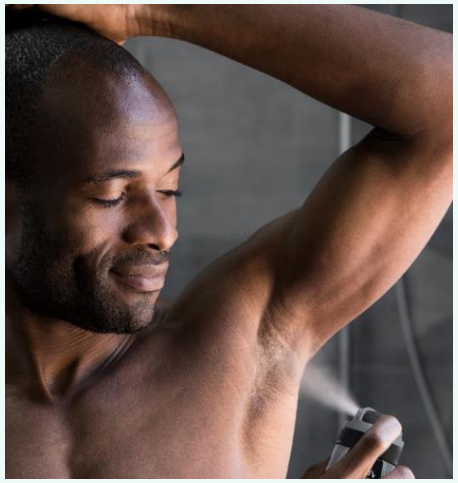
Innovating for safe and sustainable cosmetics without animal testing

Carl Westmoreland

27th December 2022

Protecting People



All Unilever's products and the ingredients they contain must be safe for consumers and for the people who work with them

.... and ensuring everyone has trust in the safety decisions

Alternatives to animal testing

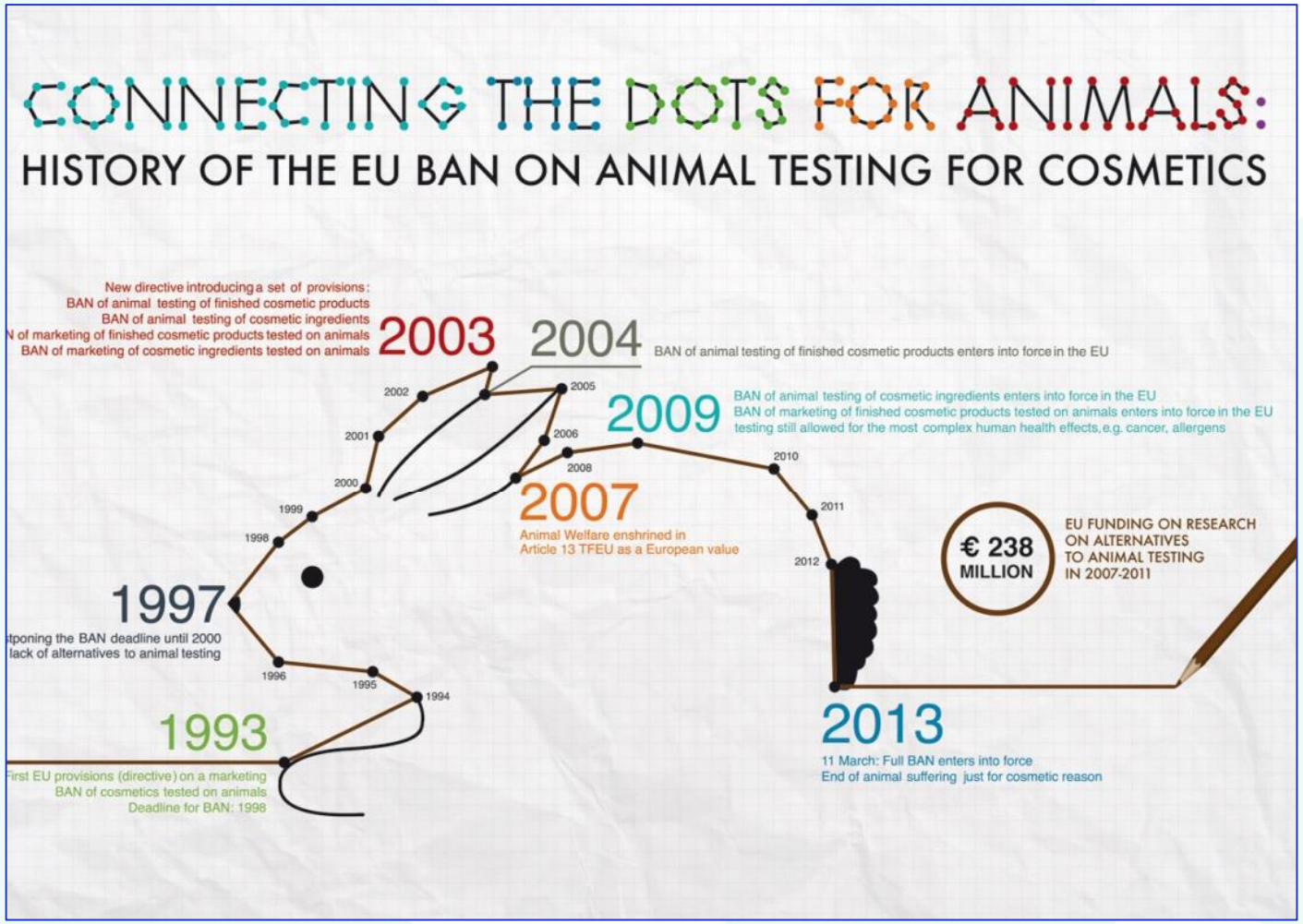
Our approach

We use a wide range of non-animal approaches to assess the safety of our products. Since the 1980s, our scientists have been developing and using alternatives to animal tests, e.g. computer modelling and cell culture-based experiments. We regularly present and publish our work, and continually collaborate with others to share our knowledge and apply exciting new science to assure product safety.

https://www.unilever.com/planet-and-society/responsible-business/alternatives-to-animal-testing/

The history of bans on animal testing for cosmetic products and ingredients in the EU – Nearly 10 years since the ban

EU Cosmetics Product Regulation: (EC) No 1223/2009



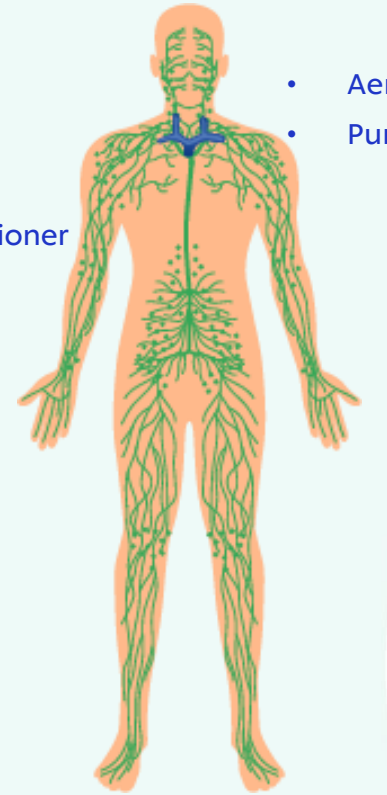
Source: https://ec.europa.eu/growth/sectors/cosmetics/ban-animal-testing_en

Assessing the consumer safety of cosmetic ingredients for the Cosmetic Product Regulation is exposure-led

Consumers

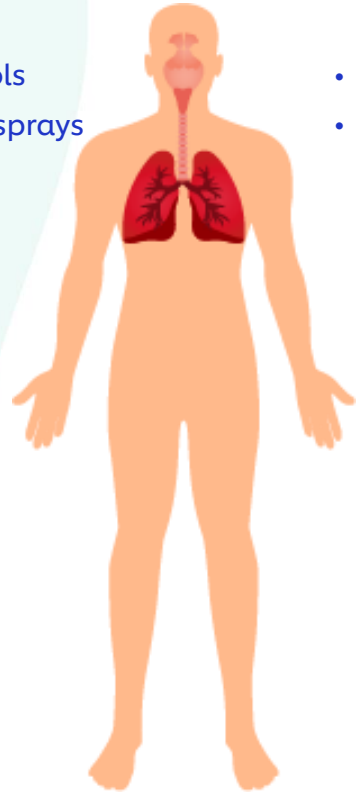
Skin

- Skin creams
- Deodorants
- Soap/cleansers
- Shampoo/ conditioner
- Shower gel



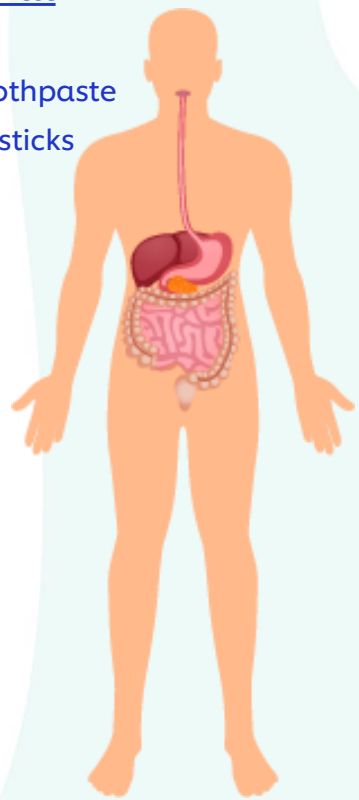
Inhalation*

- Aerosols
- Pump sprays

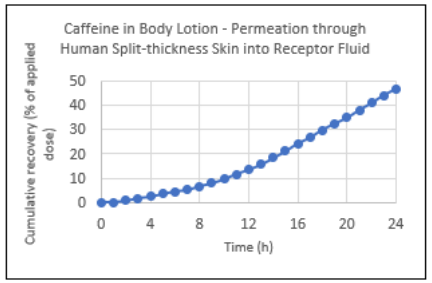


Oral

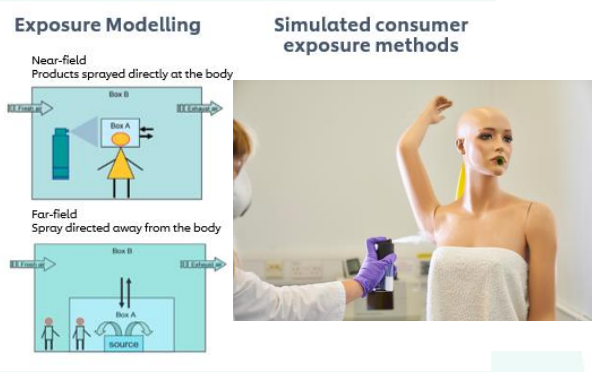
- Toothpaste
- Lipsticks



Skin Penetration



Inhalation



Steiling et al (2014) *Toxicology Letters*, **227**, 41-49

Images from: AFSA training module 'Consumer Exposure', 2022

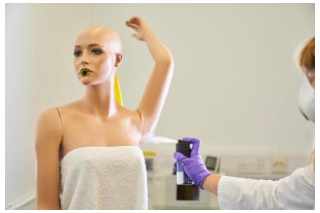
* Generally, depends on delivery system rather than product type.

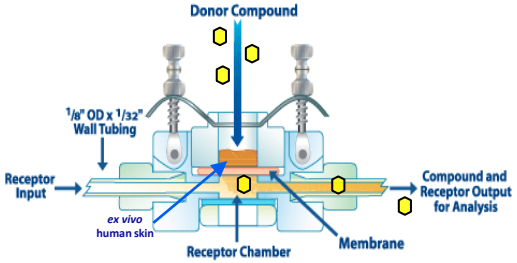
Assuring consumer safety without animal testing: Maximising use of existing information and non-animal approaches

- All our risk assessments are exposure-led

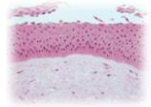
Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall *et al.*, 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor [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



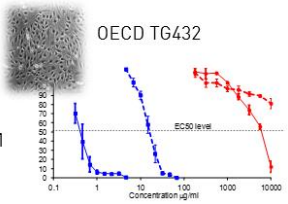


- Use all available safety data on the ingredient
  - Clinical, epidemiological, animal (if dates permit), *in vitro* etc
- Exposure-based waiving approaches (e.g. TTC, DST, Inhalation TTC)
- *in silico* predictions
- History of safe use
- Read across
- Use of existing OECD *in vitro* approaches
- Next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

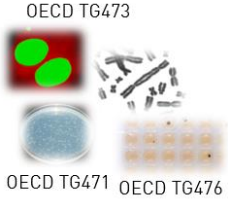


OECD TG437

OECD TG430/431
OECD TG439



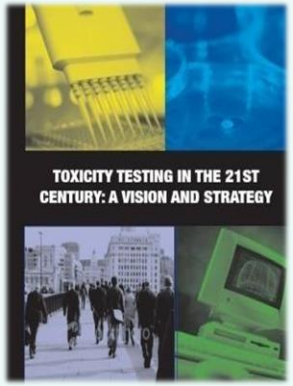
OECD TG432

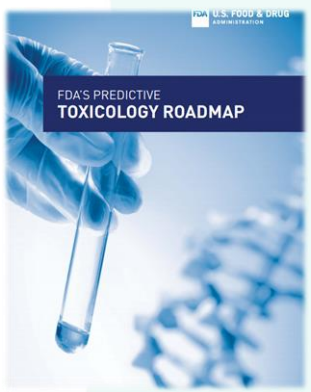


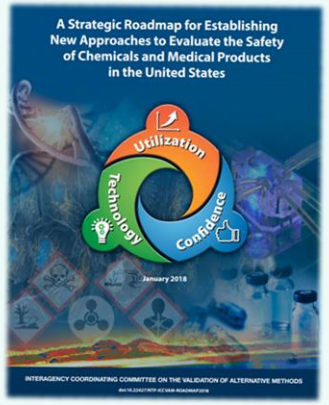
OECD TG473
OECD TG471
OECD TG476

Next Generation Risk Assessment (NGRA)

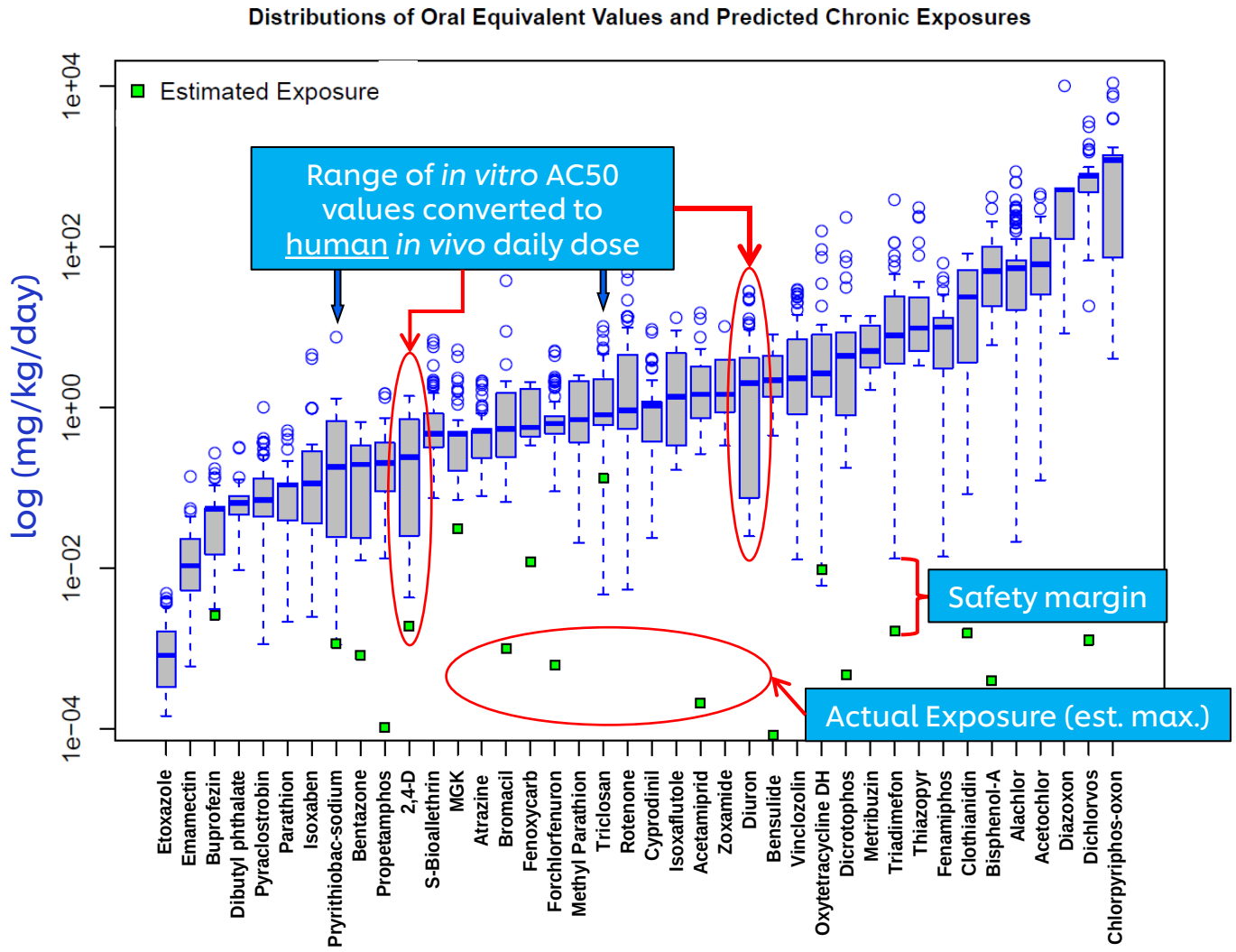
NGRA is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing







NGRA: Protection not prediction



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

Recognition of Next Generation Risk Assessment (NGRA) in cosmetic safety assessment

Computational Toxicology 7 (2018) 20–26

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Computational Toxicology

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

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

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ARTICLE INFO

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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 on Consumer Safety and on Health, Environmental and Emerging Risks

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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ICCR International Cooperation on Cosmetics Regulation

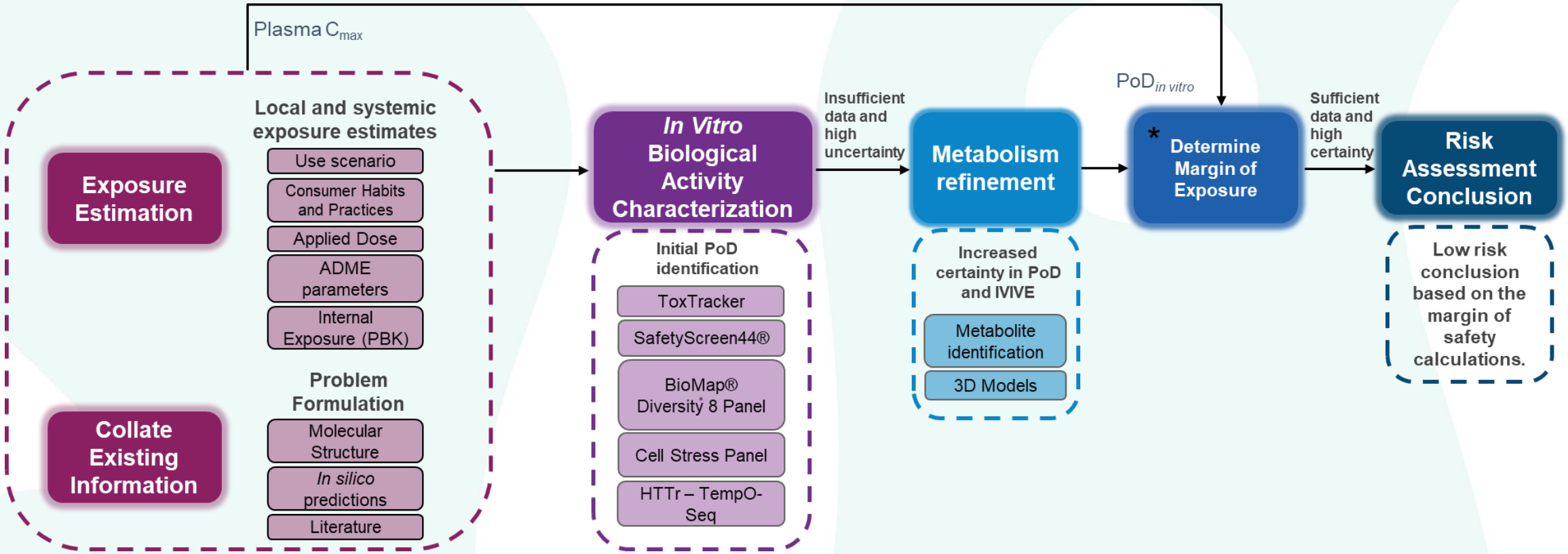
International Cooperation on Cosmetics Regulation (2018)

European Commission

European Commission: Scientific Committee on Consumer Safety (2021)

Unilever

NGRA: case study workflow for systemic effects

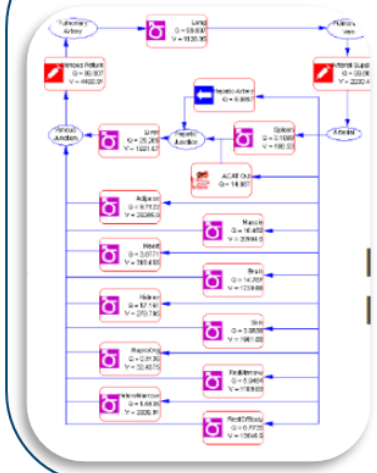


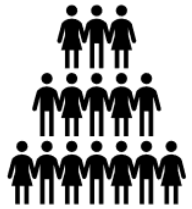
Baltazar *et al.*, (2020) *Toxicol Sci* **176**, 236–252

*or Bioactivity exposure ratio (BER)

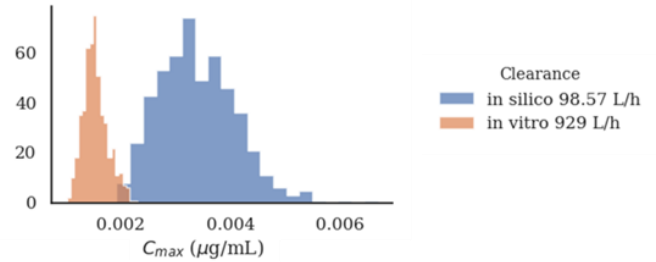
Key tools in our NGRA approach for systemic effects

PBK Modelling





Face Cream



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

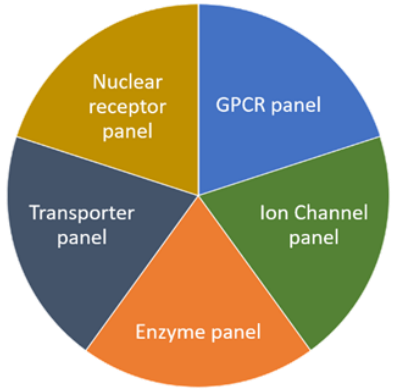
In vitro pharmacological profiling

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

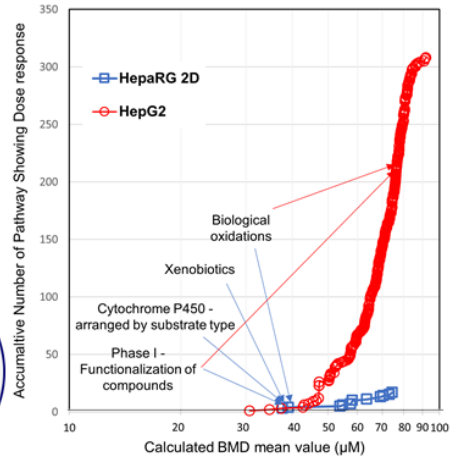


eurofins | Cerep

Transcriptomics

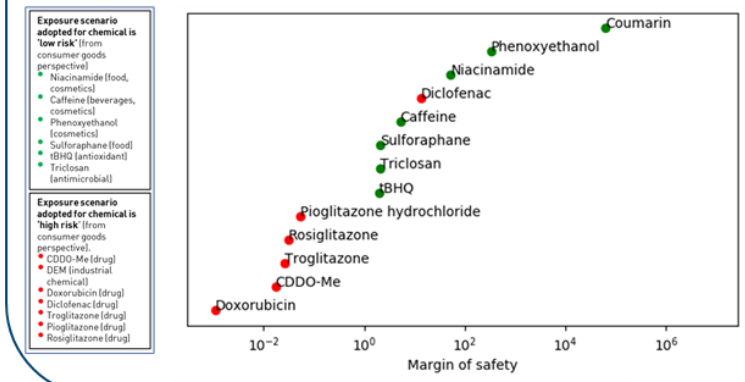
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDExpress 2

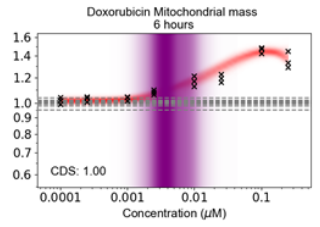


Cellular Stress Pathways

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



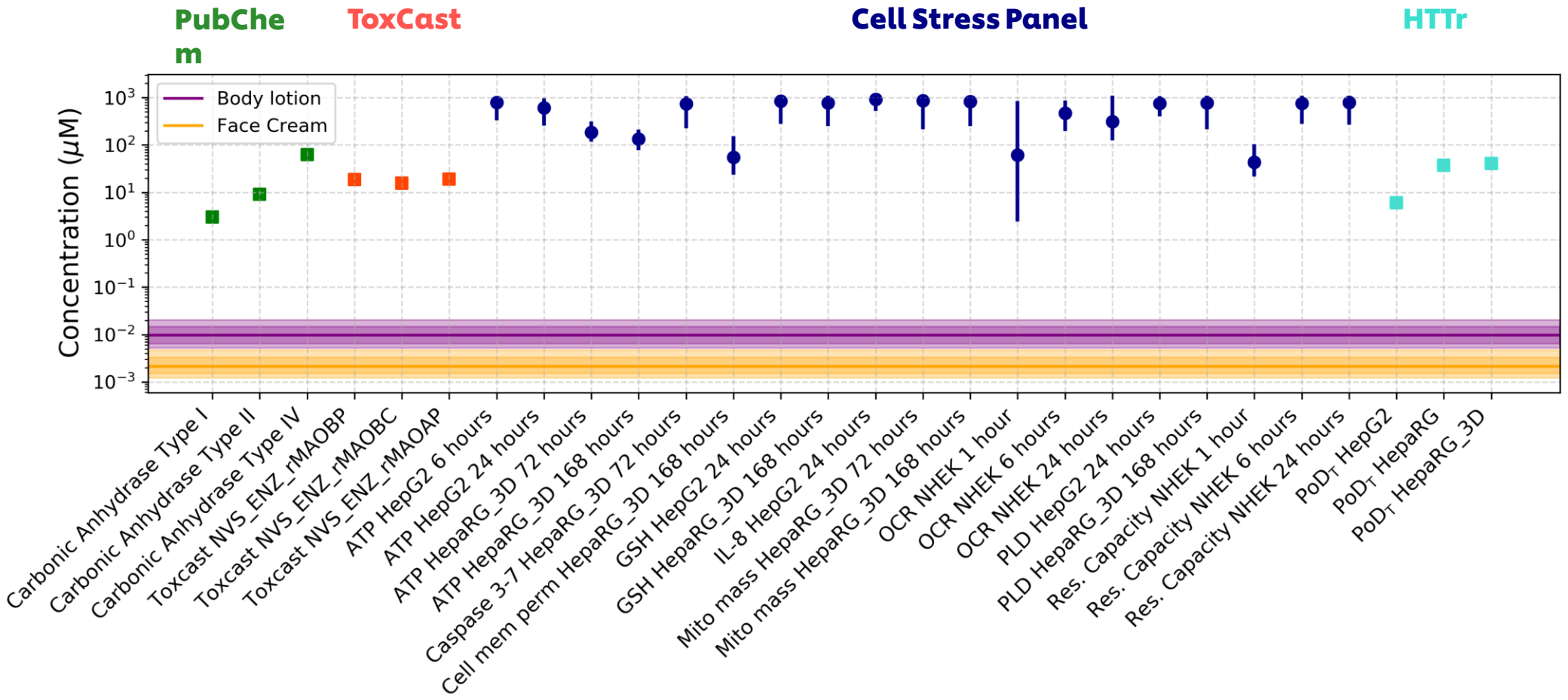
cyprotex AN EVOTEC COMPANY



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

Unilever

Exposure and PoD are plotted and used to derive a Bioactivity-Exposure Ratio (MoE/BER)



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

PoD = Point of Departure
MoE = Margin of Exposure
BER = Bioactivity / Exposure ratio
HTTr = High throughput transcriptomics

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

TOXICOLOGICAL SCIENCES, 189(1), 2022, 124–147

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Research article

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

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ABSTRACT

An important question in toxicological risk assessment is whether non-animal new approach methodologies (NAMs) can be used to make safety decisions that are protective of human health, without being overly conservative. In this work, we propose a core NAM toolbox and workflow for conducting systemic safety assessments for adult consumers. We also present an approach for evaluating how protective and useful the toolbox and workflow are by benchmarking against historical safety decisions. The toolbox includes physiologically based kinetic (PBK) models to estimate systemic C_{max} levels in humans, and 3 bioactivity platforms, comprising high-throughput transcriptomics, a cell stress panel, and *in vitro* pharmacological profiling, from which points of departure are estimated. A Bayesian model was developed to quantify the uncertainty in the C_{max} estimates depending on how the PBK models were parameterized. The feasibility of the evaluation approach was tested using 24 exposure scenarios from 10 chemicals, some of which would be considered high risk from a consumer goods perspective (eg, drugs that are systemically bioactive) and some low risk (eg, existing food or cosmetic ingredients). Using novel protectiveness and utility metrics, it was shown that up to 69% (9/13) of the low risk scenarios could be identified as such using the toolbox, whilst being protective against all (5/5) the high-risk ones. The results demonstrated how robust safety decisions could be made without using animal data. This work will enable a full evaluation to assess how protective and useful the toolbox and workflow are across a broader range of chemical-exposure scenarios.

Key words: Bayesian modelling; new approach methodologies; point of departure; physiologically based pharmacokinetics; probabilistic risk assessment.

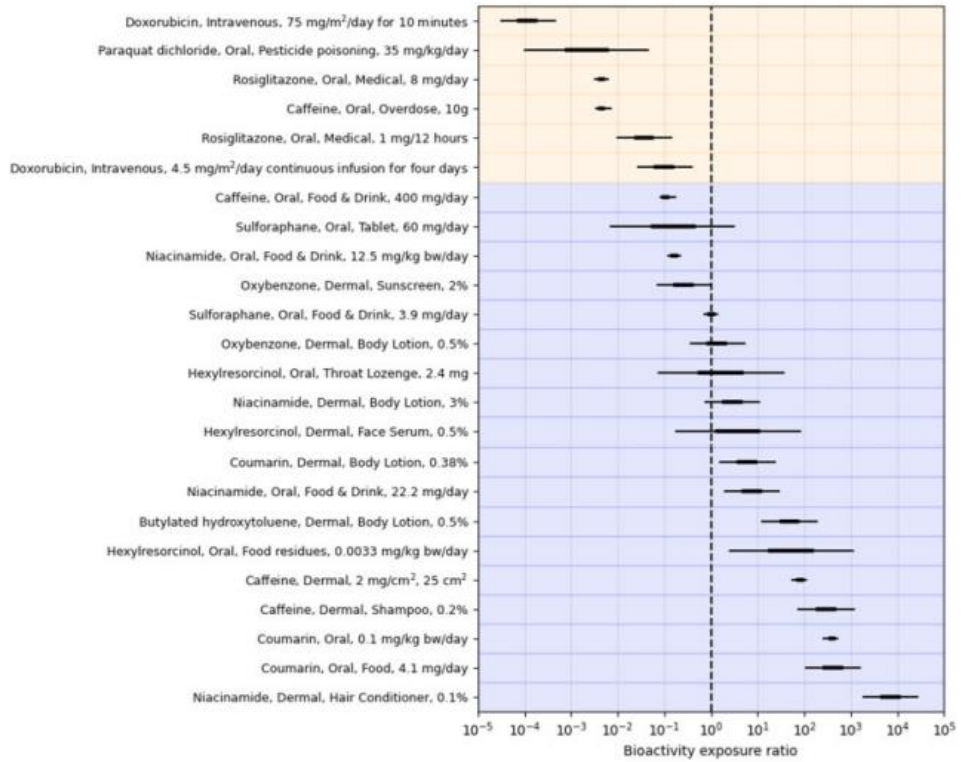
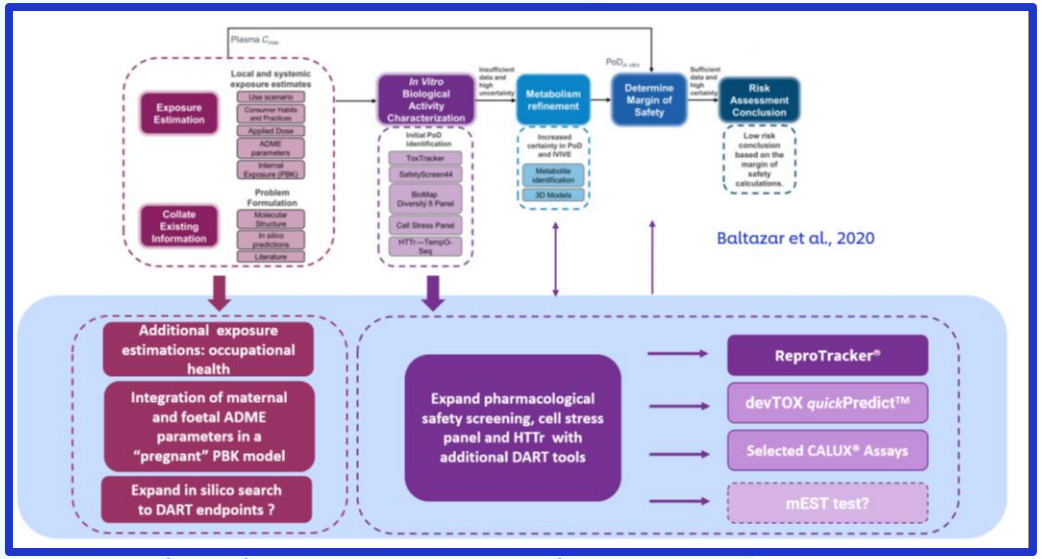


Figure 5. Centered 50% and 95% credible intervals summarizing the distribution of the bioactivity exposure ratio (BER) when using all available predicted C_{max} estimates. Background colors indicate the assigned risk category for each benchmark chemical-exposure scenario assigned at stage 1 (blue—low, yellow—high). The vertical dashed line indicates a BER equal to 1.

Middleton et al (2022) Toxicol Sciences, **189**, 124-147

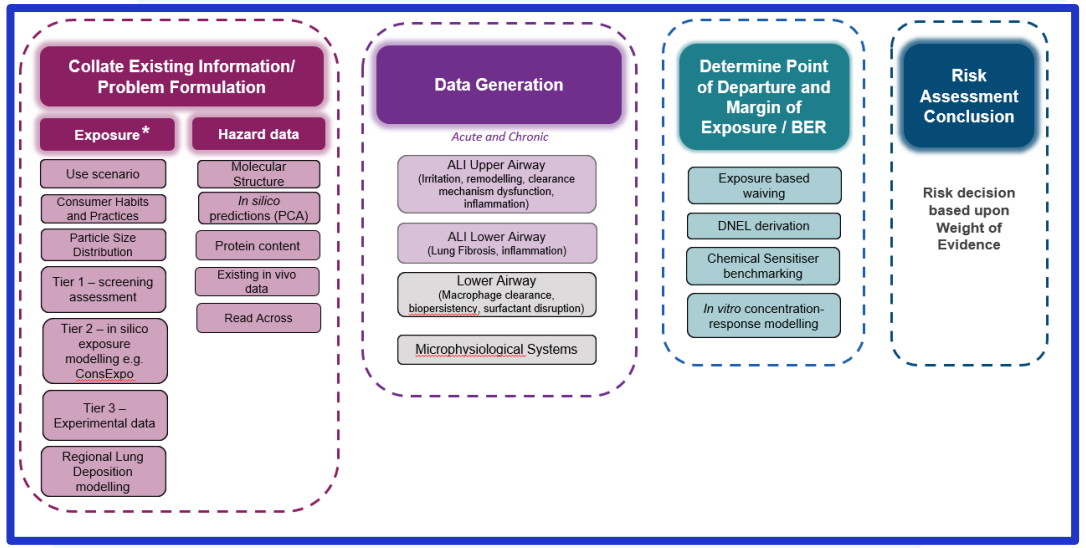
Other NGRA approaches for human health

DART*

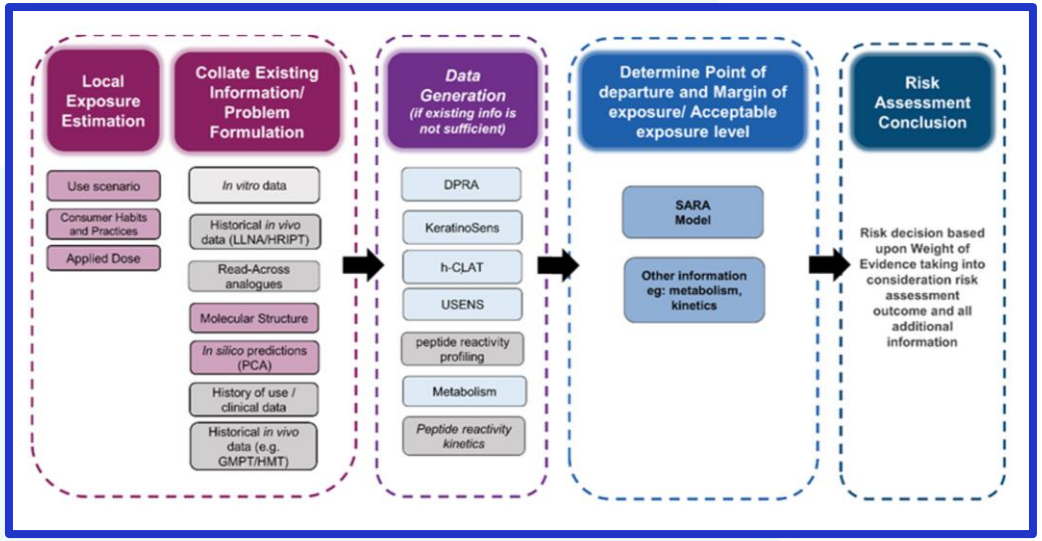


Rajagopal et al (2022) Front Toxicol, **4**, 838466

Inhalation



Skin Sensitisation



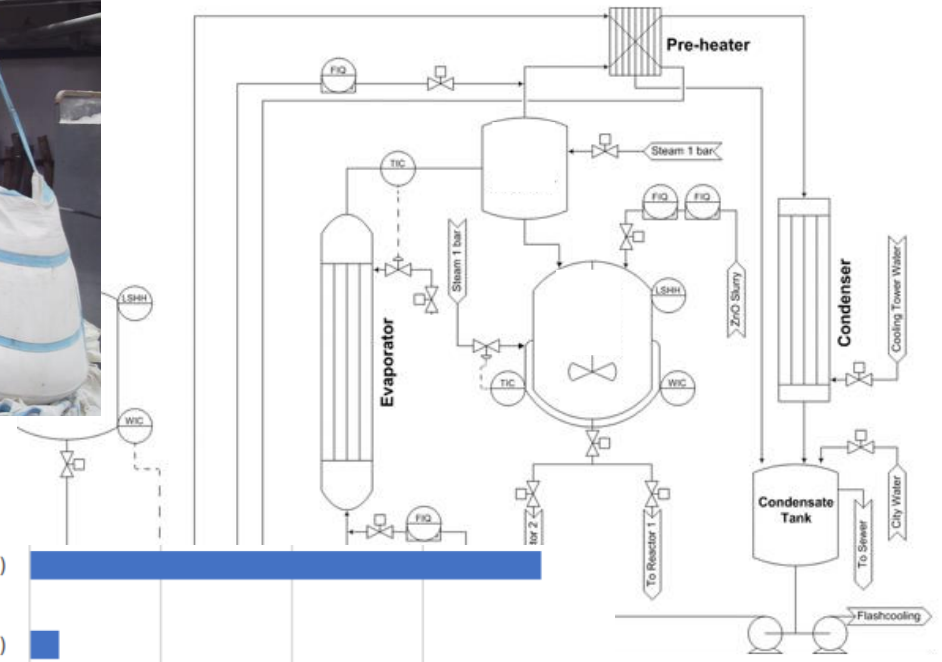
Reynolds et al (2021) Reg Tox Pharmacol, **127**, 105075

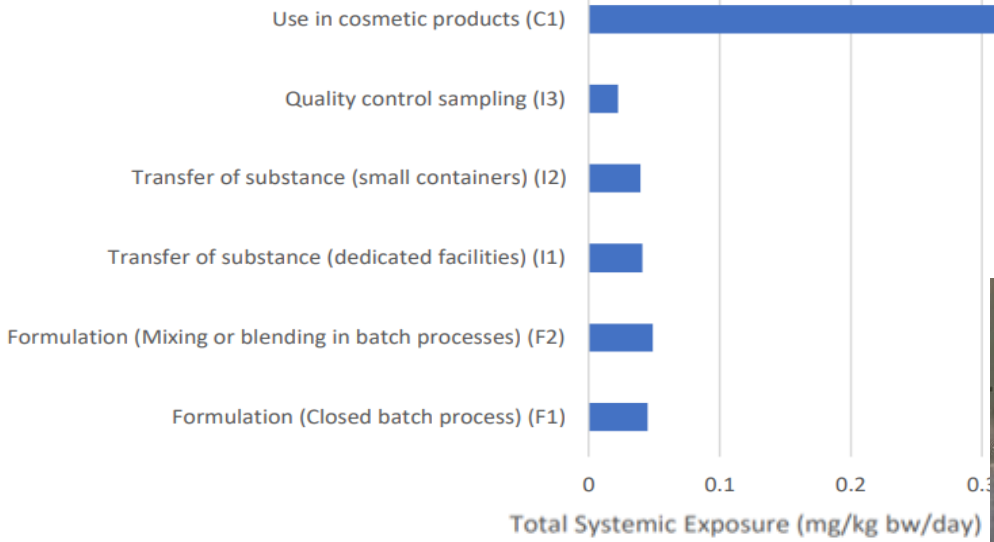
* DART = Developmental and Reproductive Toxicology

NGRA and Worker Safety

- Understanding worker exposure
  - Routes
  - Levels of exposure
  - Personal Protective Equipment

- NGRA for worker safety
  - BER approach for worker exposure





Recognition of NGRA in cosmetic safety assessment…

… Could similar, NAM-based approaches also be used for chemical registration?

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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]

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ABSTRACT

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SCCS

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Scientific Committees

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

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Scientific Committee on Consumer Safety (2021)

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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]

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

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

The importance of scientific partnership and publication

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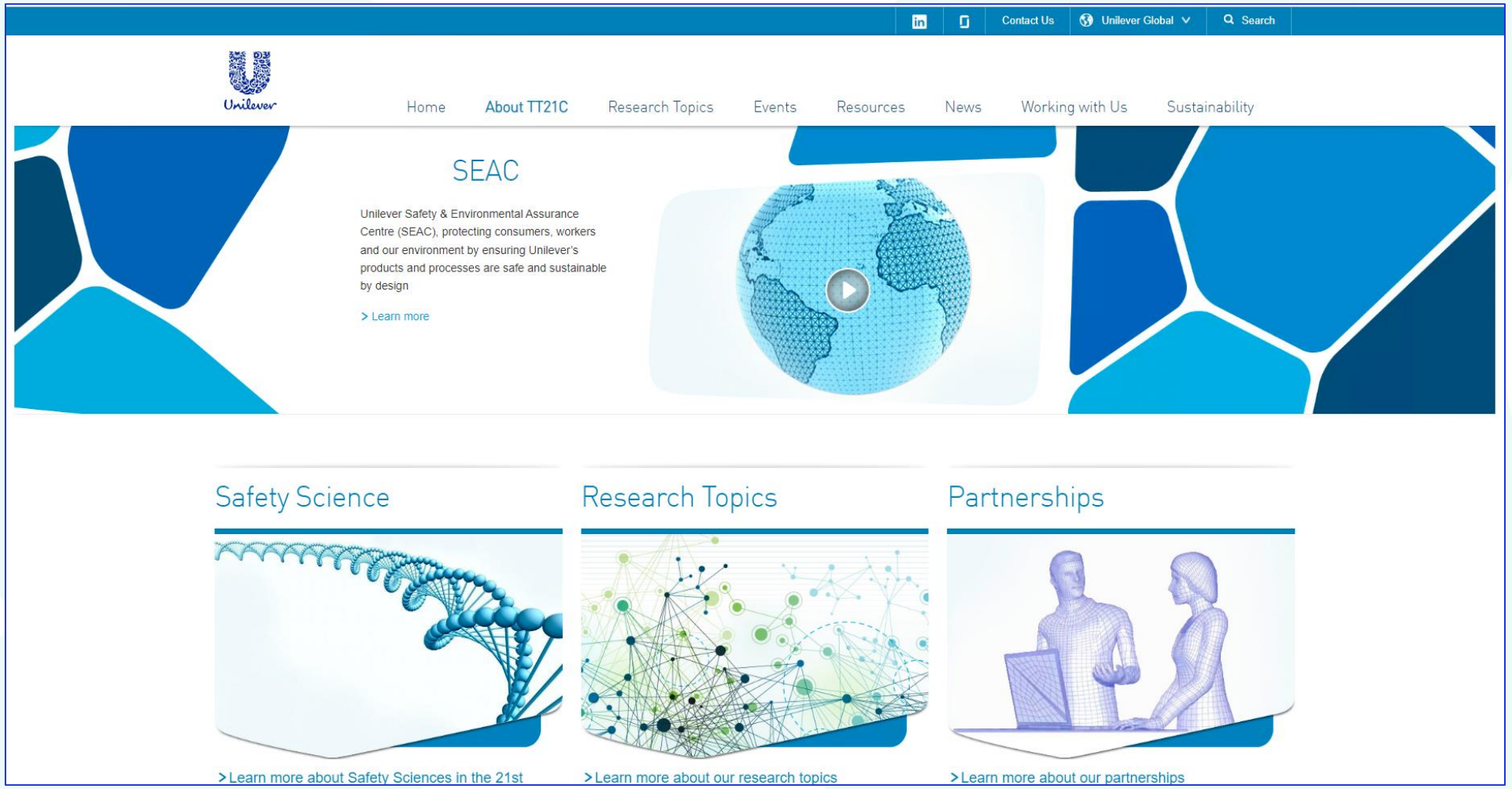
SEAC's Scientific Website



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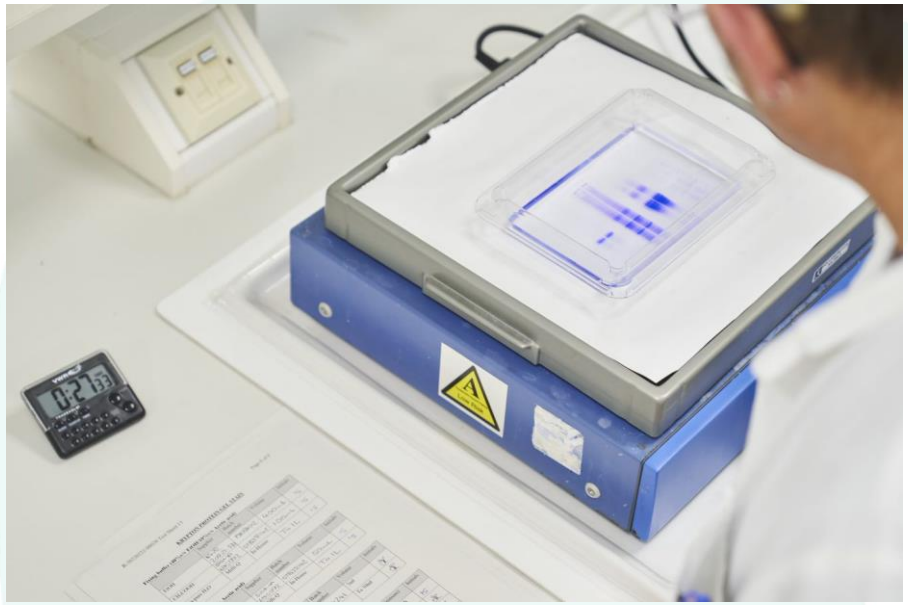

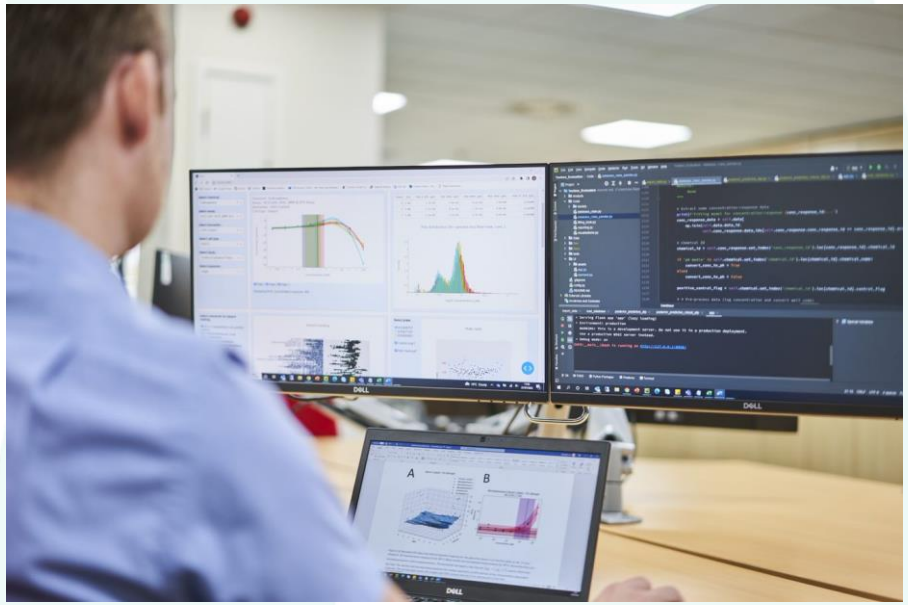

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