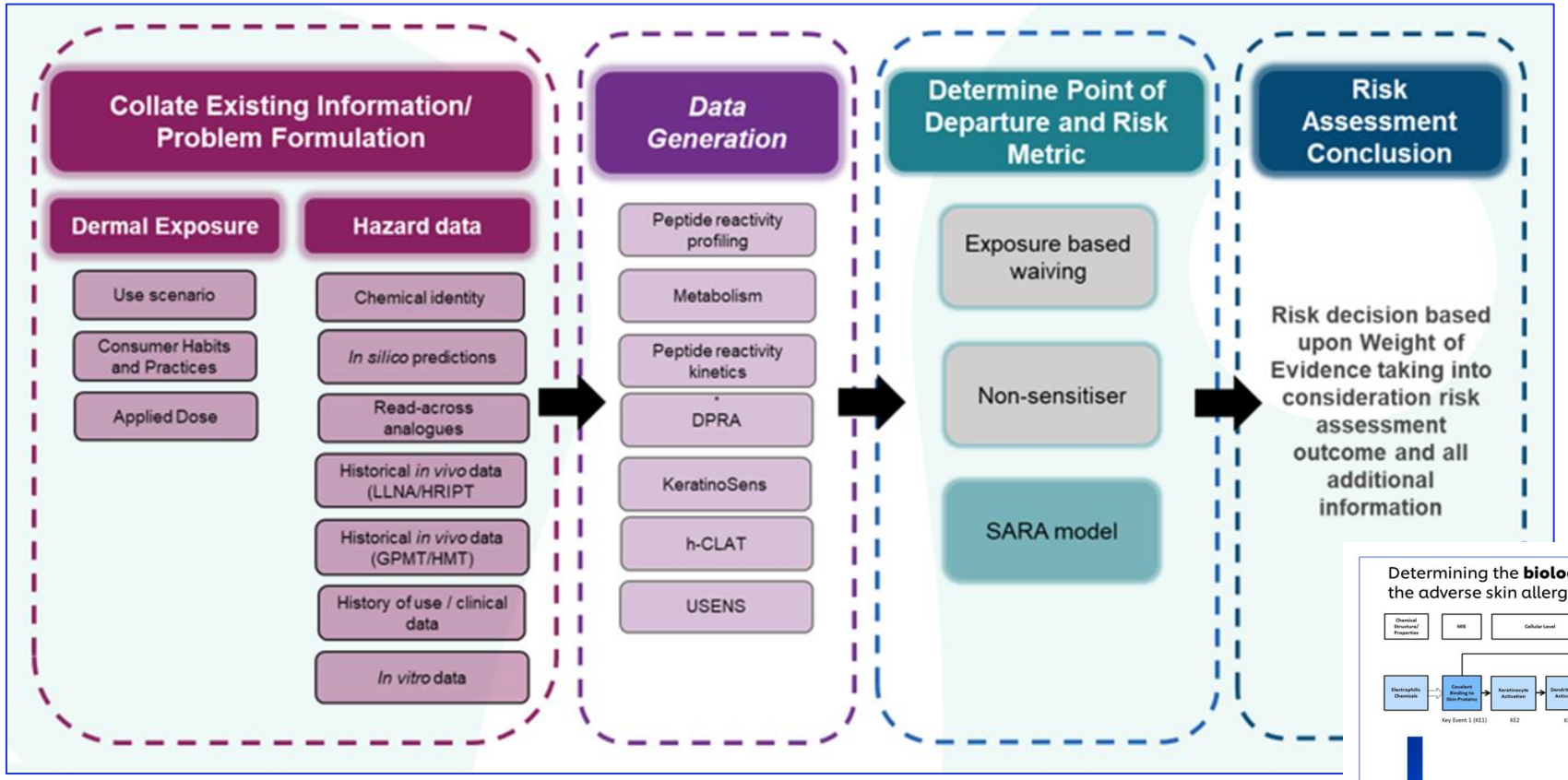
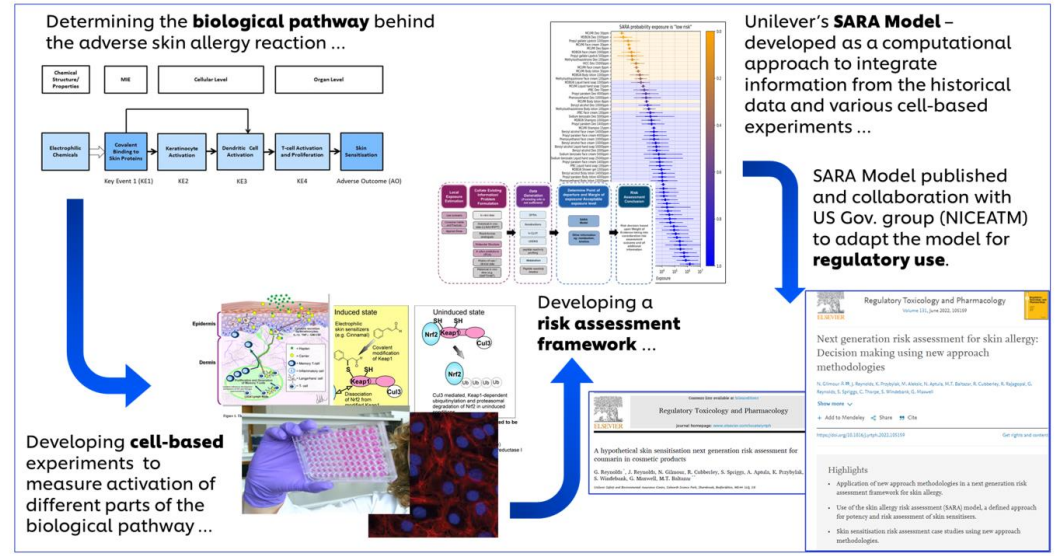


Figure 3. Summary of the key results from each step on the Next-Generation Risk Assessment case study workflow (see Figure 1) for 0.1% coumarin in face cream and body lotion. Abbreviations: HTTr, high-throughput transcriptomics; MoS, margin of safety; PBK, physiologically based kinetic; PoD, point of departure.

Unilever NGRA framework for skin allergy





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

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

Unilever

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[1] · João Barroso[2] · Patience Browne[3] · Warren Casey[4] · John Gordon[5] · Tala R. Henry[6] · Nicole C. Kleinstreuer[7] · Anna B. Lowit[6] · Monique Perron[8] · Amy J. Clippinger[1]

Received: 17 May 2022 / Accepted: 11 August 2022 / Published online: 20 August 2022

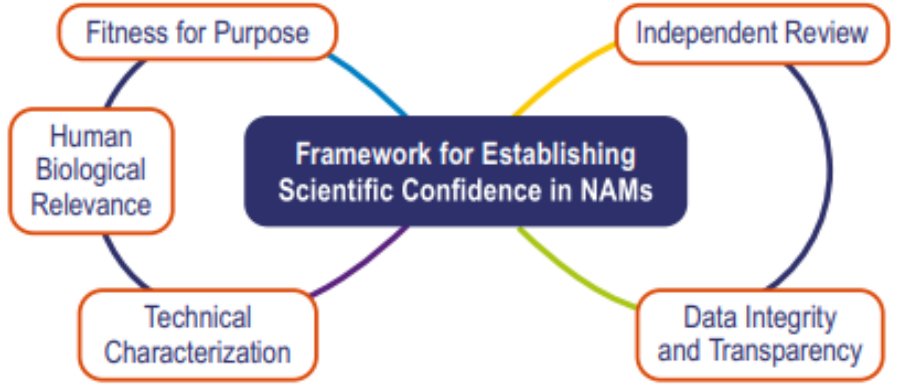


Fig. 1 Schematic illustrating the interconnectedness of the five essential elements for establishing scientific confidence in NAMs for assessing human health effects

Evaluating the new non-animal toolbox for systemic safety assessments

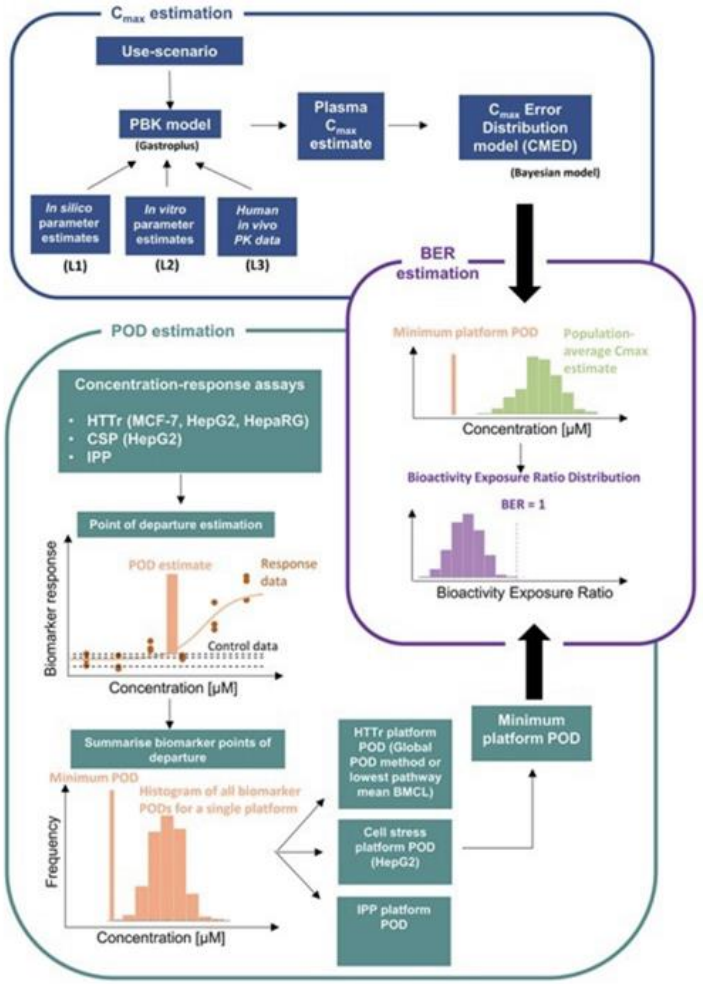
JOURNAL ARTICLE FEATURED

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.*



Are Non-animal Systemic Safety Assessments Protective? A Toolbox and Workflow - Abstract. A...
academic.oup.com • 2 min read

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

Alternatives to Laboratory Animals
2021, Vol. 49(4) 122–132

DOI: 10.1177/02611929211040824
journals.sagepub.com/home/atl
SAGE

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

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

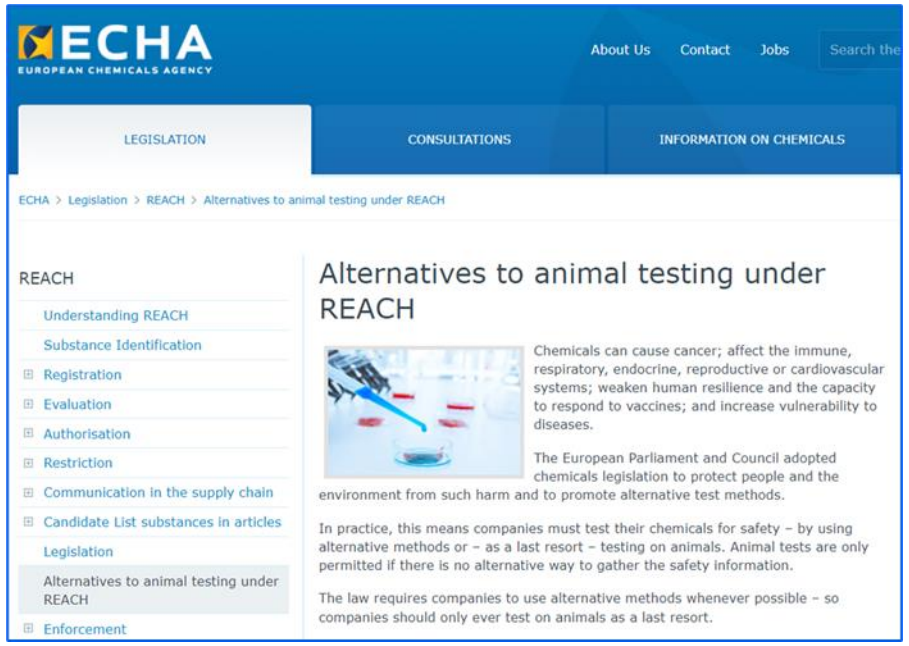
By Kacey Culliney
20-Oct-2021 - Last updated on 20-Oct-2021 at 09:54 GMT

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.

Unilever

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



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.

Unilever

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.

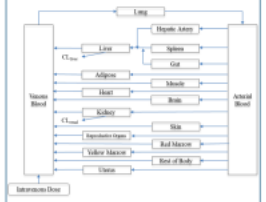
Worker Exposure Data

Data Generation

In vitro data on SI:

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

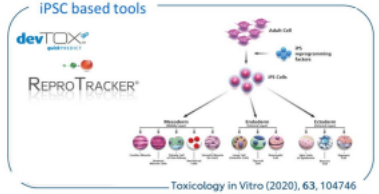
PBK Modelling



In Vitro Biological Activity Characterisation

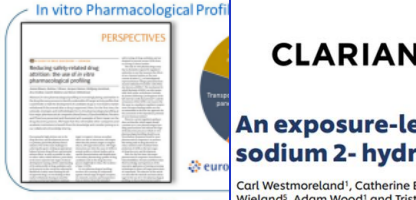
The bioactivity of SI was assessed in a battery of NAMs relevant to systemic [6], reproductive, and developmental toxicity [7]. Concentration-response curves were derived for 40 cell stress markers and High Throughput Transcriptomics was conducted in HepG2, HepaRG and MCF7 cells. Pharmacological profiling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

iPSC based tools



Toxicology in Vitro (2020), **63**, 104746

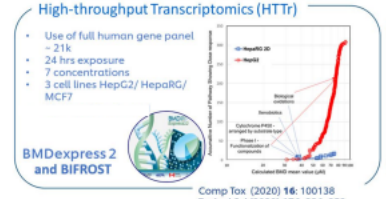
In vitro Pharmacological Profi



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

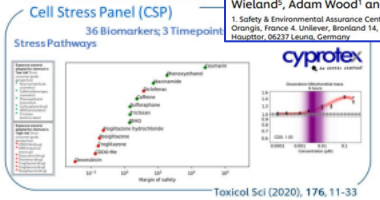


Comp Tox (2020) **16**: 100138
Toxicol Sci (2020) **176**, 236–252

Cell Stress Panel (CSP)

36 Biomarkers; 3 Timepoint

Stress Pathways

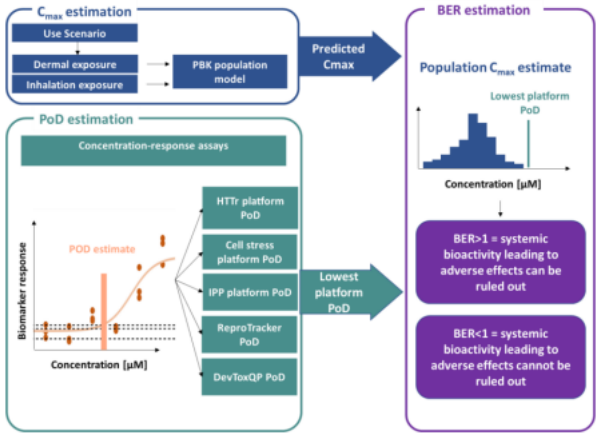


Toxicol Sci (2020), **176**, 11-33

(12 different assays, 107 Experiments, 8 CROs)

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

Bioactivity: Exposure Ratio (BER)



Results

- The PBK modelling indicated a worst-case plasma Cmax 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
			(BIFROST PoD)				
PoD (µM)	5044	>100	104	1728	829	>1000	>1000

- The lowest PoD of 104 µM was compared with the highest, worst case Cmax 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.

CLARIANT ERM Vantage® Unilever

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

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

1. Safety & Environmental Assurance Centre, Unilever, Colworth Park, Sharnbrook, MK44 1LQ, UK 2. Clariant Produkte Deutschland GmbH, Brüningstrasse 50, 65929 Frankfurt am Main, Germany 3. Vantage Specialty Chemicals, 3 rue Jules Guesde, 91130 Ris-Orangis, France 4. Unilever, Bronland 14, 6708 WH Wageningen, The Netherlands 5. Environmental Resources Management Limited. ERM Nederland B.V., Burg. De Raadtsingel 55, 3311 JG Dordrecht, The Netherlands 6. Vantage Leuna GmbH, Bau 7302, Am Haupttor, 06237 Leuna, Germany

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

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

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 on the establishment of frameworks ternative 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.

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.

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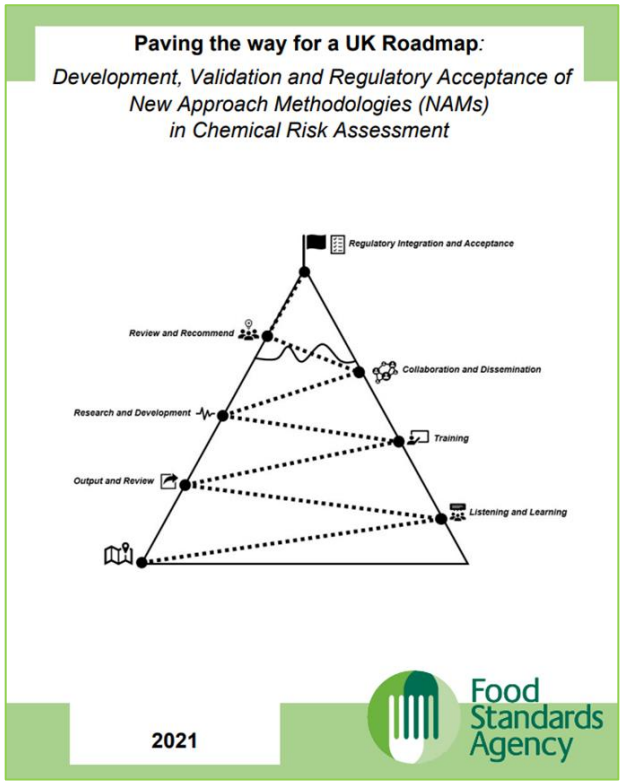
Enabling application of modern safety science for regulatory purposes in UK

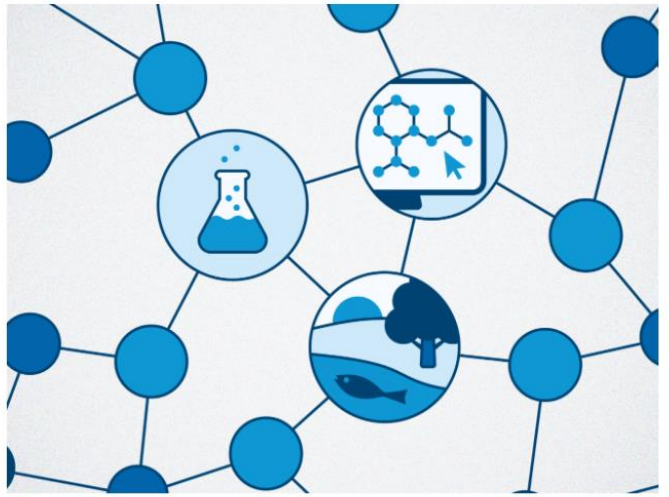


Overall objectives of the roadmap are to:

- 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.

NC 3Rs 20 YEARS
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).

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Joining forces in advocating for regulatory application of innovative toxicological science to "Close the Gap"

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

bts driving excellence in toxicology

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.

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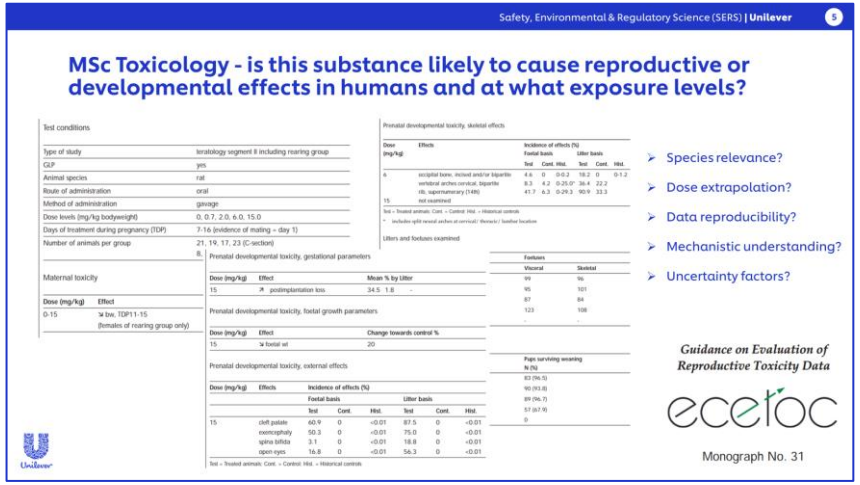
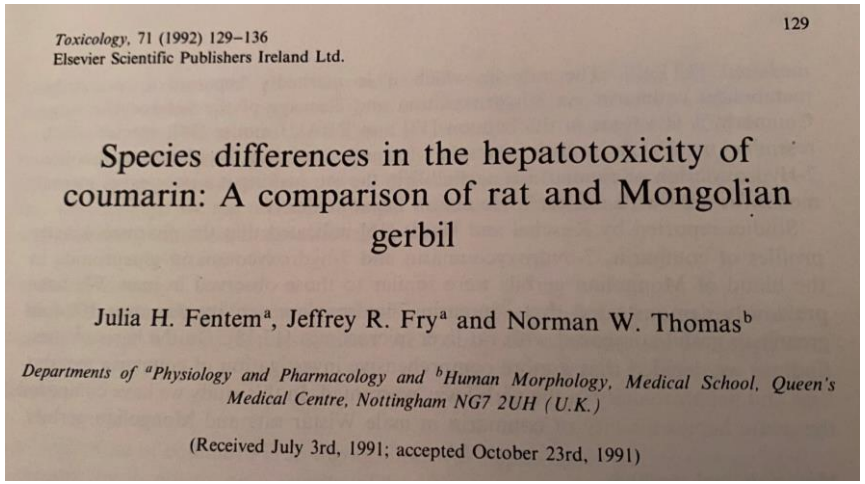
A biochemist's view today: good progress in applying innovative toxicological science; much more to do in strengthening regulatory science & its application

1987



1991



2022

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

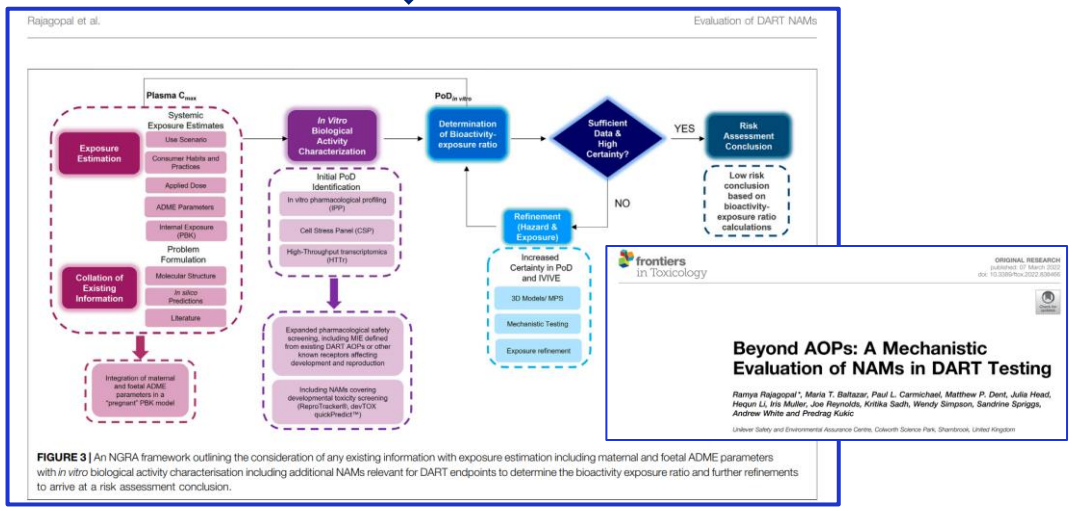


FIGURE 3 | An NGRA framework outlining the consideration of any existing information with exposure estimation including maternal and foetal ADME parameters with *in vitro* biological activity characterisation including additional NAMs relevant for DART endpoints to determine the bioactivity exposure ratio and further refinements to arrive at a risk assessment conclusion.

2020

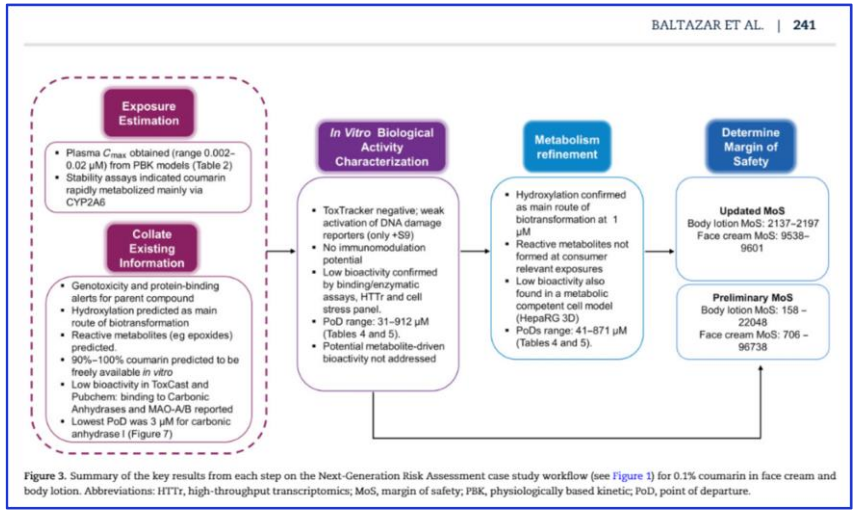


Figure 3. Summary of the key results from each step on the Next-Generation Risk Assessment case study workflow (see Figure 1) for 0.1% coumarin in face cream and body lotion. Abbreviations: HTTr, high-throughput transcriptomics; MoS, margin of safety; PBK, physiologically based kinetic; PoD, point of departure.

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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