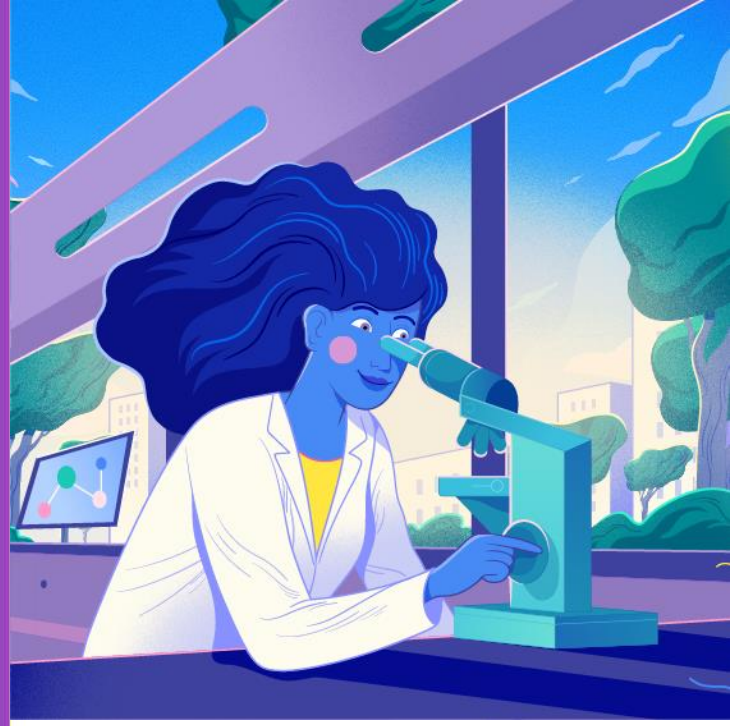
Assessing the Safety of Consumer Products by using Animal-Free Methods

Dr Julia Fentem
Head of Unilever Safety & Environmental Assurance Centre (SEAC)

We say use science.
Not animals.



Unilever

Overview

1. My Background / Unilever Safety & Environmental Assurance Centre
2. Consumer Perspective on Animal Testing
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4. Alternatives to Animal Testing – a short history
5. Safety Science in 2022: New Approach Methodologies (NAMs) & Next Generation Risk Assessment (NGRA) – research & application
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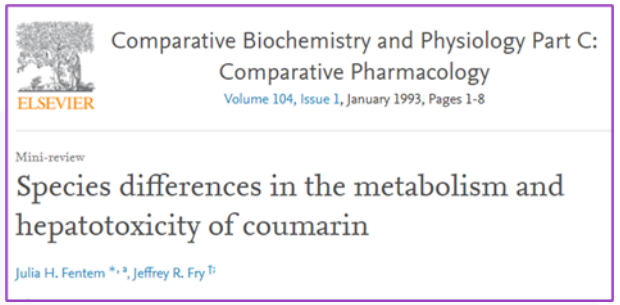
7. Closing the Science – Regulatory Use Gap
8. Looking Forwards – my thoughts on priorities

Unilever

My Background

- PhD - Biochemical Toxicology

The University of Nottingham


Comparative Biochemistry and Physiology Part C: Comparative Pharmacology
Volume 104, Issue 1, January 1993, Pages 1-8
Mini-review
Species differences in the metabolism and hepatotoxicity of coumarin
Julia H. Fentem, Jeffrey R. Fry

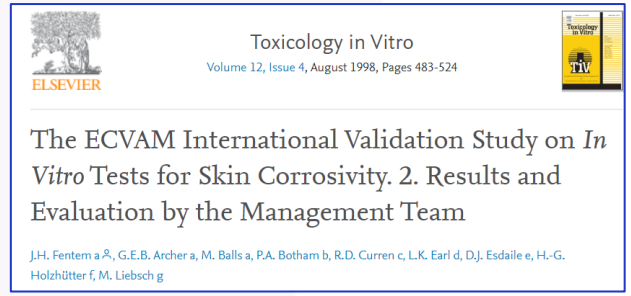
- Science Lead for a scientific animal welfare charity (FRAME, UK)

FRAME
WWW.FRAME.ORG.UK


The Use of Basal Cytotoxicity and Target Organ Toxicity Tests in Hazard Identification and Risk Assessment
Michael Balls, Julia H. Fentem
First Published July 1, 1992 | Research Article
https://doi.org/10.1177/026119299202000304

- Toxicology Section Lead for ECVAM (European Commission JRC, Italy)

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing


Toxicology in Vitro
Volume 12, Issue 4, August 1998, Pages 483-524
The ECVAM International Validation Study on *In Vitro* Tests for Skin Corrosivity. 2. Results and Evaluation by the Management Team
J.H. Fentem a, G.E.B. Archer a, M. Balls a, P.A. Botham b, R.D. Curren c, L.K. Earl d, D.J. Esdaile e, H.-G. Holzhütter f, M. Liebsch g

- Toxicologist / Head of Product Safety (SEAC, Unilever)

SEAC SAFETY & ENVIRONMENTAL ASSURANCE CENTRE
Scientific Excellence And Collaboration


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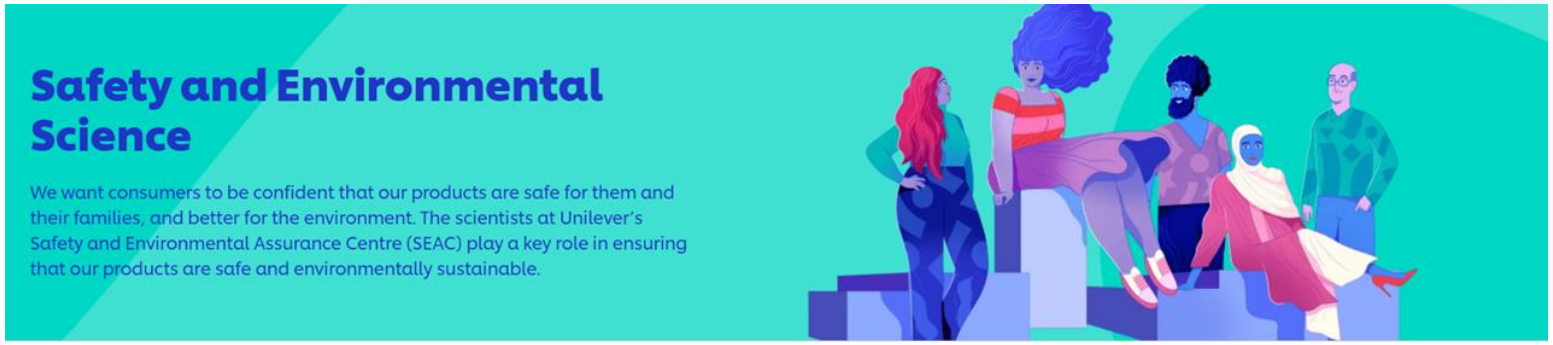
sagepub.com/journals-permissions
DOI: 10.1177/02611929211040824
journals.sagepub.com/home/atl
SAGE

Unilever

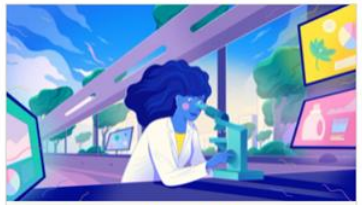
Unilever – Safety & Environmental Assurance Centre (SEAC)

Ensuring Unilever's Innovations & Products are Safe & Sustainable by Design




Leading safety and environmental sustainability sciences
The scientists behind our safe and sustainable products


Safe and sustainable by design
How we build safety and sustainability into every product innovation.


Keeping people and the environment safe
The science-based approaches we use to keep our consumers, workers and the environment safe.

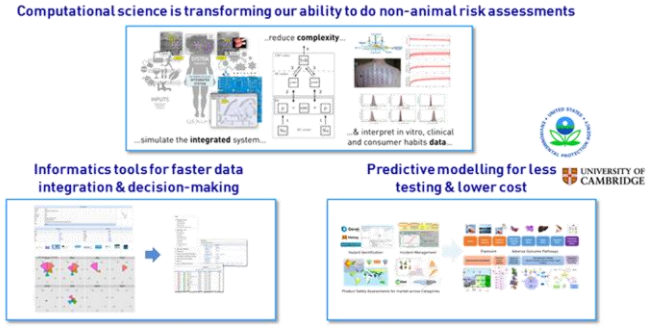

Reducing our environmental impact
How we harness the latest science to minimise our environmental footprint.

Unilever Product / Ingredient Safety Governance

- Provide scientific evidence to manage safety risks & environmental impacts

Industry-leading Safety & Environmental Sustainability Science Capability

- Deploy expertise on higher risk business projects
- Collaborate with leading external research teams to develop & apply new capability
- Leverage our science & global networks for consumer trust & freedom to operate



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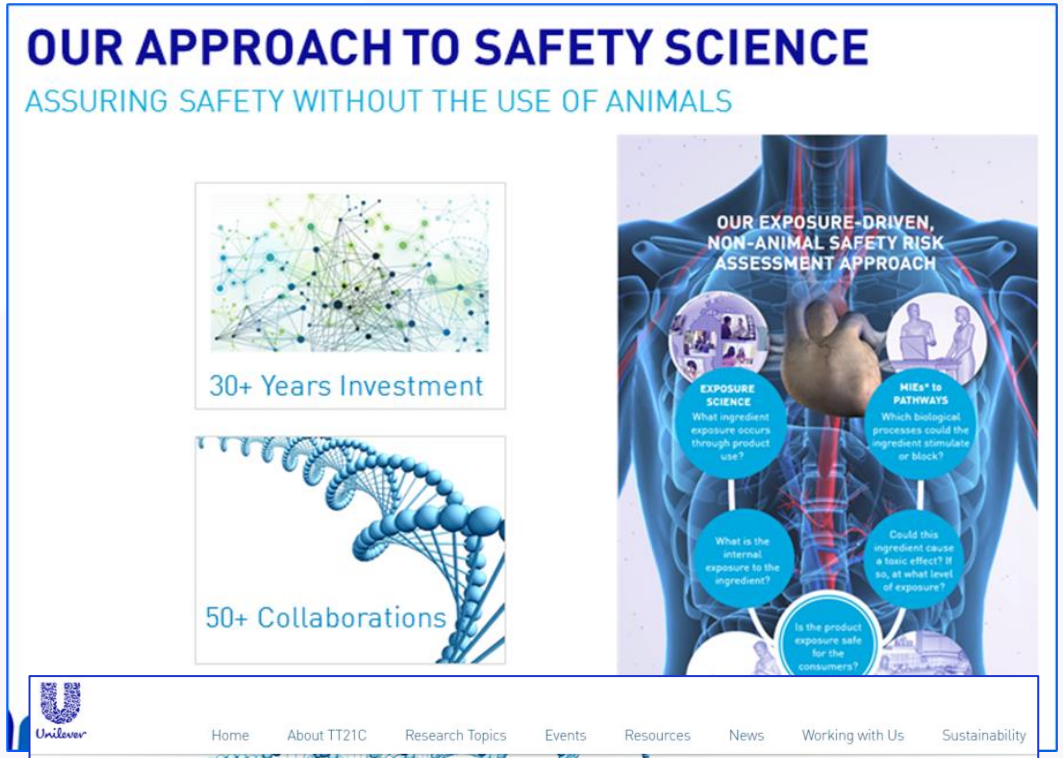
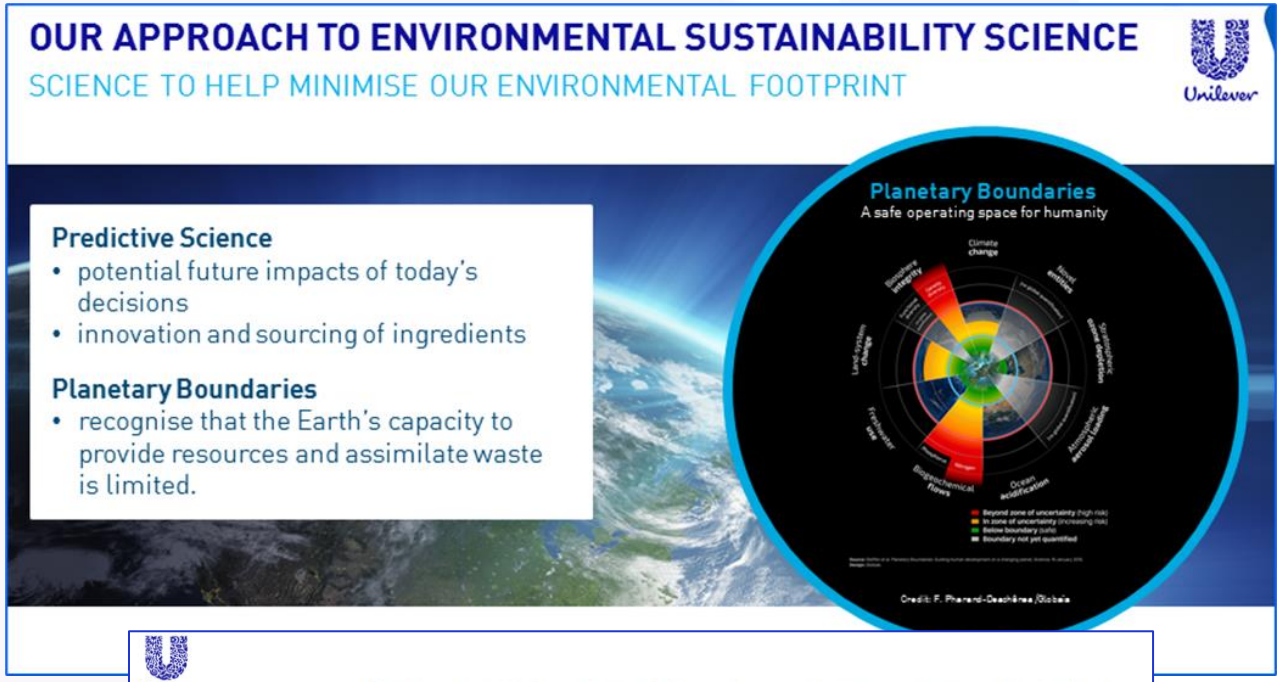
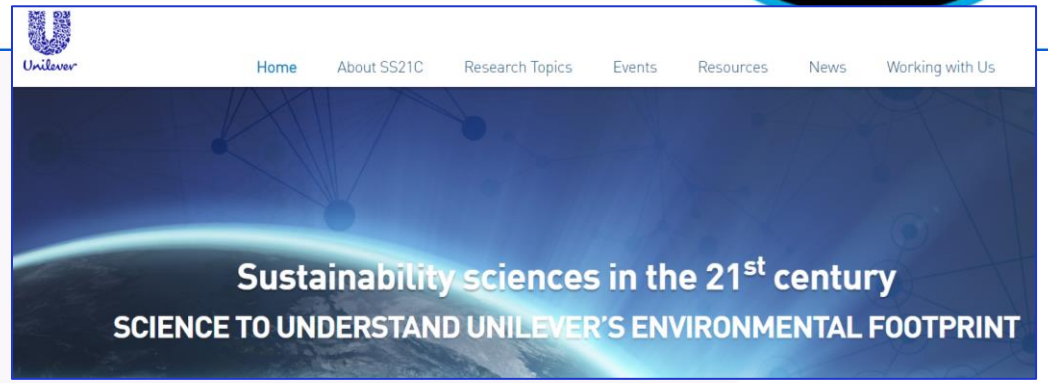
SEAC focuses on helping shape solutions to big scientific & societal challenges in Product Safety & Environmental Sustainability







[Safety Homepage « Safety Science in the 21st Century (tt21c.org)]

[Sustainability Homepage « Safety Science in the 21st Century (tt21c.org)]

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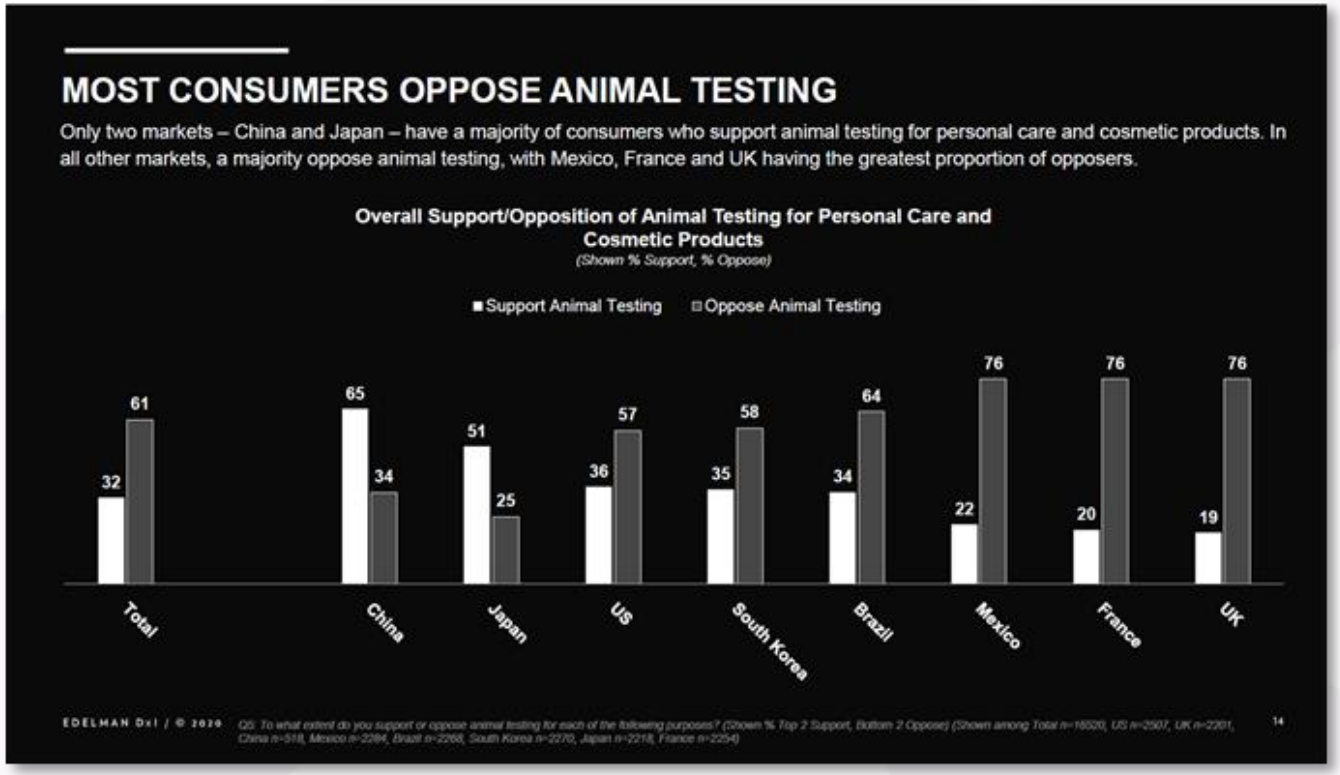
Consumer Perspective on Animal Testing



Top 5 Global Issues

- Reducing Waste & Pollution
- Reducing Plastic Packaging
- Ending Animal Testing
- Ingredient Transparency
- Tackling Climate Change (CO_2)

United Kingdom		United States		Brazil	
Reducing waste and pollution	30%	Reducing and eliminating plastic	28%	Reducing and eliminating plastic	29%
Reducing and eliminating plastic	27%	Reducing waste and pollution	25%	Ending animal testing	25%
Ending animal testing	24%	Ending animal testing	19%	Reducing waste and pollution	24%
Paying a fairer share of tax	24%	Transparent on product ingredients	19%	Transparent on product ingredients	18%
Tackling climate change	19%	Making products affordable for all	19%	Making products affordable for all	16%

Consumers #1 ask of global consumer products companies

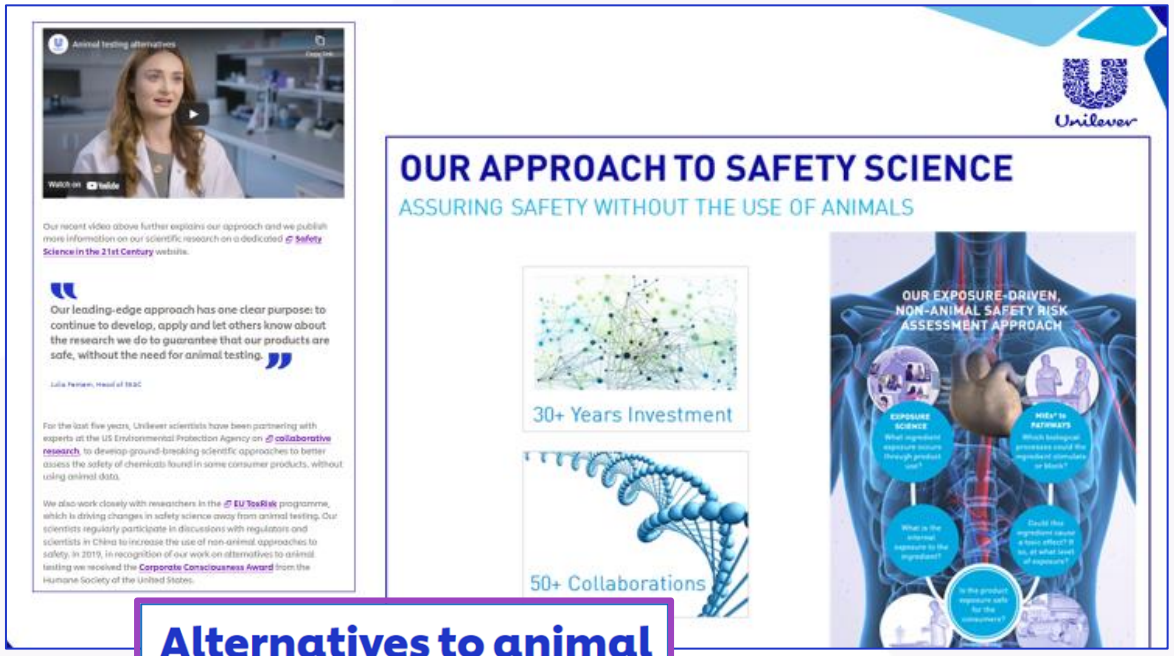
EU

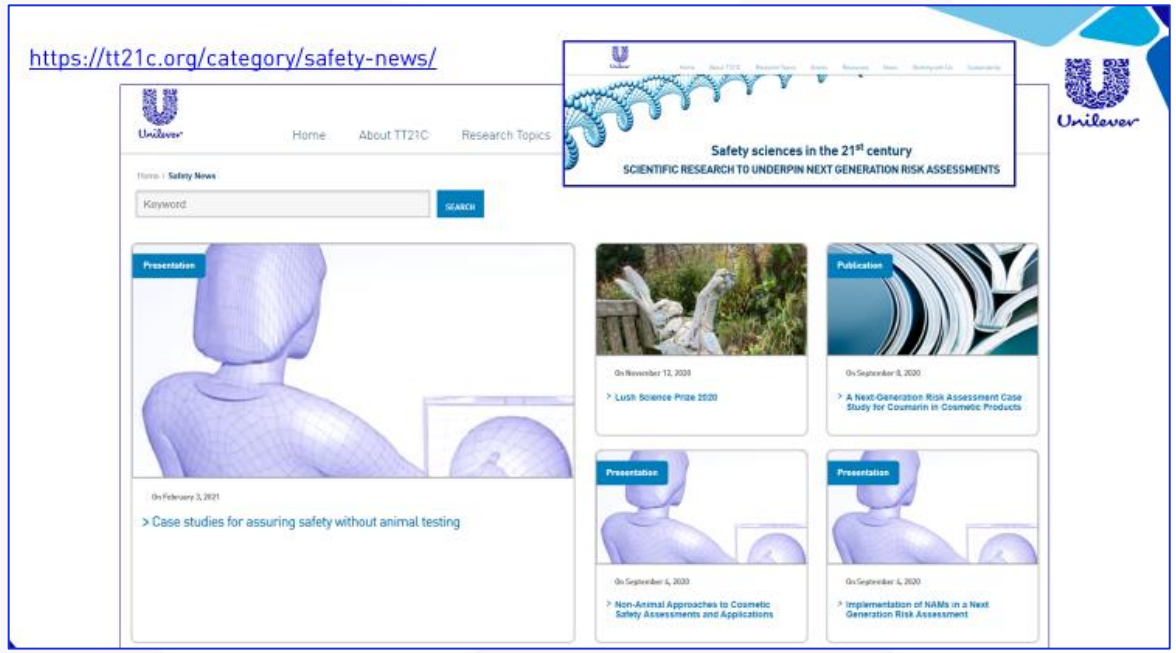
76% of EU adults think testing for household cleaning products should be banned

74% of EU adults think testing for cosmetics products and their ingredients should be banned

Unilever

Transforming safety science methods to meet consumer expectations



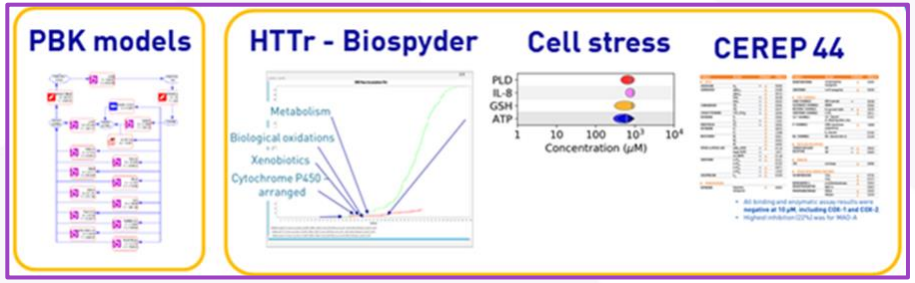


Alternatives to animal testing

Average read time: **4 minutes**

Every product Unilever makes must be safe for people to use and safe for our planet. We believe that animal experiments should not be used to make sure that our products are safe.

CONSUMER TRUST



- Human-relevant approaches – designed to assess the safety of ingredients
- Exposure measurements and modelling
- Computational modelling replicating human biology and chemical interactions
- Cell culture methods, using tissue grown in labs, and chemical and biological analytical techniques

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Unilever

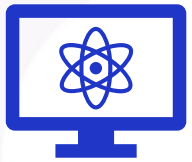
Unilever Policy & Approach
Safe & Sustainable Products without Animal Testing

We say use science.
Not animals.

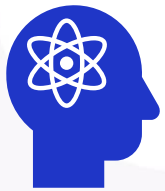
What we believe

- Every Unilever product must be safe for people and our environment
- Animal testing is not needed to assess product safety – there are a wide range of non-animal alternatives grounded in modern science and new technology

How we do it



40+ years of developing non-animal safety science

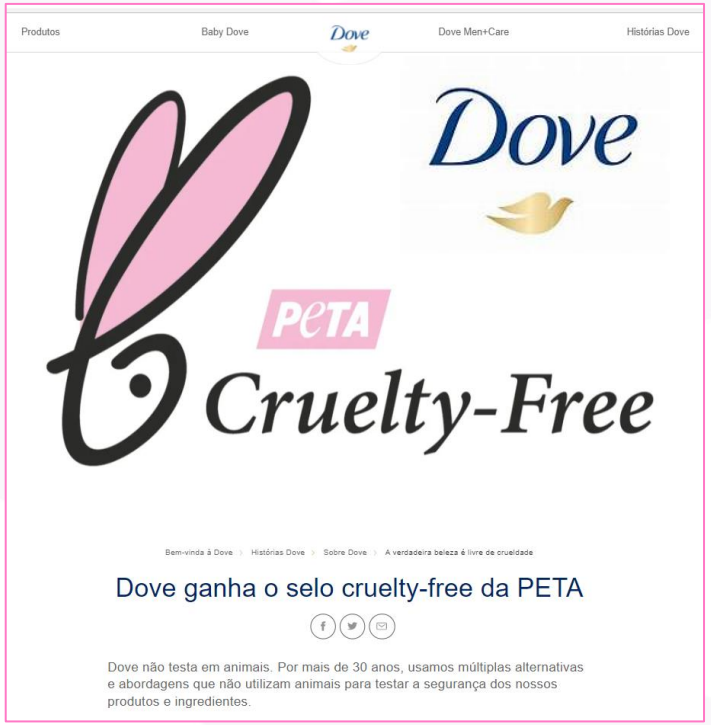


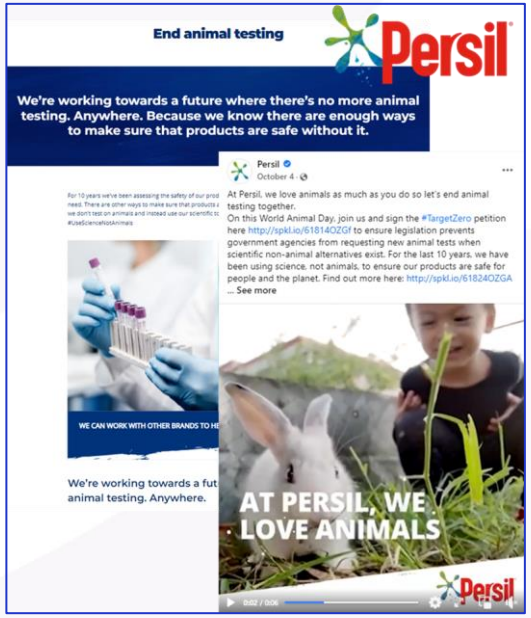
70+ collaborations

600+ publications

Unilever

Unilever Policy & Brands – no animal testing





Posição da Unilever sobre Abordagens Alternativas para Testes em Animais

Não testamos nossos produtos em animais e estamos comprometidos com o banimento desses testes em nível global. Usamos uma ampla variedade de abordagens não relacionadas a animais para avaliar a segurança de nossos produtos para os consumidores, para os nossos trabalhadores e para o meio ambiente. Também desenvolvemos métodos de avaliação de segurança de "próxima geração", que não dependem de dados obtidos de animais.

Como parte de nosso compromisso de encerrar os testes em animais globalmente, um número crescente de nossas marcas garante que seus produtos e ingredientes não sejam submetidos a eles tanto por parte da Unilever, como por nossos fornecedores ou por autoridades regulatórias.

O compromisso dessas marcas é certificado por grupos globais de proteção animal. A Unilever apoia a proibição mundial de testes em animais para cosméticos até 2023.

Ocasionalmente, considerando o mais amplo e completo portfólio de marcas da Unilever, há ingredientes que ainda precisam ser testados pelos fornecedores para cumprir os requisitos legais e regulamentares em alguns mercados; e algumas autoridades governamentais testam certos produtos em animais como parte de sua legislação.

Unilever

Unilever's approach: science-based safety, claims & advocacy - working with others to end animal testing of consumer products

1 Use Science, Not Animals

We use science, not animals – our industry leading capability in animal-free safety science means we do not need to use animal testing to ensure safety.

2 Independent Brand Certification

Building consumer confidence through NGO accreditation and consumer-facing no animal testing claims.
Starting with Dove in 2018, we have 30 NGO-certified cruelty free brands.

3 Partnerships

Our partnerships – with global animal protection NGOs, leading research teams, other companies and government scientists – support wider acceptance and use of alternatives to animal testing.

4 Advocate for Regulatory Change

We work to end the animal testing of consumer products worldwide.

We are recognised by PETA as a company working for regulatory change.

Unilever

Scientific partnership & publication underpin our approach

2015

Details of SEAC's presentations & publications on www.tt21c.org

SEAC NGRA videos:
https://www.youtube.com/watch?v=tJWG3YCXT0Y&t=10s
https://www.youtube.com/watch?v=5Z2S8MnKp7g

2021

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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Environmental Topics | Laws & Regulations | Report a Violation | About EPA

News Releases from Headquarters > Research and Development (ORD) CONTACT US

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.

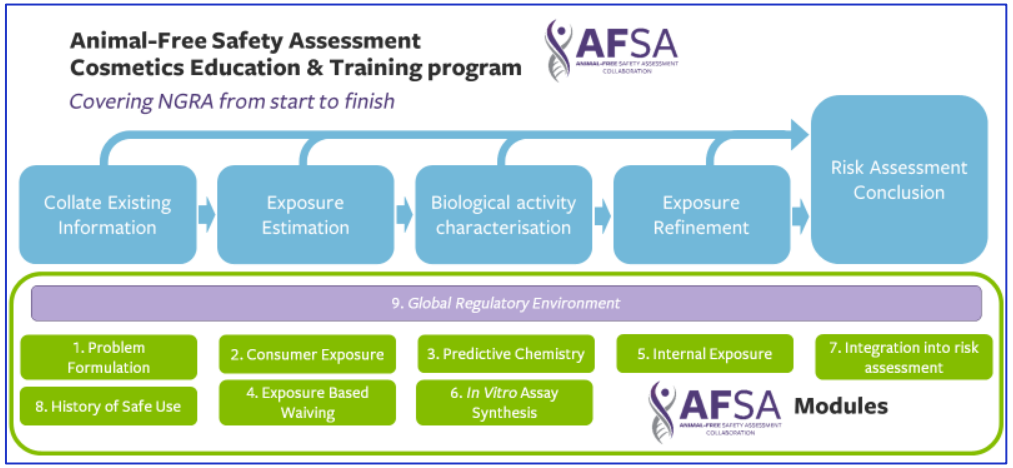
EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

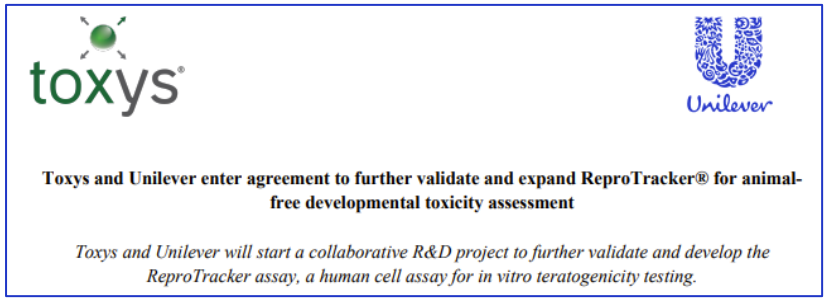
"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited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

Unilever

Partnerships with over 70 leading science groups to develop & build capacity in non-animal approaches for safety assessment

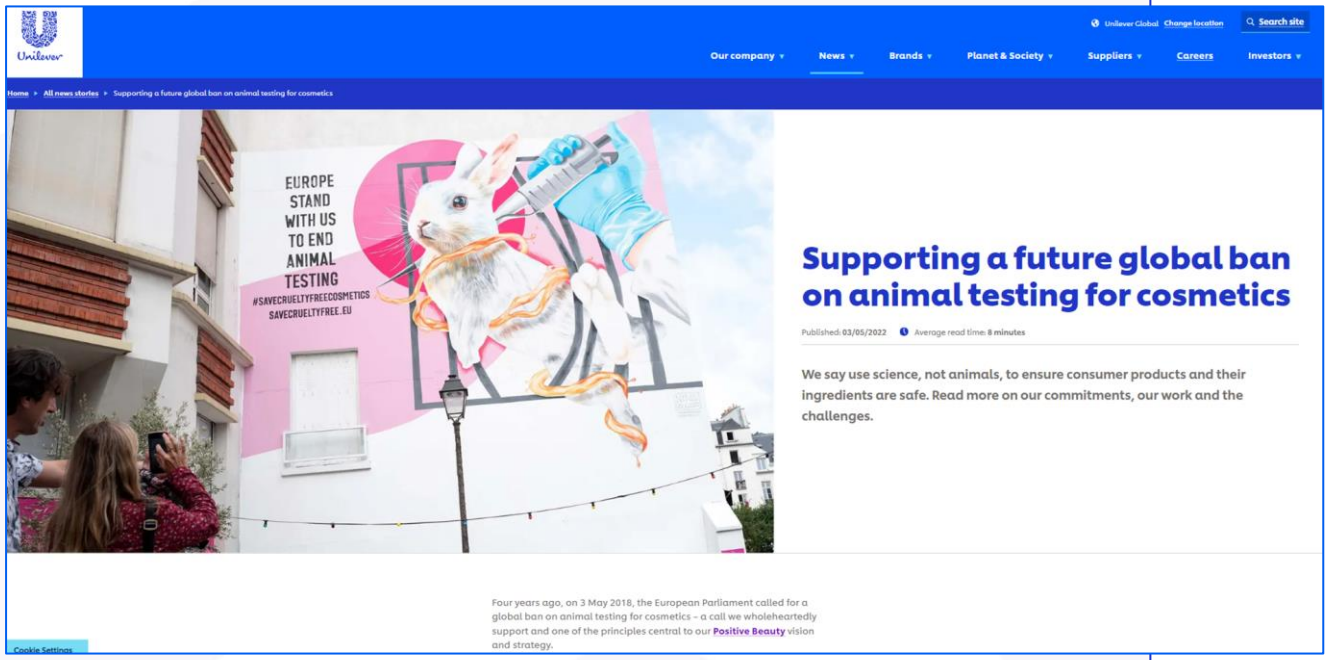
Some Examples – government researchers, NGO, assay developer, supply partner

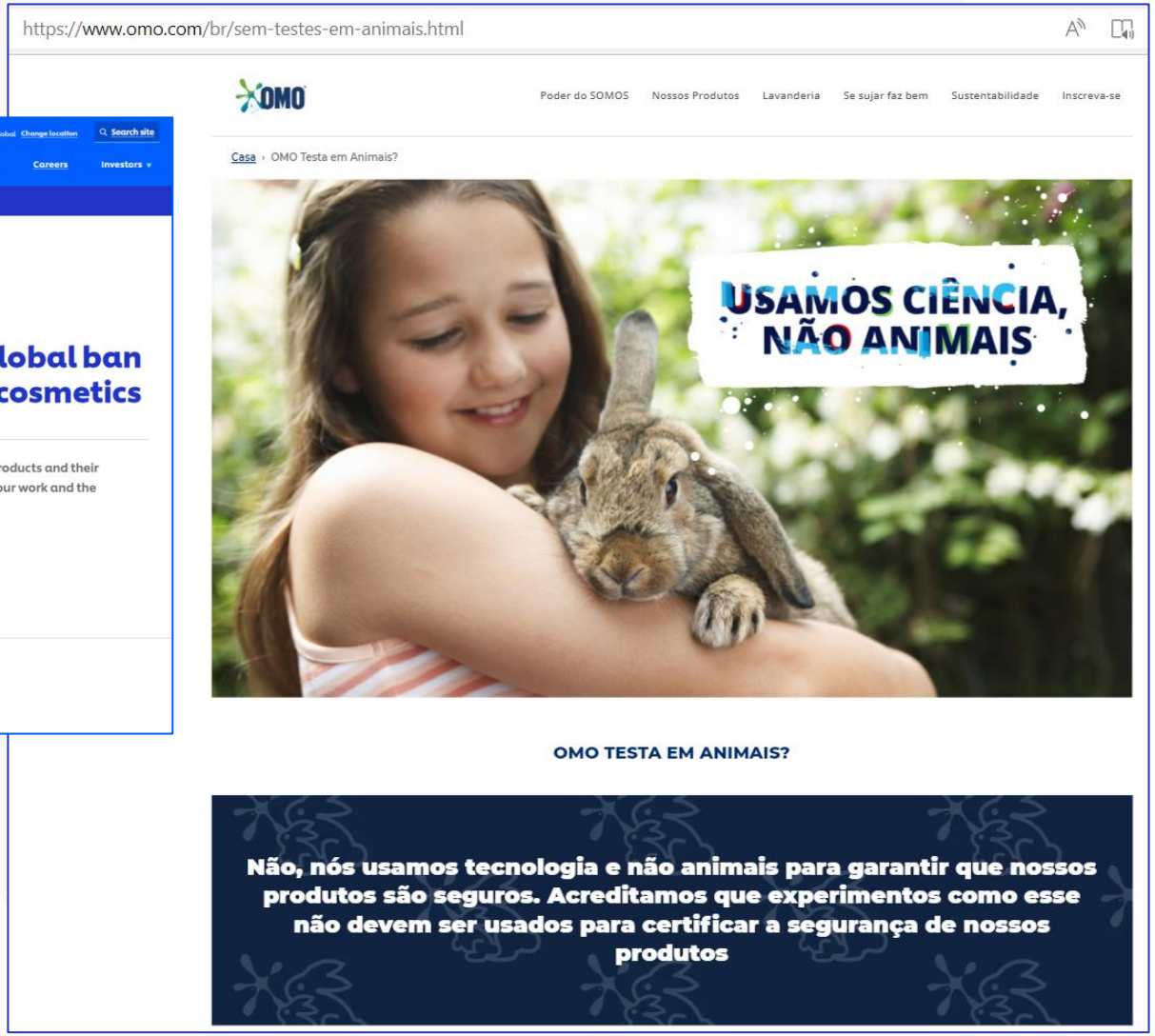




Unilever

Advocating for change to promote regulatory use of innovative animal-free safety science & technology





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Unilever

Alternatives to Animal Testing – a short history (1)

An Alternative to the LD50?

First Published March 1, 1984 | Editorial
https://doi.org/10.1177/096032718400300201

Article information

Department Of Health And Social Security. (1982). Guidelines for the Testing of Chemicals for Toxicity . on Health and Social Subjects 27. London: HMSO.
Google Scholar To full text

HOME OFFICE Report on the LD50 Test. (1979). Presented to the Secretary of State by the Advisory Committee on the Administration of Cruelty to Animals Act 1876. London.
Google Scholar To full text

Toxicol In Vitro. Feb-Apr 1997;11(1-2):141-79. doi: 10.1016/s0887-2333(96)00069-0.

A summary report of the COLIPA international validation study on alternatives to the draize rabbit eye irritation test

ELSEVIER

Toxicology in Vitro
Volume 12, Issue 4, August 1998, Pages 483-524

The ECVAM International Validation Study on *In Vitro* Tests for Skin Corrosivity. 2. Results and Evaluation by the Management Team

J.H. Fentem a, G.E.B. Archer a, M. Balls a, P.A. Botham b, R.D. Curren c, L.K. Earl d, D.J. Esdaile e, H.-G. Holzhütter f, M. Liebsch g

ELSEVIER

Toxicology in Vitro
Volume 15, Issue 1, February 2001, Pages 57-93

Validation

A prevalidation study on in vitro tests for acute skin irritation: results and evaluation by the Management Team

J.H Fentem [a], D Briggs [a], C Chesné [b], G.R Elliott [c], J.W Harbell [d], J.R Heylings [e], P Portes [f], R Roguet [f], J.J.M van de Sandt [g], P.A Botham [e]

Guideline No. 497: Defined Approaches on Skin Sensitisation

A Defined Approach (DA) consists of a selection of information sources (e.g in silico predictions, in chemico, in vitro data) used in a specific combination, and resulting data are interpreted using a fixed data interpretation procedure (DIP) (e.g. a mathematical, rule-based model). DAs use methods in combination and are intended to overcome some limitations of the individual, stand-alone methods. The first three DAs included in this Guideline use combinations of OECD validated More

Published on June 22, 2021 Also available in: French

A Review of *In Silico* Tools as Alternatives to Animal Testing: Principles, Resources and Applications

Judith C. Madden, Steven J. Enoch, Alicia Paini, Mark T.D. Cronin

First Published October 29, 2020 | Review Article | Find in PubMed | Check for updates
https://doi.org/10.1177/0261192920965977

Adverse outcome pathways: a concise introduction for toxicologists

Mathieu Vinken, Dries Knapen, Lucia Vergauwen, Jan G. Hengstler, Michelle Angrish & Maurice Whelan

Archives of Toxicology **91**, 3697–3707 (2017) | Cite this article

1980s → in vitro & in silico tests for hazard identification / characterisation
2007 → toxicity pathways / adverse outcome pathways / "IATA"

Unilever

Alternatives to Animal Testing – a short history (2)

Fentem, Chamberlain, Sangster. 2004. *ATLA*. 32. 617-623

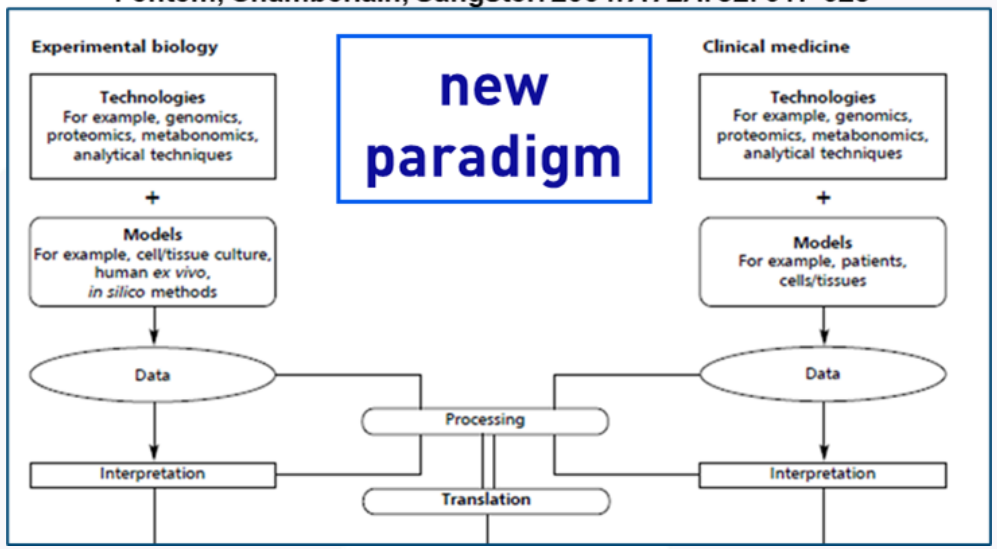


Figure 2: Safety assessment — future needs

exposure-based

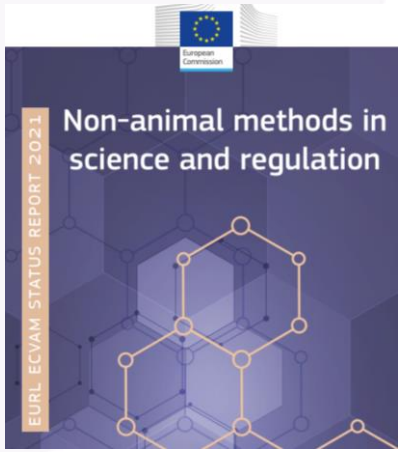
Safety assessment — future needs

- 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

Fentem 2006 *ATLA* 34, 11-18

2007

2021



2022

2008

Brazil Moves Toward the Replacement of Animal Experimentation

Alternatives to Laboratory Animals
2019, Vol. 47(2) 71–81
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DOI: 10.1177/0261192919856806
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SAGE

Renato Ivan de Ávila and Marize Campos Valadares

Abstract

In Brazil, efforts towards the regulatory acceptance and implementation of innovative methods to replace experimental animal use in various fields began to gather force in 2008, with the approval of *Law No. 11,794/2008* (the Arouca Law). This law represented a milestone, as it created the National Council for the Control of Animal Experimentation (CONCEA) to deal with the ethical and legal issues related to the use of laboratory animals. In 2014, CONCEA put together a framework for expanding the implementation of non-animal methodologies for use in research and education. It also promoted the regulatory acceptance in Brazil of 24 test guidelines, including 15 *in vitro* approaches. It should be emphasised that, in Brazilian legislation, *replacement* is generally based on the toxicological endpoint and not on the category of product, as tends to be the case in other countries (e.g. cosmetics in the European Union). The resolution-dependent deadlines for the obligatory replacement of *in vivo* methods with the CONCEA-approved tests are 2019 and 2021. Brazil has advanced considerably towards the replacement of animal experimentation, and in certain aspects, this has been in a highly progressive manner. However, there is still a lot of work to be done, especially considering the current political scenario with reduced investment in research, development and innovation. The chronology of significant events following the approval of the Arouca Law, which have contributed to the promotion of the Three Rs alternatives in Brazil, will be examined.

2008: Law no. 11,794/2008 (Lei Arouca) represents a regulatory milestone in the implementation of alternative methods

Presidência da República
Casa Civil
Subchefia para Assuntos Jurídicos

LEI Nº 11.794, DE 8 DE OUTUBRO DE 2008.

Regulamenta o inciso VII do § 1º do art. 225 da Constituição Federal, estabelecendo procedimentos para o uso científico de animais; revoga a Lei nº 6.638, de 8 de maio de 1979; e dá outras providências.

2012: creation of RENAMA

Ministério da Ciência, Tecnologia e Inovação

GABINETE DO MINISTRO

PORTARIA Nº 491, DE 3 DE JULHO DE 2012

Institui a Rede Nacional de Métodos Alternativos - RENAMA e sua estrutura no âmbito do Ministério da Ciência, Tecnologia e Inovação - MCTI, que será supervisionada por um Conselho Diretor.

2012: ANVISA publishes guidance for cosmetics safety assessment

Agência Nacional de Vigilância Sanitária

Ministério da Ciência, Tecnologia
e Inovação

CONSELHO NACIONALDE CONTROLE
DE EXPERIMENTAÇÃO ANIMAL

RESOLUÇÃO NORMATIVA Nº 17, DE 3 DE JULHO DE 2014

Dispõe sobre
no Brasil e dá

2014: CONCEA recognized alternative methods

DIÁRIO OFICIAL DA UNIÃO

Publicado em: 17/01/2022 | Edição: 11 | Seção: 1 | Página: 18

Órgão: Ministério da Ciência, Tecnologia e Inovações/Conselho Nacional de Controle de Experimentação Animal

RESOLUÇÃO NORMATIVA CONCEA Nº 54, DE 10 DE JANEIRO DE 2022

Dispõe sobre o reconhecimento de métodos alternativos ao uso de animais em atividades de ensino e pesquisa científica e dá outras providências.

2015: ANVISA starts to accept the methods recognized by CONCEA

Agência Nacional de Vigilância Sanitária

RESOLUÇÃO - RDC Nº 35, DE 7 DE AGOSTO DE 2015

Dispõe sobre a aceitação dos métodos alternativos de experimentação animal reconhecidos pelo Conselho Nacional de Controle de Experimentação Animal - Concea.

A Diretoria Colegiada da Agência Nacional de Vigilância Sanitária, no uso das atribuições que lhe conferem os incisos III e IV, do art. 15, da Lei nº 9.782, de 26 de janeiro de 1999, inciso V e §§

CONCEA currently recognizes **25 testing guidelines**: 17 1R (replacement) guidelines and 8 2R (refinement & reduction) guidelines

Ministério da Ciência, Tecnologia
e Inovação

GABINETE DO MINISTRO

RESOLUÇÃO NORMATIVA Nº 18, DE 24 DE SETEMBRO DE 2014

Reconhece métodos alternativos ao uso de animais em atividades de pesquisa no Brasil, nos termos da Resolução Normativa nº 17, de 03 de julho de 2014, e dá outras providências.

Ministério da Ciência, Tecnologia,
Inovações e Comunicações

CONSELHO NACIONAL DE CONTROLE
DE EXPERIMENTAÇÃO ANIMAL

RESOLUÇÃO NORMATIVA Nº 31, DE 18 DE AGOSTO DE 2016

Reconhece métodos alternativos ao uso de animais em atividades de pesquisa no Brasil.

DIÁRIO OFICIAL DA UNIÃO - Seção 1

CONSELHO NACIONAL DE CONTROLE
DE EXPERIMENTAÇÃO ANIMAL

RESOLUÇÃO Nº 45, DE 22 DE OUTUBRO DE 2019

Reconhece método alternativo ao uso de animais em atividades de pesquisa no Brasil.

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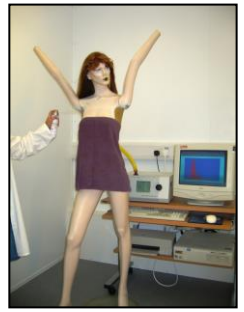
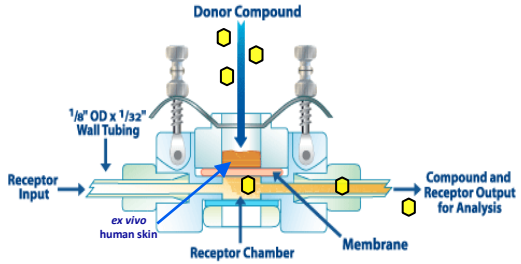
Assuring consumer safety without animal testing - maximising use of existing information and animal-free approaches

- All our risk assessments are exposure-led

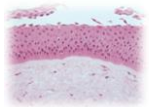
Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall *et al.*, 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor [1]	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 [2]	20.00 g	-	0.01	0.20 [3]	3.33
Hair care					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner [2]	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74



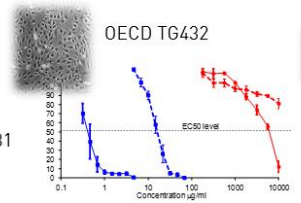


- Use all available safety data on the ingredient
  - clinical, epidemiological, animal (if dates permit), *in vitro*, etc.
- Exposure-based waiving approaches (e.g. toxicological threshold of concern)
- *In silico* predictions
- History of safe use
- Read-across
- Use of existing OECD *in vitro* approaches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

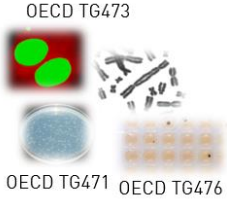


OECD TG437

OECD TG430/431
OECD TG439



OECD TG432



OECD TG473
OECD TG471
OECD TG476

Unilever

Overview

1. My Background / Unilever Safety & Environmental Assurance Centre
2. Unilever Policy & Approach
3. Consumer Perspective on Animal Testing
4. Alternatives to Animal Testing – a short history
5. **Safety Science in 2022: New Approach Methodologies (NAMs) & Next Generation Risk Assessment (NGRA) – research & application**
6. Regulatory Acceptance – cosmetics, foods, chemicals
7. Closing the Science – Regulatory Use Gap
8. Looking Forwards – my thoughts on priorities

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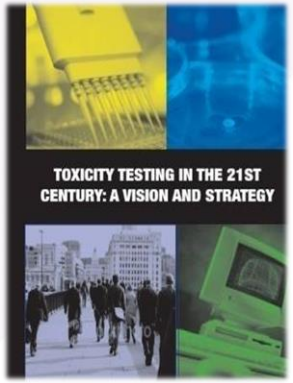
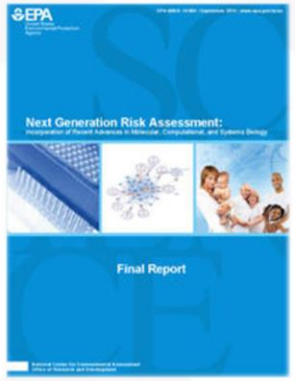
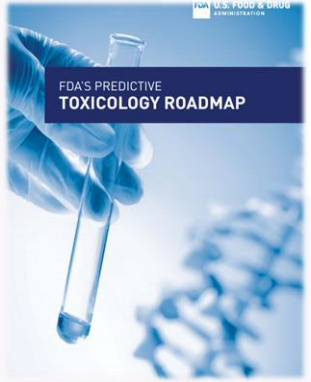
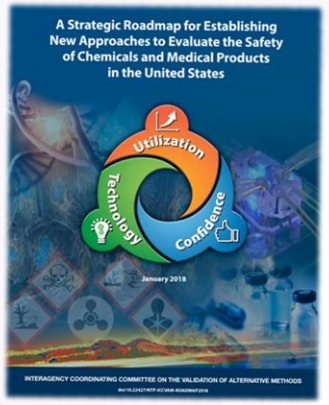
Safety Science in 2022: NAMs & NGRA – research & application

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

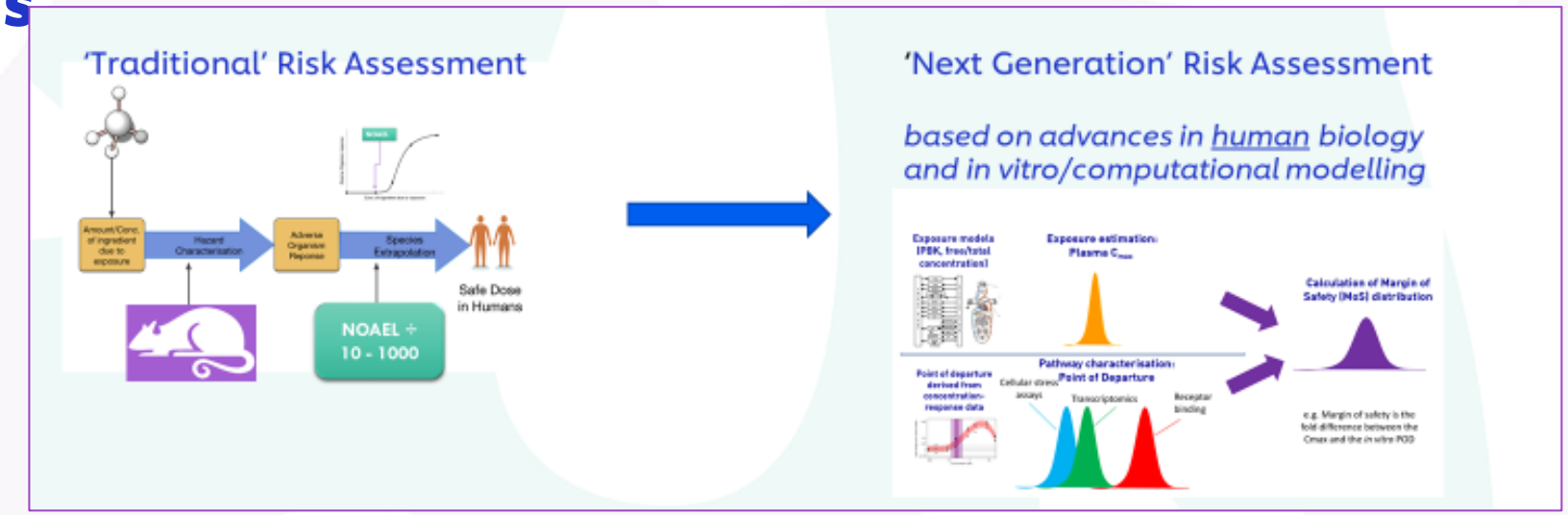


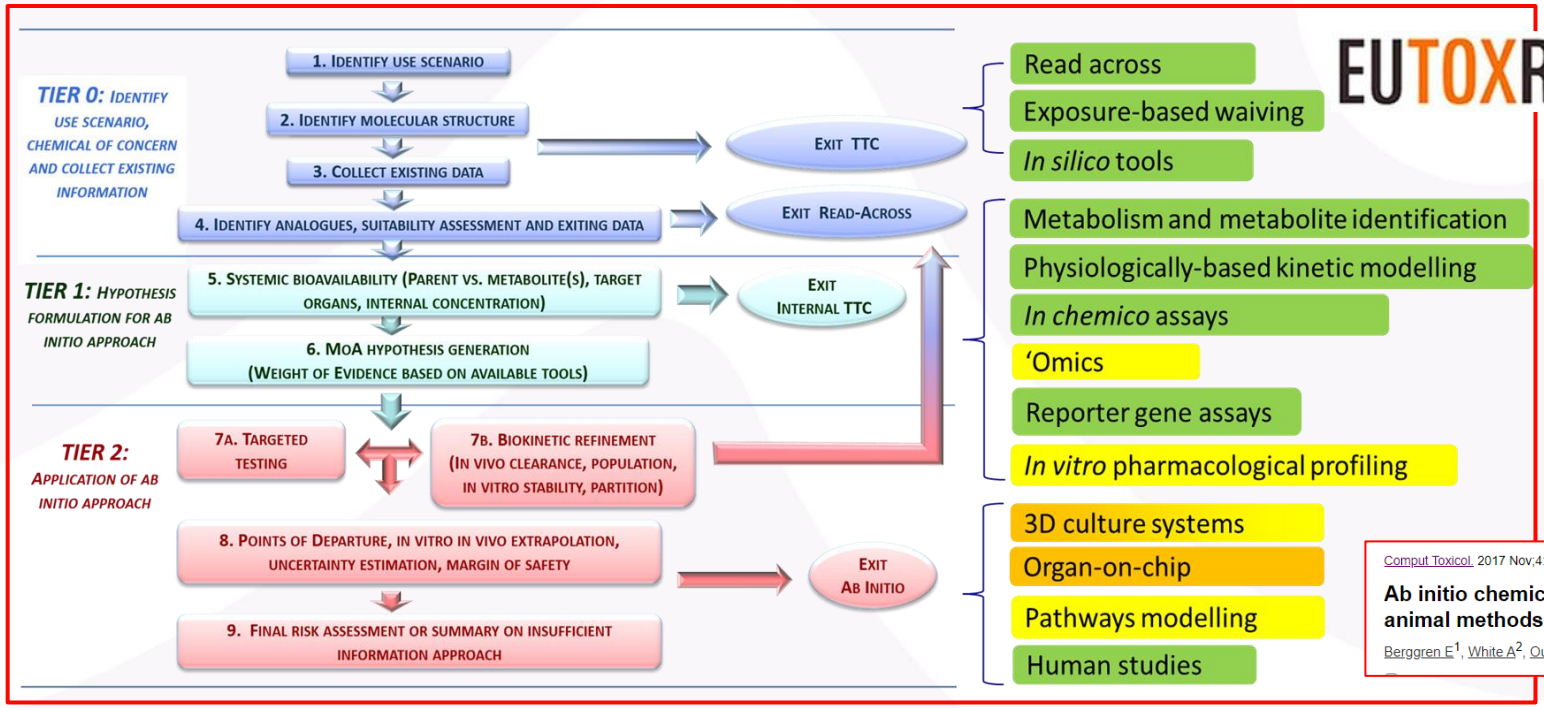






Applying new scientific human-relevant tools for safety decisions





EUTOXRISK

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].

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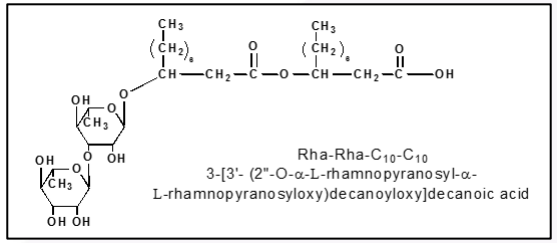
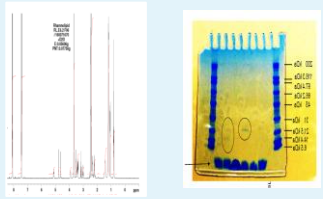
Case Study – Rhamnolipid Safety Assessment

novel biosurfactant



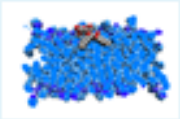


Complex chemical characterisation – protein identification in RL prep

Regulatory approach to address systemic health effects – animal testing

SEAC approach to systemic health assessment – application of next generation non-animal approaches

MODELLING



- *In silico* prediction of Rl membrane interaction

- Consumer hand dish wash (HDW) habits from 15 geographies evaluated and modelled to inform *in vitro* assay design

MECHANISTIC IN VITRO ASSAYS

- Immunostimulatory potential evaluated *in vitro* and No Effect Concentration (NEC) determined
- Comparison to modelled human internal exposure – **low risk**

EXPOSURE-BASED WAIVING

- Primary route of exposure from HDW is via skin – *in vitro* skin penetration study demonstrates **no systemic exposure**
- Weight of evidence approach for metabolites – **low risk**

MECHANISTIC CHEMISTRY

- Peptide reactivity assay – components of prep bind to model peptides
- Read-across approach – **low risk**

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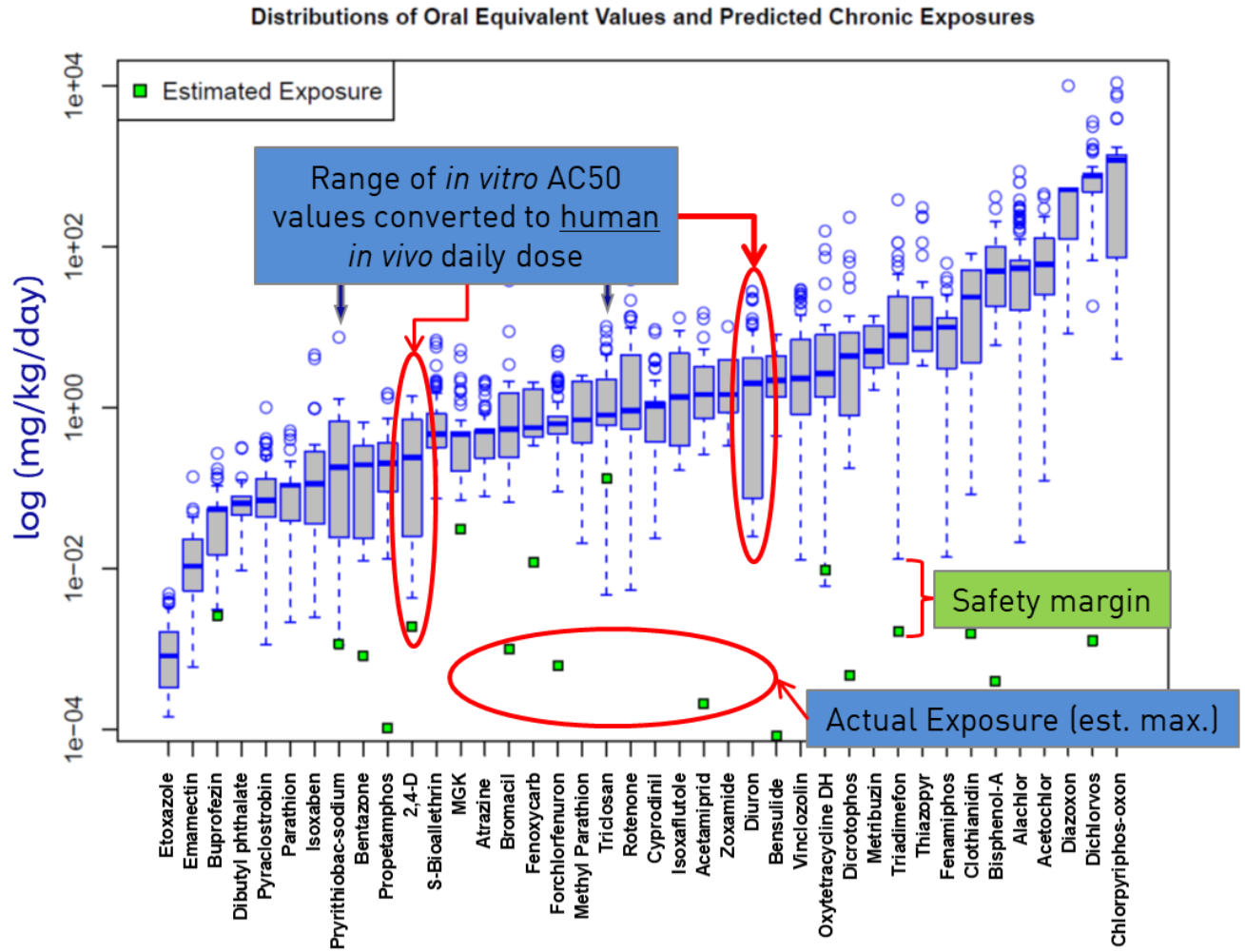
A fundamental principle of NGRA: 'Protection not Prediction'



NGRA uses new exposure science and understanding of human biology.

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

NGRA does <u>not</u> attempt to predict the results of high dose toxicology studies in animals.

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

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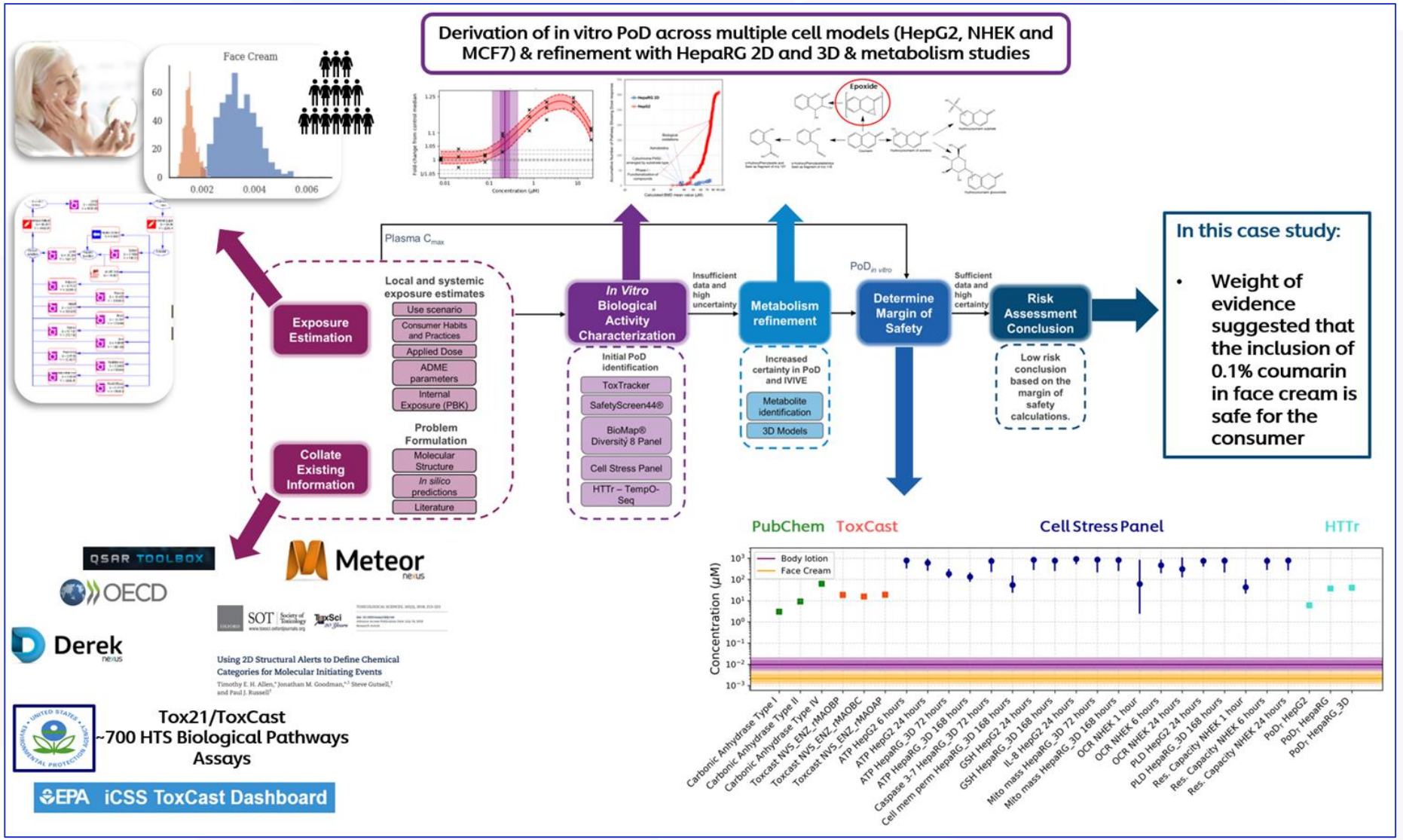
A large toolbox of modern scientific methods (NAMs) is used



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

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

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

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

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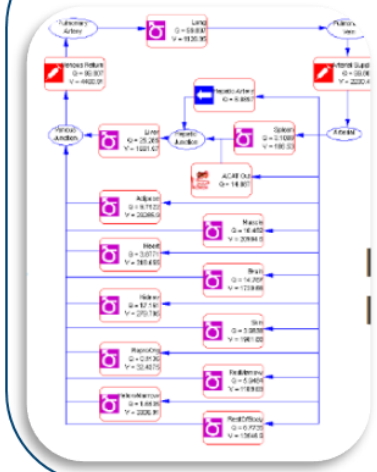
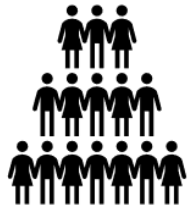
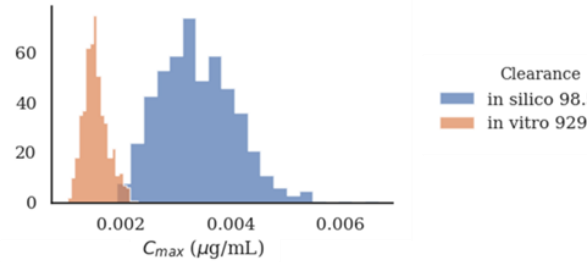
Key tools (NAMs) in our NGRA approach for systemic effects

PBK Modelling







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

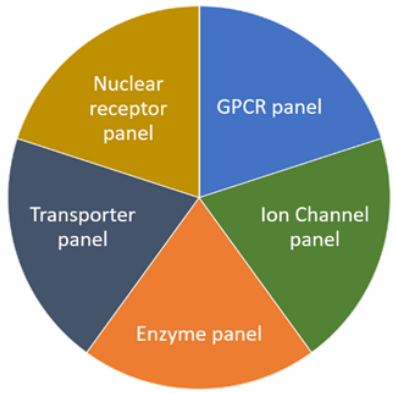
In vitro pharmacological profiling


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

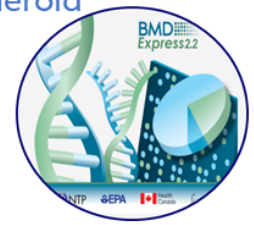


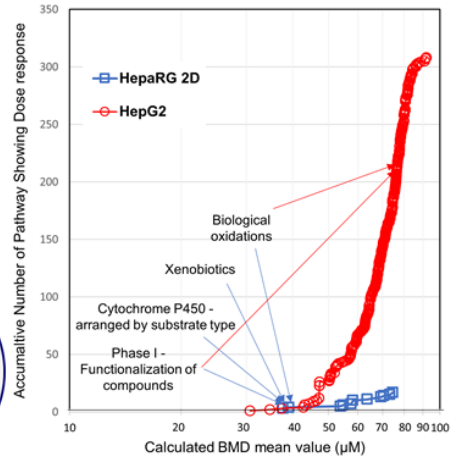
eurofins | Cerep

Transcriptomics

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

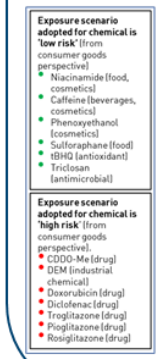
BMDExpress 2

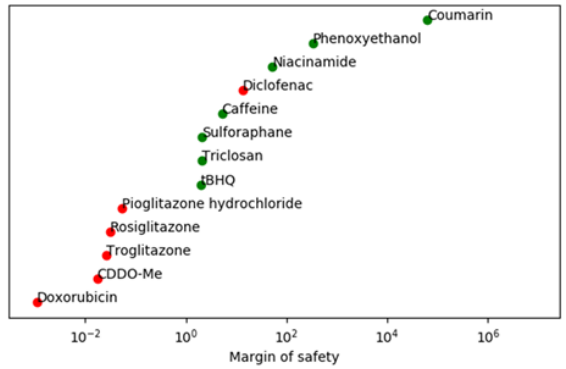




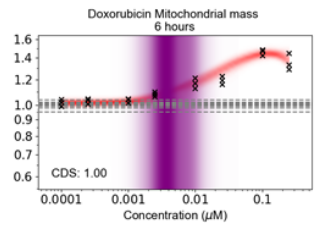
Cellular Stress Pathways

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





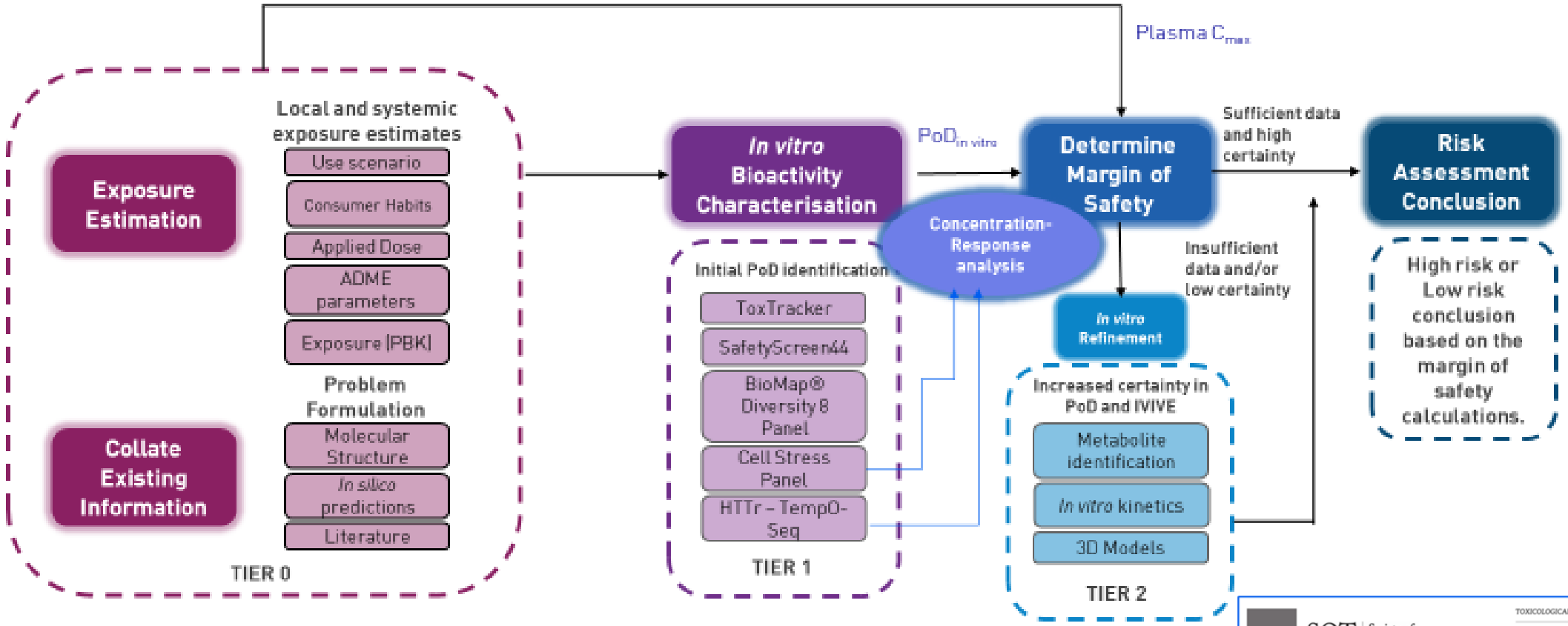
cyprotex AN EVOTEC COMPANY

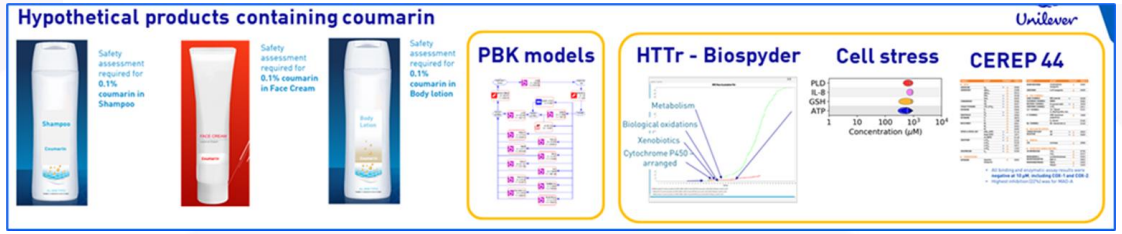


Toxicol Sci (2020), **176**, 11-33

Unilever

Unilever Next Generation Risk Assessment Framework
Systemic Exposure



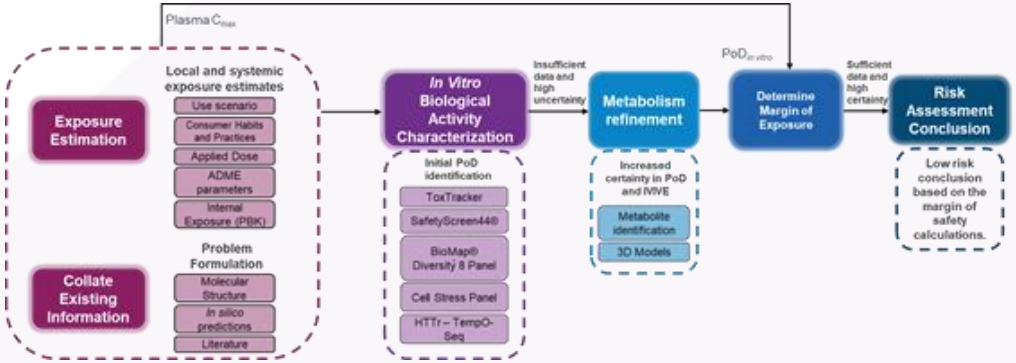


Baltazar *et al.*, (2020) *Toxicol Sci* **176**, 236–252

Unilever

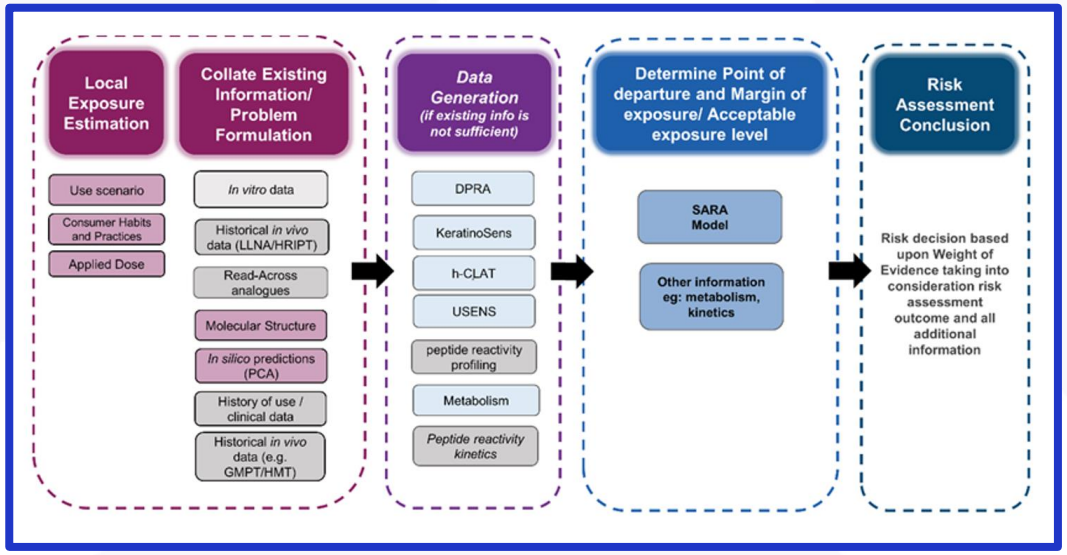
Unilever Frameworks for using NAMs to make Human Safety Decisions

Systemic



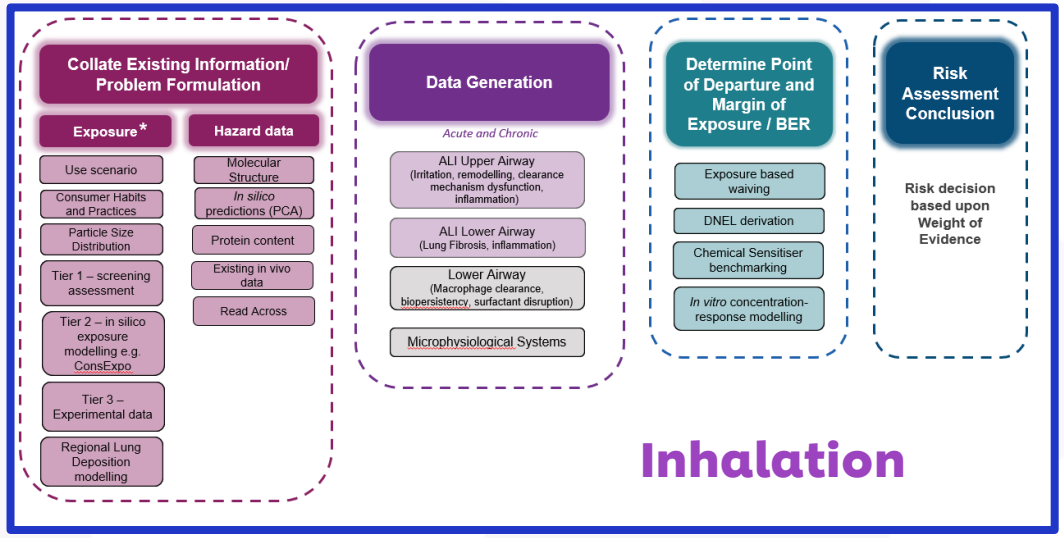
Baltazar et al (2020) *Toxicol Sci*, 176, 236-252

Skin Sensitisation

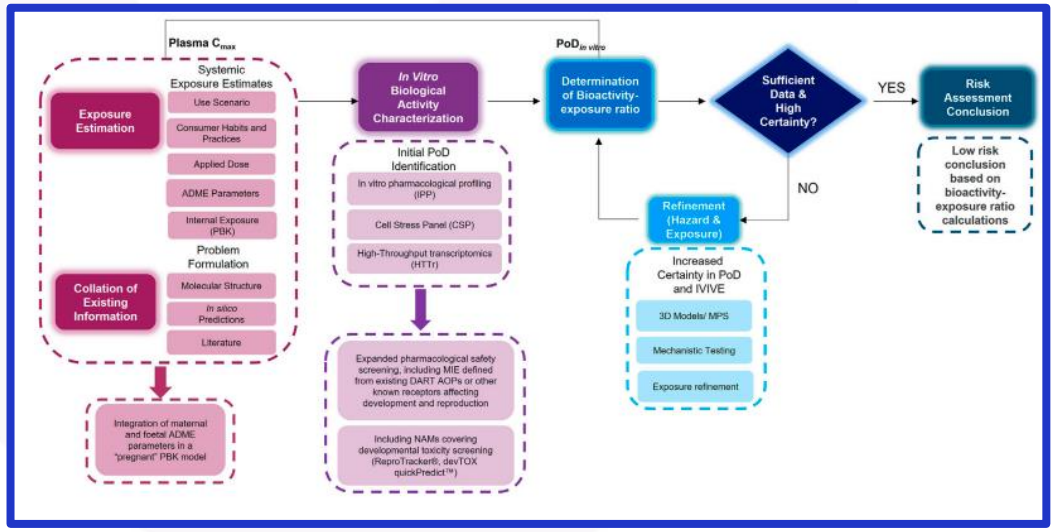


Reynolds et al (2021) *Reg Tox Pharmacol*, **127**, 105075

Inhalation



Developmental & Reproductive (DART)



Rajagopal et al (2022) *Frontiers in Toxicology*, doi: 10.3389/ftox.2022.838466

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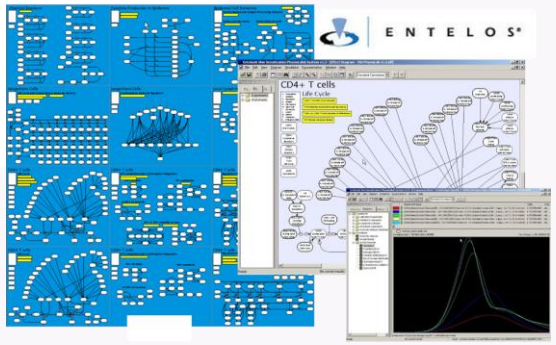
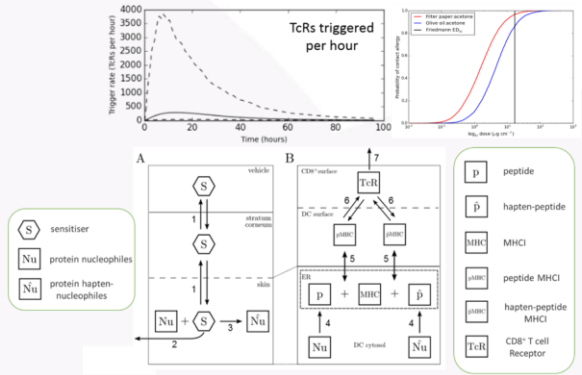
Skin Allergy Risk Assessment



Entelos model

[Maxwell G. & MacKay C. 2008](#).



SARA TKTD qAOP model

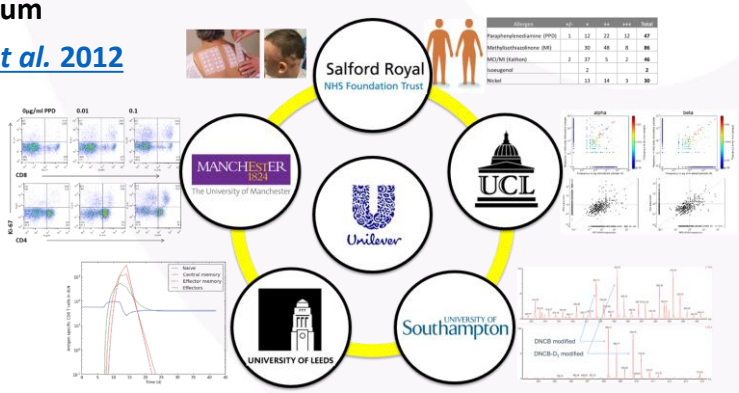
[Mackay et al. 2013](#)

SARA Bayesian Model

[Reynolds *et al.* 2019](#)

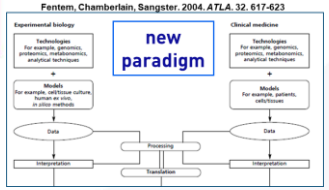
T cell Forum

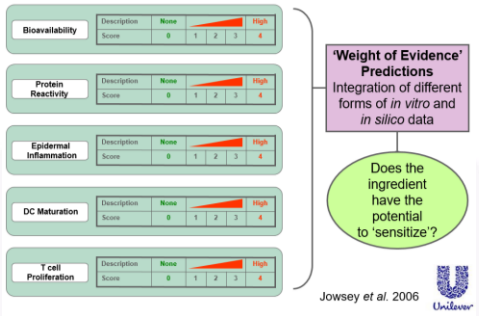
[Kimber et *al.* 2012](#)



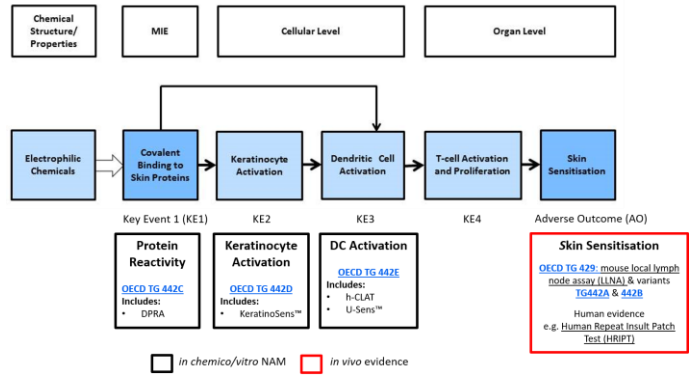
Integration of non-animal data

[Jowsey *et al.* 2006](#)

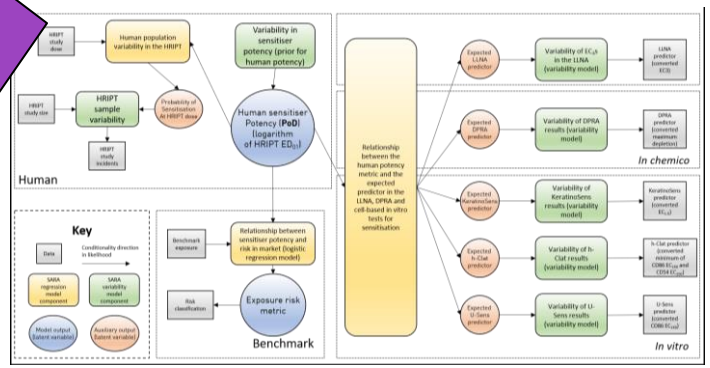




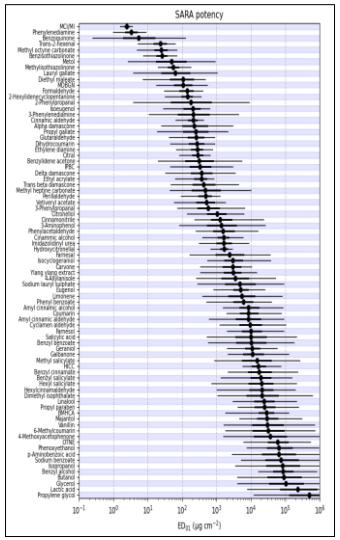
Skin Allergy AOP and SARA inputs



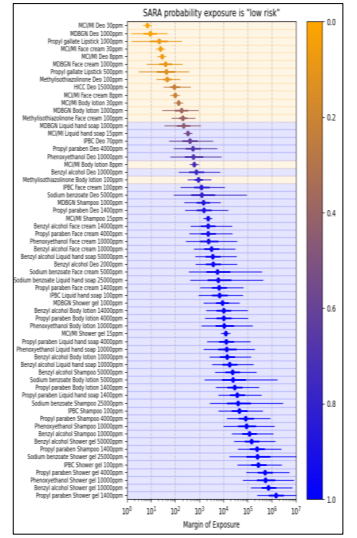
SARA Model Structure



SARA Human Potency

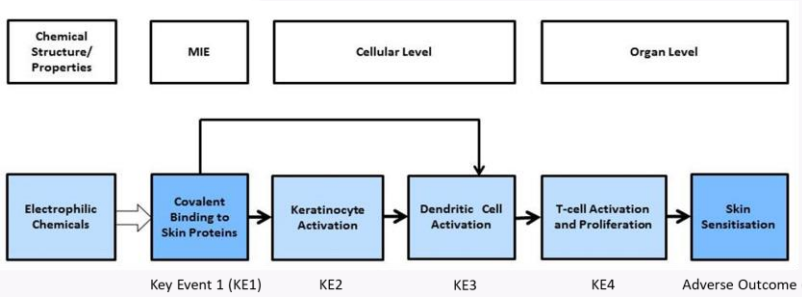


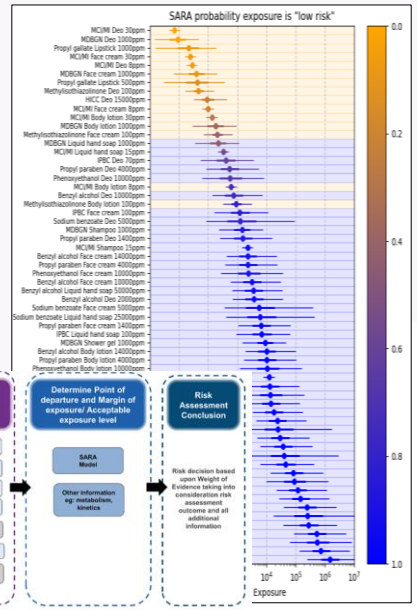
SARA Consumer Risk

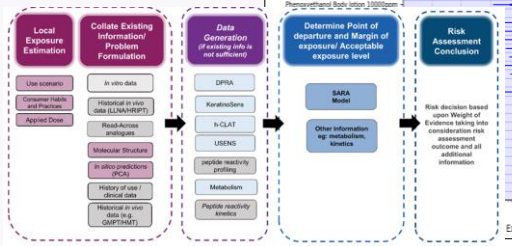


Non-Animal Methods for Skin Allergy Risk Assessment (SARA)

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



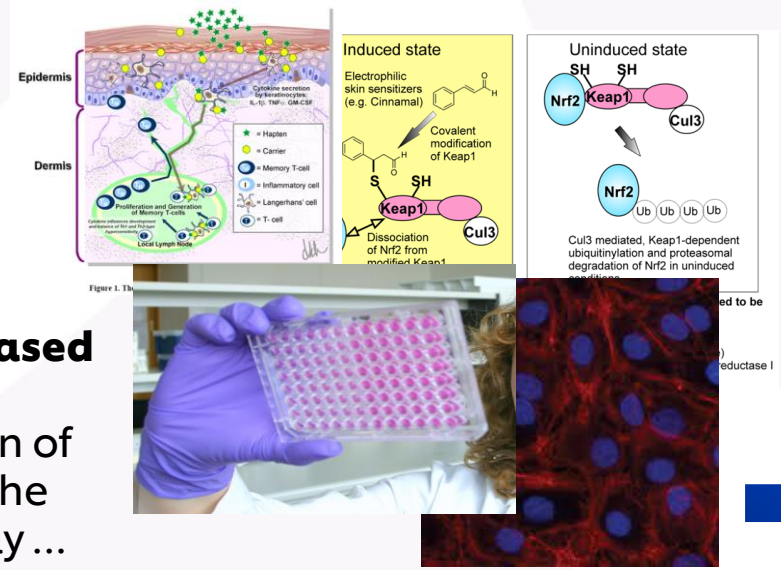




Unilever's **SARA Model** – developed as a computational approach to integrate information from the historical data and various cell-based experiments …

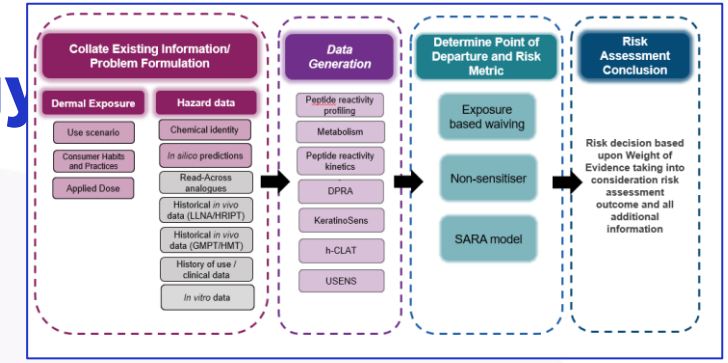
SARA Model published and collaboration with US Gov. group (NICEATM) to adapt the model for **regulatory use**.

Developing a **risk assessment framework** …



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

Application of NGRA Framework for Skin Allergy



Regulatory Toxicology and Pharmacology 127 (2021) 105075

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

A hypothetical skin sensitisation next generation risk assessment for coumarin in cosmetic products

G. Reynolds *, J. Reynolds, N. Gilmour, R. Cubberley, S. Spriggs, A. Aptula, K. Przybylak, S. Windebank, G. Maxwell, M.T. Baltazar **

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

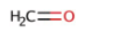
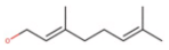
ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords and highlights:
Skin sensitisation
Allergic contact dermatitis
Next generation risk assessment
Non-animal alternatives
New approach methodologies
Consumer exposure
Uncertainty analysis
Decision making
Metabolism

ABSTRACT

Next generation Risk Assessment (NGRA) is an exposure-led, hypothesis-driven approach which integrates new approach methodologies (NAMs) to assure safety without generating animal data. This hypothetical skin allergy risk assessment of two consumer products – face cream containing 0.1% coumarin and deodorant containing 1% coumarin – demonstrates the application of our skin allergy NGRA framework which incorporates our Skin Allergy Risk Assessment (SARA) Model. SARA uses Bayesian statistics to provide a human relevant point of departure and risk metric for a given chemical exposure based upon input data that can include both NAMs and historical *in vivo* studies. Regardless of whether NAM or *in vivo* inputs were used, the model predicted that the face cream and deodorant exposures were low and high risk respectively. Using only NAM data resulted in a minor underestimation of risk relative to *in vivo*. Coumarin is a predicted pro-hapten and consequently, when applying this mechanistic understanding to the selection of NAMs the discordance in relative risk could be minimized. This case study demonstrates how integrating a computational model and generating bespoke NAM data in a weight of evidence framework can build confidence in safety decision making.

Chemical	(±)-Lactic acid	Formaldehyde	Geraniol
CAS	50-21-5	50-00-0	106-24-1
SMILES	CC(O)C(O)=O	C=O	CC(=CCC\C(=C\CO)\C)C
Structure			
MW (g/mol)	90.078	30.026	154.25

Regulatory Toxicology and Pharmacology

Volume 131, June 2022, 105159

Next generation risk assessment for skin allergy: Decision making using new approach methodologies

N. Gilmour, 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

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https://doi.org/10.1016/j.yrtph.2022.105159

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Highlights

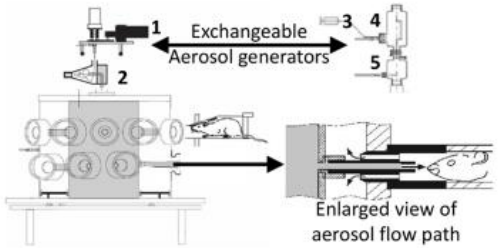
- Application of new approach methodologies in a next generation risk assessment framework for skin allergy.
- Use of the skin allergy risk assessment (SARA) model, a defined approach for potency and risk assessment of skin sensitisers.
- Skin sensitisation risk assessment case studies using new approach methodologies.

Unilever

Inhalation Risk Assessment

Several Unilever products lead to an unintentional inhalation exposure

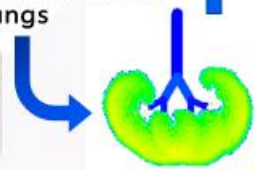
Historically risk assessment of ingredients in aerosols and sprays formulations relied on animal tests in rats exposed to aerosols for 28 or 90-days, 6h/day



Realistic exposure
Simulation of how consumers use our products

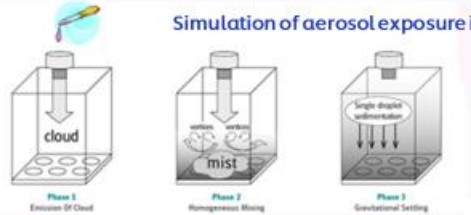
Realistic exposure
Simulation of particle fate in the lungs

MPPD

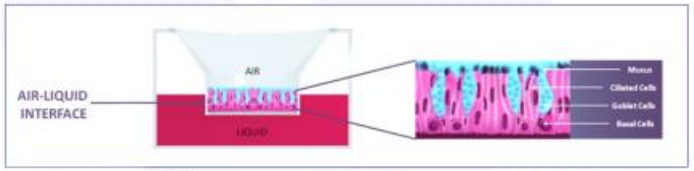


State of the art non-animal technologies to evaluate the safety of new ingredients

Simulation of aerosol exposure in vitro



Simulation of human biology in vitro



Swansea University Prifysgol Abertawe
THE UNIVERSITY of EDINBURGH
MRC
UNIVERSITY OF CAMBRIDGE

General strategy to developing an inhalation toolbox

Hypothetical Case study based approach

New polymers for use in antiperspirants & silanes for use in general purpose cleaners

- Chemistry; phys-chem properties
- Potential hazards
- Existing information

Exposure- led

Exposure is calculated using consumer habits and practices.
A tiered modelling approach is applied to simulate realistic consumer exposure

- **Product type**: formulation & hardware
- **Particle size** distribution
- **Consumer habits and practices**:
  - E.g. antiperspirant: application 2x/day, 2s per axillae, exposure duration 10 min, room volume 10m³.
- **Tiered modelling approach.**
- **In vitro exposure doses** are informed by predictions from **MPPD** (Multiple Path Particle Dosimetry) model.

Hypothesis-driven

Identification of key hazard concerns for the chemicals of interest

Lung fibrosis (lower airway)

Impairment of mucociliary clearance

Lung surfactant inhibition

Biopersistency/ Clearance

NAMs identification and evaluation using benchmark compounds

Ongoing development of an Inhalation Framework

Collate Existing Information/ Problem Formulation

Exposure*	Hazard data
Use scenario	Molecular Structure
Consumer Habits and Practices	*In silico* predictions (PCA)
Particle Size Distribution	Protein content
Tier 1 – screening assessment	Existing in vivo data
Tier 2 – in silico exposure modelling e.g. ConsExpo/2-box	Read Across
Tier 3 – Experimental data	
Regional Lung Deposition modelling	

Data Generation

Acute and Chronic

- ALI Upper Airway (Irritation, remodelling, clearance mechanism dysfunction, inflammation)
- ALI Lower Airway (Lung Fibrosis, inflammation)
- Lower Airway (Macrophage clearance, biopersistency, surfactant disruption)
- Microphysiological Systems

Determine Point of Departure and Margin of Exposure / BER

- Exposure based waiving
- DNEL derivation
- Chemical Sensitiser benchmarking
- *In vitro* concentration-response modelling

Risk Assessment Conclusion

Risk decision based upon Weight of Evidence

IVAMSS Webinar: Inhalation Toxicity: *In Vitro* to Human Risk Assessment
https://www.toxicology.org/groups/ss/IVSS/Events.asp

*Consumer Exposure in Inhalation risk assessment

Unilever

Frameworks for using NAMs to make safety decisions: DART

Front Toxicol. 2022 Mar 7;4:838466. doi: 10.3389/ftox.2022.838466. eCollection 2022.

Beyond AOPs: A Mechanistic Evaluation of NAMs in DART Testing

Ramya Rajagopal [1], Maria T Baltazar [1], Paul L Carmichael [1], Matthew P Dent [1], Julia Head [1], Hequn Li [1], Iris Muller [1], Joe Reynolds [1], Kritika Sadh [1], Wendy Simpson [1], Sandrine Spriggs [1], Andrew White [1], Predrag Kukic [1]

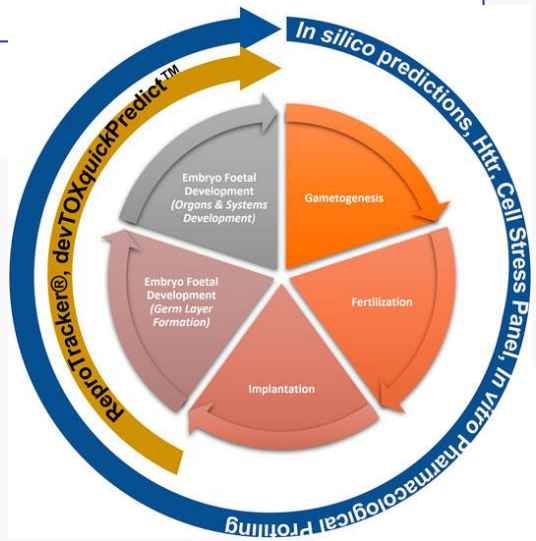
Affiliations – collapse

Affiliation

1 Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, United Kingdom.

PMID: 35295212 PMCID: PMC8915803 DOI: 10.3389/ftox.2022.838466

Free PMC article



Abstract

New Approach Methodologies (NAMs) promise to offer a unique opportunity to enable human-relevant safety decisions to be made without the need for animal testing in the context of exposure-driven Next Generation Risk Assessment (NGRA). Protecting human health against the potential effects a chemical may have on embryo-foetal development and/or aspects of reproductive biology using NGRA is particularly challenging. These are not single endpoint or health effects and risk assessments have traditionally relied on data from Developmental and Reproductive Toxicity (DART) tests in animals. There are numerous Adverse Outcome Pathways (AOPs) that can lead to DART, which means defining and developing strict testing strategies for every AOP, to predict apical outcomes, is neither a tenable goal nor a necessity to ensure NAM-based safety assessments are fit-for-purpose. Instead, a pragmatic approach is needed that uses the available knowledge and data to ensure NAM-based exposure-led safety assessments are sufficiently protective. To this end, the mechanistic and biological coverage of existing NAMs for DART were assessed and gaps to be addressed were identified, allowing the development of an approach that relies on generating data relevant to the overall mechanisms involved in human reproduction and embryo-foetal development. Using the knowledge of cellular processes and signalling pathways underlying the key stages in reproduction and development, we have developed a broad outline of endpoints informative of DART. When the existing NAMs were compared against this outline to determine whether they provide comprehensive coverage when integrated in a framework, we found them to generally cover the reproductive and developmental processes underlying the traditionally evaluated apical endpoint studies. The application of this safety assessment framework is illustrated using an exposure-led case study.

Keywords: DART; NAMs; NGRA; mechanistic evaluation; non-animal alternatives.

Unilever

Overview

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4. Alternatives to Animal Testing – a short history
5. Safety Science in 2022: New Approach Methodologies (NAMs) & Next Generation Risk Assessment (NGRA) – research & application
6. **Regulatory Acceptance – cosmetics, foods, chemicals**
7. Closing the Science – Regulatory Use Gap
8. Looking Forwards – my thoughts on priorities

Unilever

Regulatory Acceptance – cosmetics, foods, chemicals

We are advocating for regulatory change around the world

Unilever supports calls for a global ban on animal testing for cosmetics by 2023

Product testing

Hygiene products & disinfectants

Home care products

Ingredient testing – existing ingredients

ECHA
EUROPEAN CHEMICALS AGENCY

Ingredient testing – new ingredients

Partner With Purpose

Unilever

Use of animal-free approaches / NAMs for Cosmetics Safety - scientific weight-of-evidence safety risk assessments

Computational Toxicology 7 (2018) 20–26

Contents lists available at ScienceDirect

Computational Toxicology

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

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[l], Nashira Vieira O'Reilly Cabral Posada[l], Craig Weiss[p], Hajime Kojima[f]

ARTICLE INFO

Keywords:
Next Generation Risk Assessment
New approach methodologies
Cosmetics risk assessment

ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis driven risk assessment approach that integrates in silico, in chemico and in vitro approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic Industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles

SCCS/1628/21

Scientific Committee on Consumer Safety

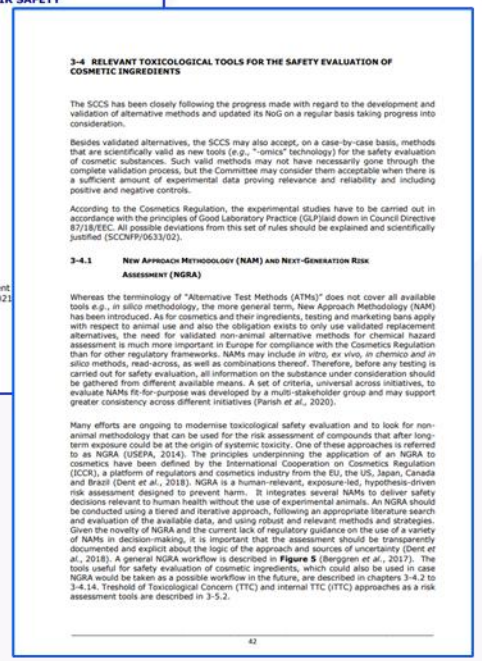
SCCS

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



3-4 RELEVANT TOXICOLOGICAL TOOLS FOR THE SAFETY EVALUATION OF COSMETIC INGREDIENTS

The SCCS has been closely following the progress made with regard to the development and validation of alternative methods and updated its NoG on a regular basis taking progress into consideration.

Besides validated alternatives, the SCCS may also accept, on a case-by-case basis, methods that are scientifically valid as new tools (*e.g.*, "-omics" technology) for the safety evaluation of cosmetic substances. Such valid methods may not have necessarily gone through the complete validation process, but the Committee may consider them acceptable when there is a sufficient amount of experimental data proving relevance and reliability and including positive and negative controls.

According to the Cosmetics Regulation, the experimental studies have to be carried out in accordance with the principles of Good Laboratory Practice (GLP)laid down in Council Directive 87/18/EEC. All possible deviations from this set of rules should be explained and scientifically justified (SCCNFP/0633/02).

3-4.1 NEW APPROACH METHODOLOGY (NAM) AND NEXT-GENERATION RISK ASSESSMENT (NGRA)

Whereas the terminology of "Alternative Test Methods (ATMs)" does not cover all available tools *e.g., in silico* methodology, the more general term, New Approach Methodology (NAM) has been introduced. As for cosmetics and their ingredients, testing and marketing bans apply with respect to animal use and also the obligation exists to only use validated replacement alternatives, the need for validated non-animal alternative methods for chemical hazard assessment is much more important in Europe for compliance with the Cosmetics Regulation than for other regulatory frameworks. NAMs may include *in vitro, ex vivo, in chemico and in silico* methods, read-across, as well as combinations thereof. Therefore, before any testing is carried out for safety evaluation, all information on the substance under consideration should be gathered from different available means. A set of criteria, universal across initiatives, to evaluate NAMs fit-for-purpose was developed by a multi-stakeholder group and may support greater consistency across different initiatives (Parish *et al.*, 2020).

Many efforts are ongoing to modernise toxicological safety evaluation and to look for non-animal methodology that can be used for the risk assessment of compounds that after long-term exposure could be at the origin of systemic toxicity. One of these approaches is referred to as NGRA (USEPA, 2014). The principles underpinning the application of an NGRA to cosmetics have been defined by the International Cooperation on Cosmetics Regulation (ICCR), a platform of regulators and cosmetics industry from the EU, the US, Japan, Canada and Brazil (Dent *et al.*, 2018). NGRA is a human-relevant, exposure-led, hypothesis-driven risk assessment designed to prevent harm. It integrates several NAMs to deliver safety decisions relevant to human health without the use of experimental animals. An NGRA should be conducted using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies. Given the novelty of NGRA and the current lack of regulatory guidance on the use of a variety of NAMs in decision-making, it is important that the assessment should be transparently documented and explicit about the logic of the approach and sources of uncertainty (Dent *et al.*, 2018). A general NGRA workflow is described in **Figure 5** (Berggren *et al.*, 2017). The tools useful for safety evaluation of cosmetic ingredients, which could also be used in case NGRA would be taken as a possible workflow in the future, are described in chapters 3-4.2 to 3-4.14. Treshold of Toxicological Concern (TTC) and internal TTC (iTTC) approaches as a risk assessment tools are described in 3-5.2.

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OECD

Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

Unclassified — English - Or. English

27 October 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

Series on Testing and Assessment, No. 349

JT03483903

This document, as well as any data and map included herein, are without prejudice to the status of or sovereignty over any territory, to the delimitation of international frontiers and boundaries and to the name of any territory, city or area.

International Cooperation on Cosmetics Regulation (2018)

European Commission: Scientific Committee on Consumer Safety (2021)

OECD (2021)

Use of NAMs for assessing Food Safety
EFSA investing in NAMs for regulatory assessments

Finally, the development of scientific methodologies and tools, and the opportunity to refine existing ones, will offer new approaches for risk assessment in line with the 3Rs principle (Replacement, Refinement, and Reduction) to animal testing. EFSA must continue to invest in harvesting data and information to stay abreast of evolving scientific methodologies and research and develop adequate methodologies to assess new sources of potential food/feed risks such as new production technologies.

Food Safety = weight-of-evidence scientific assessments & risk control / management

Expected Operational Result 2.1.3

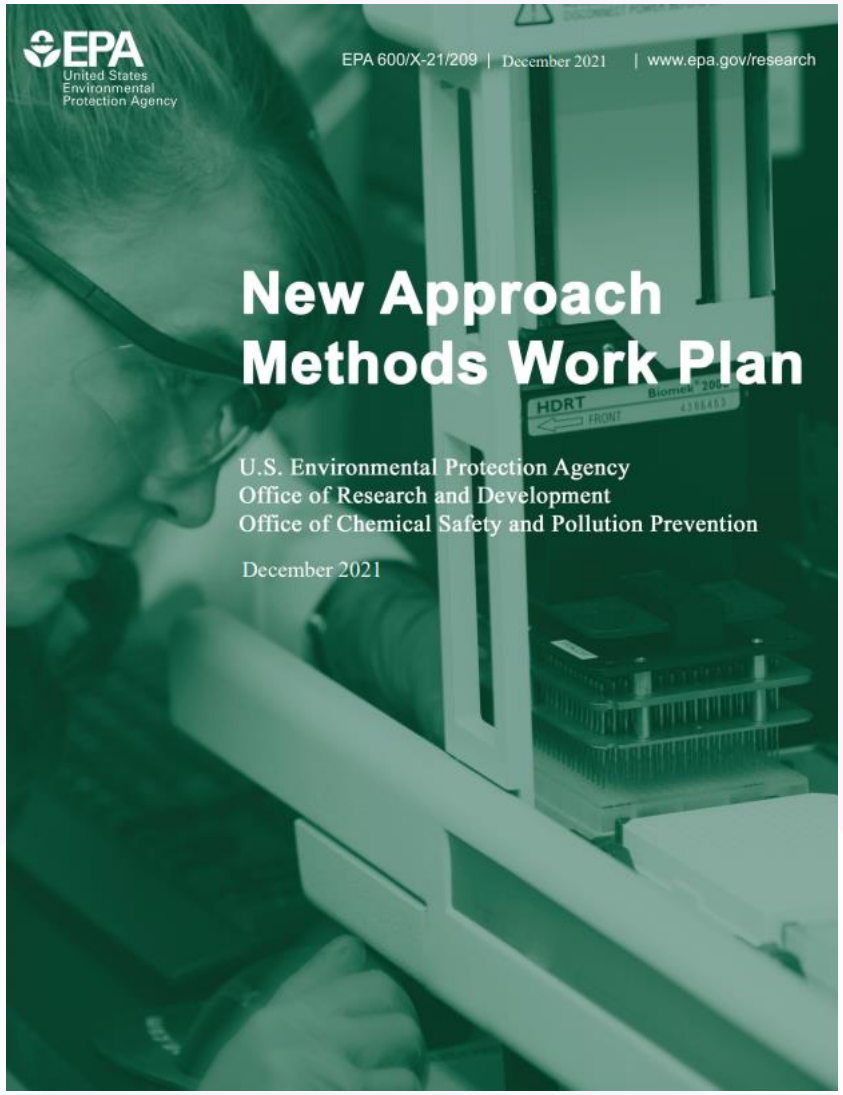
The quality of scientific guidance and methodologies, with the necessary risk assessment capabilities, is improved to address future challenges

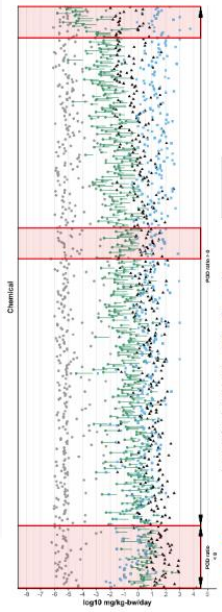
KEY ACTIONS

- Ensure forward looking engagement with partners and stakeholders to achieve synergies on Risk Assessment topics of mutual interest and facilitate the development and implementation of harmonised risk assessment methodologies
- Prepare to address risk assessment challenges associated with food and feed system innovations
- Develop risk benefit approaches for chemical and biological hazards in human and environmental risk assessment
- Develop and implement systems-based approaches for regulatory environmental risk assessment
- Establish criteria and scientific assessment options to support the application of tiered approaches of methodological complexity to deliver fit for purpose assessments
- Develop and integrate new approach methodologies (NAMs) and omics for regulatory risk assessment
- Develop risk assessment of combined exposure to multiple chemicals, across regulatory domains
- Integrate, bioinformatic and cheminformatics approaches, technologies and data into next generation risk assessment
- Consider how microbiomes could be included in risk assessment, and develop tools to enable this
- Keep EFSA's risk assessment processes updated in line with evolving regulatory, policy and quality drivers (TR)

Unilever

Uptake of NAMs for assessing Chemical Safety being led by US EPA





APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

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*

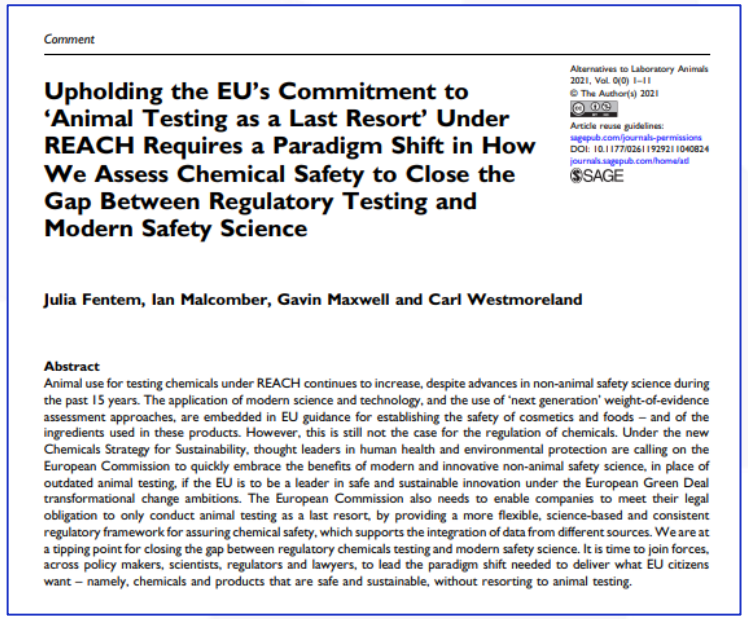
"The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals"

Unilever

NAMs and REACH / EU Chemicals Strategy for Sustainability

Re-thinking the EU's approach to chemical safety

- Whilst NAMs are increasingly used for safety assessment purposes, their application in chemicals registration remains limited
- New animal testing requested for widely used existing chemicals under REACH
- Failure of ECHA to implement 'animal testing as a last resort'
- Inconsistency in EU approaches for establishing product and ingredient (chemical) safety



Comment

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. 0(0) 1–11

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DOI: 10.1177/02611929211040824
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SAGE

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

Abstract

Animal use for testing chemicals under REACH continues to increase, despite advances in non-animal safety science during the past 15 years. The application of modern science and technology, and the use of 'next generation' weight-of-evidence assessment approaches, are embedded in EU guidance for establishing the safety of cosmetics and foods – and of the ingredients used in these products. However, this is still not the case for the regulation of chemicals. Under the new Chemicals Strategy for Sustainability, thought leaders in human health and environmental protection are calling on the European Commission to quickly embrace the benefits of modern and innovative non-animal safety science, in place of outdated animal testing, if the EU is to be a leader in safe and sustainable innovation under the European Green Deal transformational change ambitions. The European Commission also needs to enable companies to meet their legal obligation to only conduct animal testing as a last resort, by providing a more flexible, science-based and consistent regulatory framework for assuring chemical safety, which supports the integration of data from different sources. We are at a tipping point for closing the gap between regulatory chemicals testing and modern safety science. It is time to join forces, across policy makers, scientists, regulators and lawyers, to lead the paradigm shift needed to deliver what EU citizens want – namely, chemicals and products that are safe and sustainable, without resorting to animal testing.

European Union

European Citizens' Initiative

We call on the European Commission to do the following:

1. Protect and strengthen the cosmetics animal testing ban.

Initiate legislative change to achieve consumer, worker, and environmental protection for all cosmetics ingredients without testing on animals for any purpose at any time.

2. Transform EU chemicals regulation.

Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.

3. Modernise science in the EU.

Commit to a legislative proposal plotting a roadmap to phase-out all animal testing in the EU before the end of the current legislative term.

Unilever

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8. Looking Forwards – my thoughts on priorities

Unilever

Closing the Science – Regulatory Use Gap

Safety scientists are calling for paradigm shift & regulatory change - safe & sustainable ingredients without animal testing

Comment

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

Archives of Toxicology
https://doi.org/10.1007/s00204-021-03215-9

REGULATORY TOXICOLOGY

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

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

Received: 11 October 2021 / Accepted: 21 December 2021
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Cosmetics

Unilever: EU needs 'paradigm shift' in chemical safety assessment methods

By Kacey Culliney

Cosmetics

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

Time to re-think & modernise our approach …

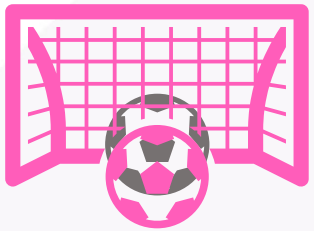
1. Conducting an animal test because it's a (perceived) regulatory requirement isn't adequate scientific justification

2. Current laws and regulations, not science, are impeding the paradigm shift to using modern animal-free safety science

3. Change regulatory approach to chemical safety to strengthen the protection of people (workers & consumers) and our environment, without that being anchored in predicting the apical toxicity effects seen in high-dose animal studies

Unilever

Using advanced science to assess chemical (ingredient) safety
- action needed to modernise chemicals regulatory frameworks



Scientifically justify 'animal testing as a last resort'
+
Paradigm shift in how we assess ingredient safety

Regulatory compliance
=
Best science to protect people & our environment

- [x] get creative using relevant NAMs* / scientific data
- [ ] modernise Legal & Regulatory requirements
- [ ] develop NAM-based regulatory frameworks

*NAM = New Approach Methodology

Comment

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

Law–Not Science–Impedes Shift to Non-Animal Safety Testing

June 18, 2021, 9:01 AM

Listen

Testing products on animals is slowly ending, but there are still some obstacles to completely ending the practice, explains Gary E. Marchant, a professor at the Sandra Day O'Connor College of Law at Arizona State University. He discusses three impediments, including legal barriers from federal regulatory agencies.

Gary Marchant
Sandra Day O'Connor College of Law

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

Overview

1. My Background / Unilever Safety & Environmental Assurance Centre
2. Unilever Policy & Approach
3. Consumer Perspective on Animal Testing
4. Alternatives to Animal Testing – a short history
5. Safety Science in 2022: New Approach Methodologies (NAMs) & Next Generation Risk Assessment (NGRA) – research & application
6. Regulatory Acceptance – cosmetics, foods, chemicals
7. Closing the Science – Regulatory Use Gap
8. **Looking Forwards – my thoughts on priorities**

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Looking Forwards – my thoughts on priorities

"Close the Investigative – Regulatory Toxicology Gap"

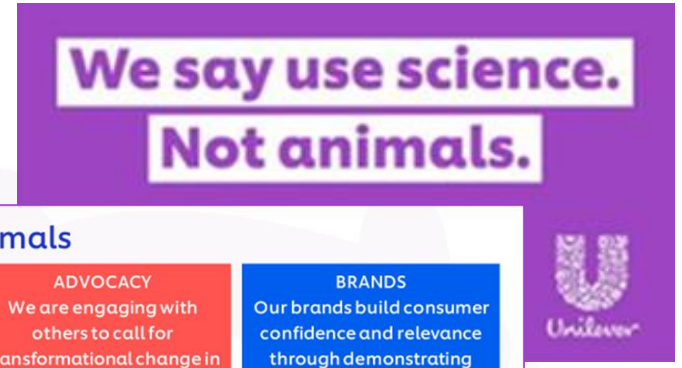
→ demonstrate how modern safety science & our new toolbox can lead to decisions which better protect human health & our environment

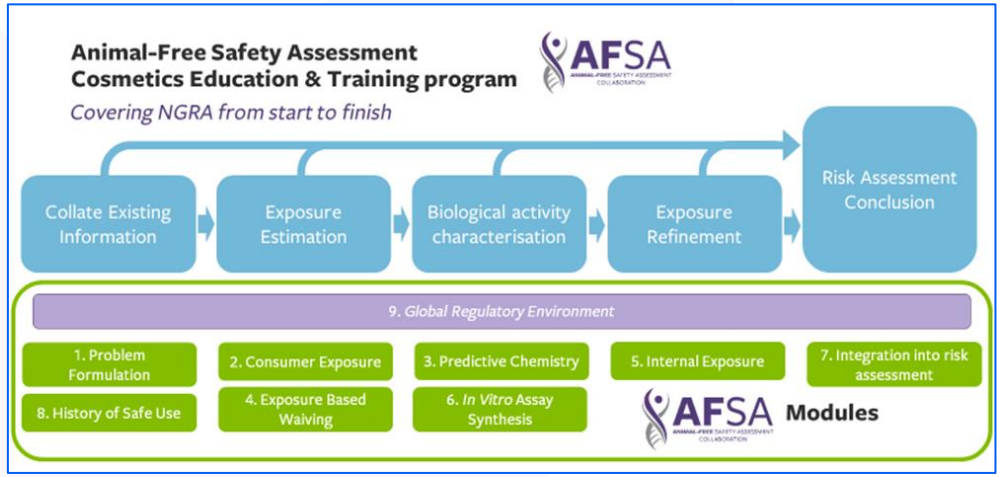
1. develop a **modern, science-based, chemicals regulatory framework**, which facilitates use of 21C science & technology to better protect people and the environment – regulatory change

2. establish open dialogue on, and **transparent scientific evaluation** of, NAM strategies for specific chemicals / chemical groups – case studies

3. accelerate **knowledge transfer & training** in advanced safety science and NAM-based chemical assessments - regulators / industry

4. stimulate **capacity building in NAMs** to increase the number of service providers of new "NAMs toolbox" – research & innovation





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Accelerating Knowledge Transfer to Build Capability & Capacity

Capacity building: Education and Training Program in Animal-Free Safety Assessment of Chemicals - AFSA (afsacollaboration.org)

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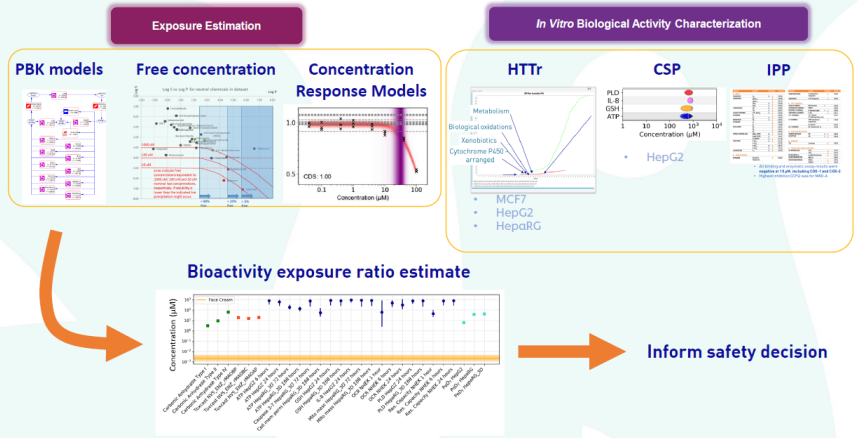
Building Confidence in using NAMs for Regulatory Purposes

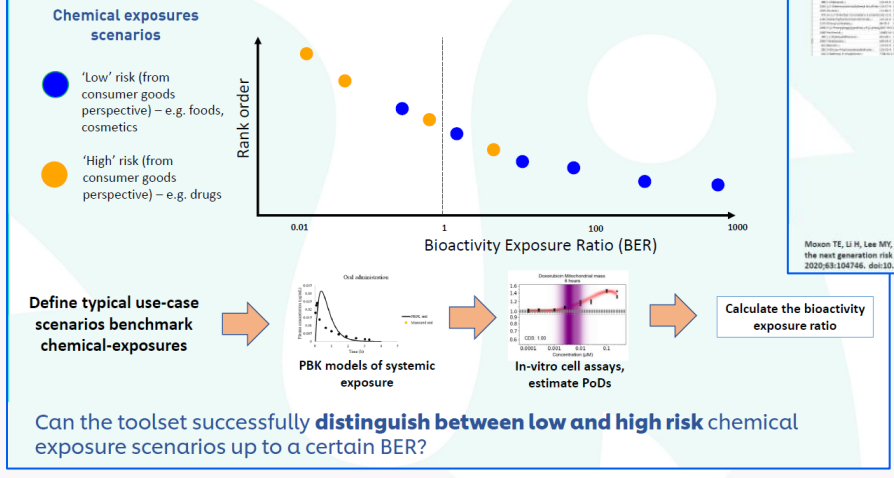
Evaluating the NAMs toolbox for consumer safety decision-making

Overview of core toolbox



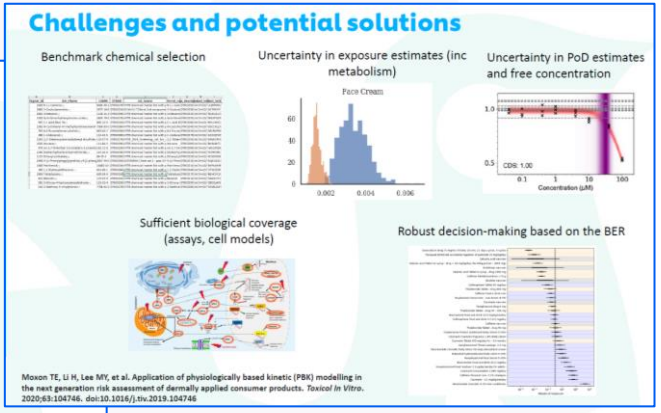
HTTr: High-throughput transcriptomics **CSP:** Cell Stress Panel **IPP:** In vitro pharmacological profiling

Evaluating the toolset for risk assessment

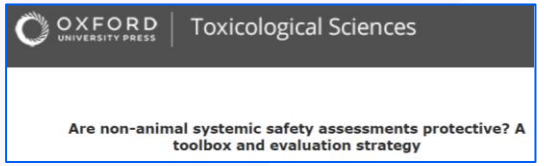


Can the toolset successfully **distinguish between low and high risk** chemical exposure scenarios up to a certain BER?

Challenges and potential solutions



Moxon TE, Li H, Lee MY, et al. Application of physiologically based kinetic (PBK) modelling in the next generation risk assessment of dermally applied consumer products. *Toxicol In Vitro.* 2020;63:104746. doi:10.1016/j.tiv.2019.104746



These case study outcomes suggest that NGRA based upon NAM and SARA model predictions are at least as protective as the historical risk assessment approaches. Through case studies such as those presented here, we are building our confidence in utilising NAM data in risk assessments for skin allergy and making decisions on consumer safety based upon the weight of all available evidence. These initial case studies represent relatively simple decisions based upon use of NAM data, additional case studies and further evaluation of the NGRA framework for skin sensitisation are required.

- Data Generation
- Case Studies
- Scientific Evaluation
- Publication

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Congratulations to ReNaMA on your 10th anniversary

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