Opportunities for NAMs in an EU regulatory context

Carl Westmoreland

21st June 2022

Unilever's products must be safe for the people who use and make them and for the planet

We say use science.
Not animals.

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.

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PETA APPROVED
Global Animal Test Policy

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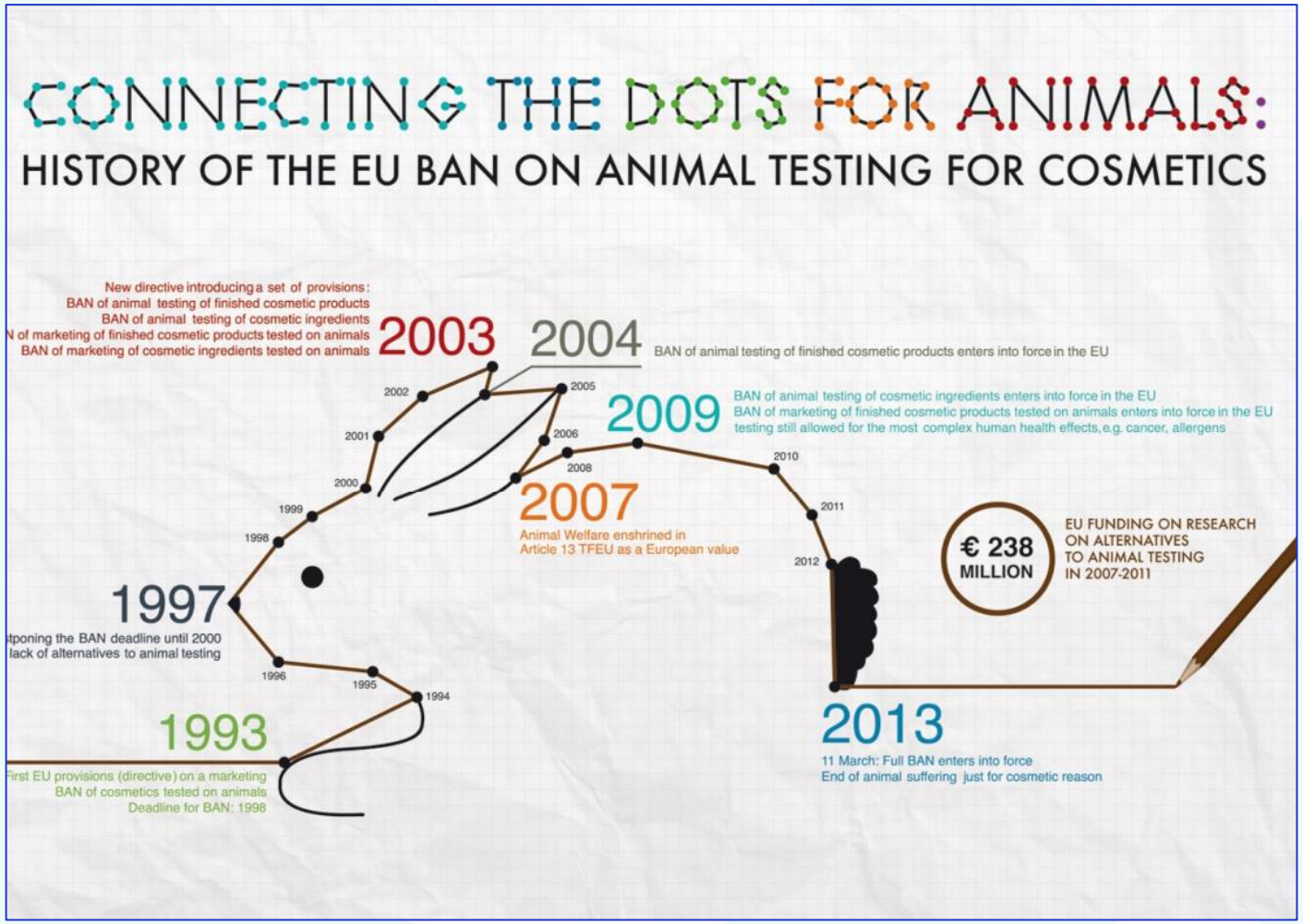
The history of bans on animal testing for cosmetic products and ingredients in the EU

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



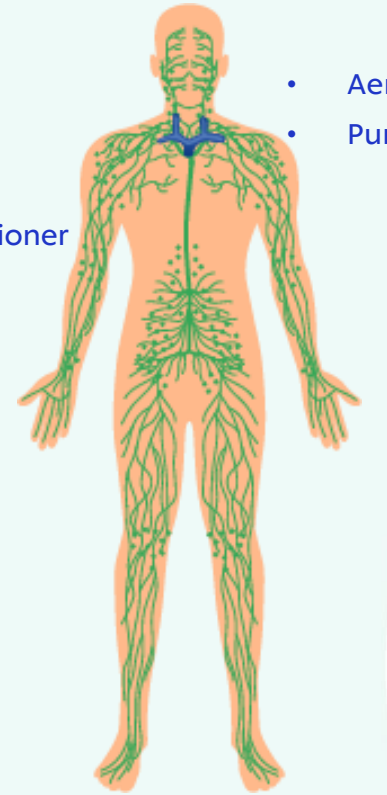
Source: https://ec.europa.eu/growth/sectors/cosmetics/ban-animal-testing_en

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

Consumers

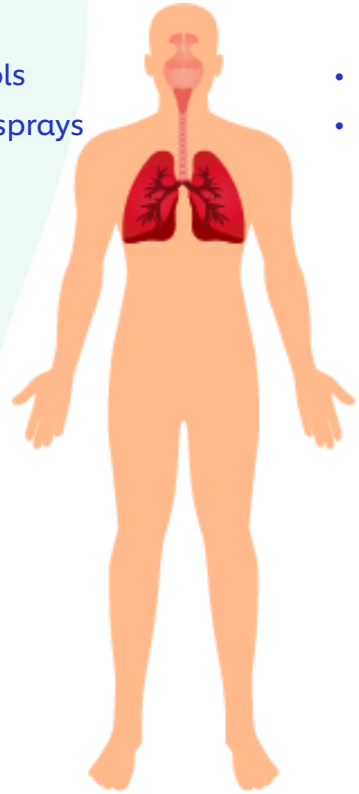
Skin

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



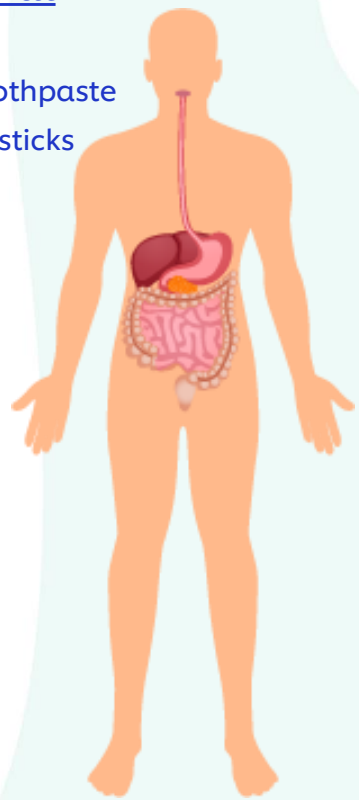
Inhalation*

- Aerosols
- Pump sprays

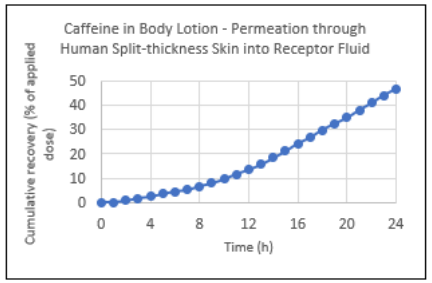


Oral

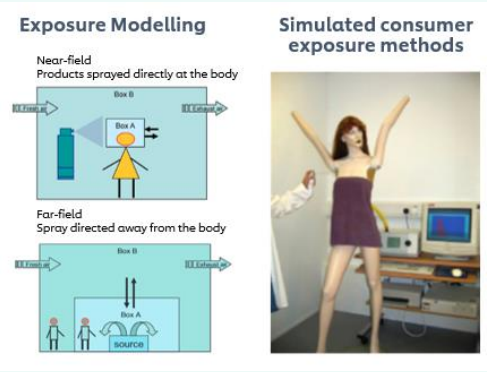
- Toothpaste
- Lipsticks



Skin Penetration



Inhalation



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

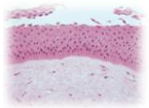
Images from: AFSA training module 'Consumer Exposure', 2022

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

Assessing the consumer safety of cosmetic ingredients for the Cosmetic Product Regulation without new animal testing

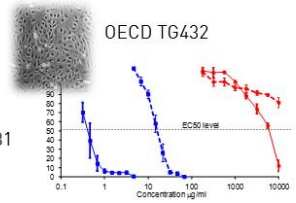
Is the predicted consumer exposure safe? A tiered approach is routine

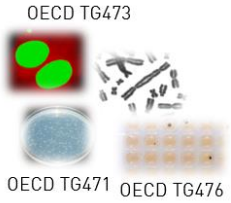
- Use all available safety data on the ingredient
  - Clinical, epidemiological, animal (if dates permit), *in vitro* etc
- Exposure-based waiving approaches (e.g. TTC, DST, Inhalation TTC)
- *in silico* predictions
- History of safe use
- Read across
- Use of existing OECD *in vitro* approaches
- Next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



OECD TG437

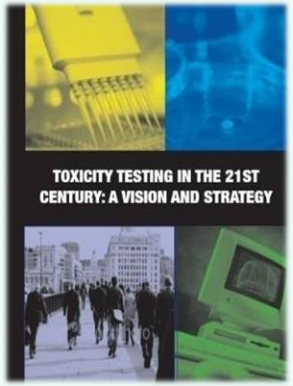
OECD TG430/431
OECD TG439

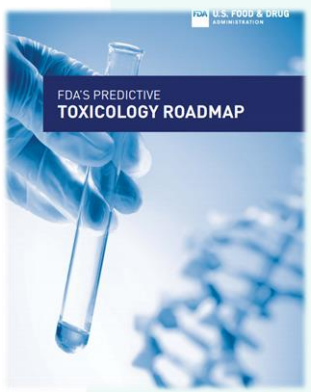


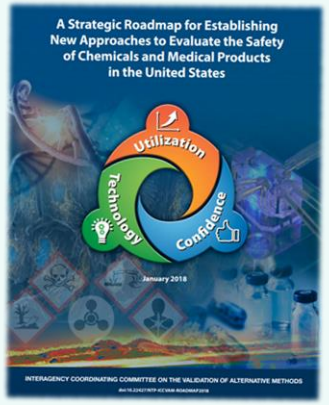


Next Generation Risk Assessment (NGRA)

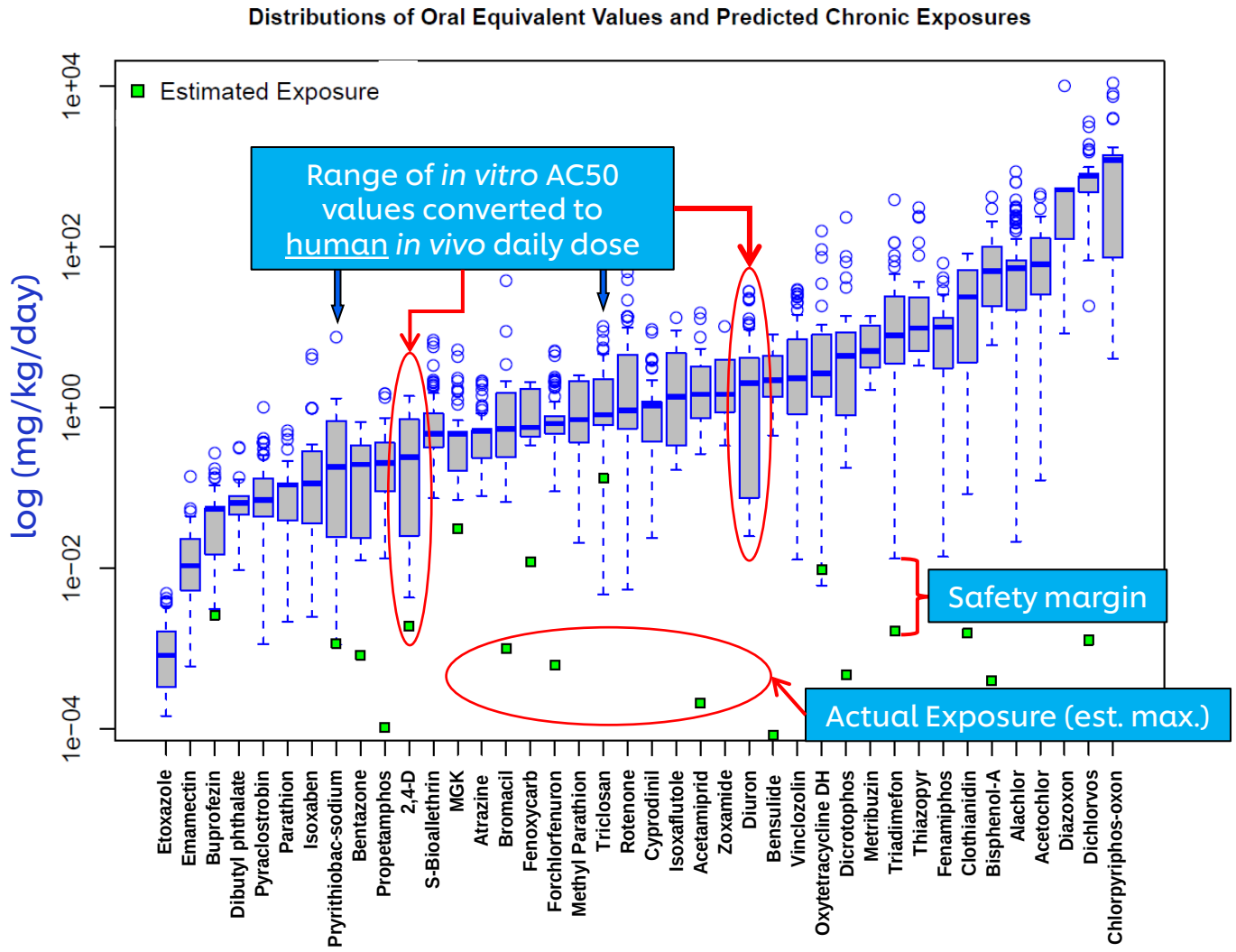
NGRA is defined as an exposure-led, hypothesis-driven risk assessment approach that integrates New Approach Methodologies (NAMs) to assure safety without the use of animal testing







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

Principles of Next Generation Risk Assessment from ICCR
Non-animal approaches in Cosmetic Risk Assessment

International Cooperation on Cosmetics Regulation

4 Main overriding principles:

- The overall goal is a human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

- Following an appropriate appraisal of existing information
- Using a tiered and iterative approach
- Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

- Sources of uncertainty should be characterized and documented
- The logic of the approach should be transparently and documented

Dent *et al* (2018), Computational Toxicology, **7**, 20-26: https://doi.org/10.1016/j.comtox.2018.06.001

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Use of non-animal approaches for cosmetic safety

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

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, 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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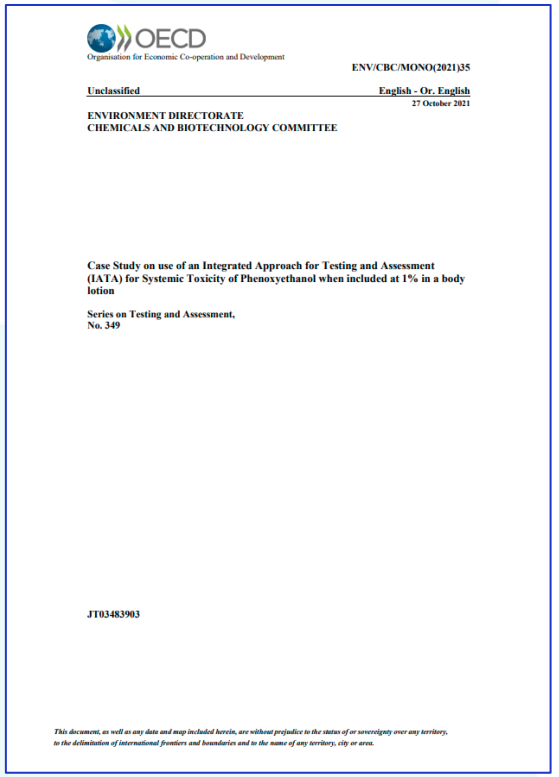

OECD

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.

ICCR International Cooperation on Cosmetics Regulation

International Cooperation on Cosmetics Regulation (2018)

European Commission

European Commission: Scientific Committee on Consumer Safety (2021)

OECD

OECD (2021)

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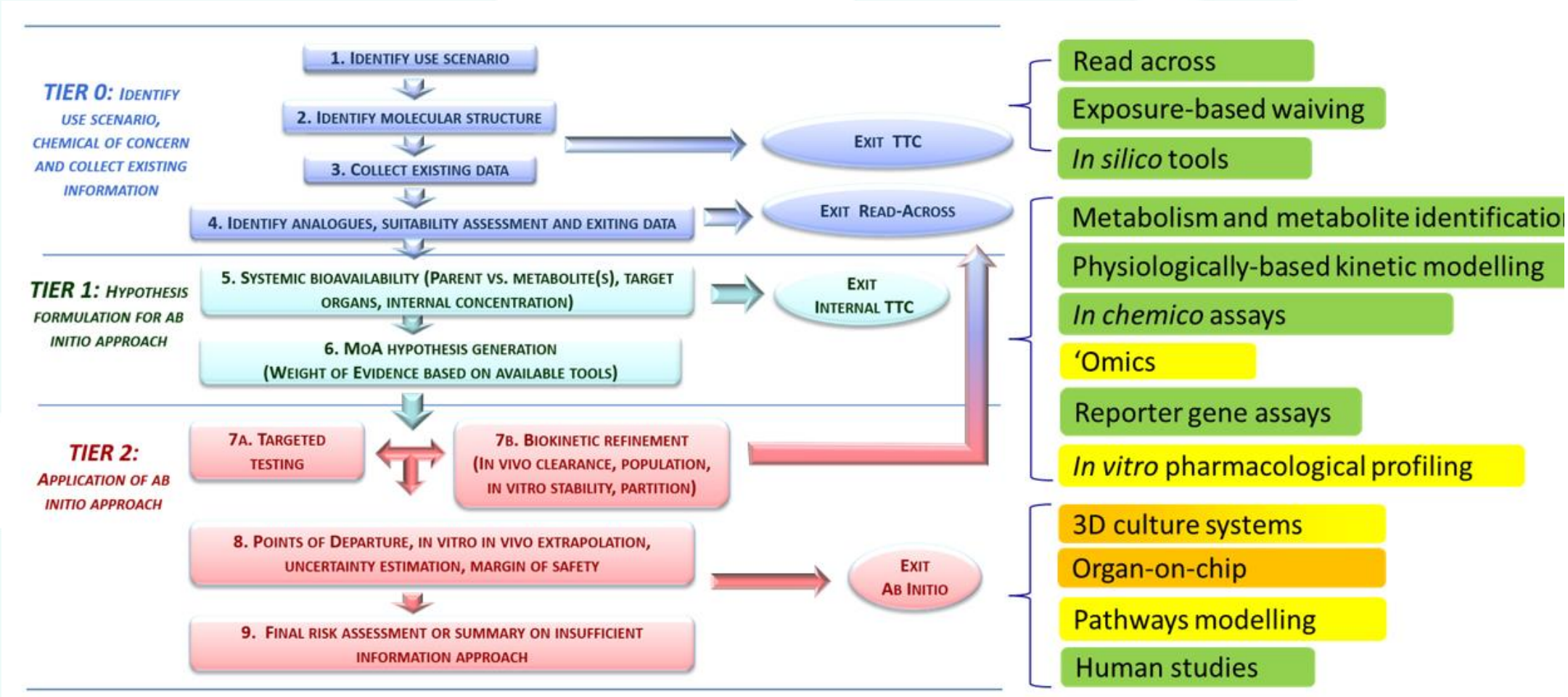
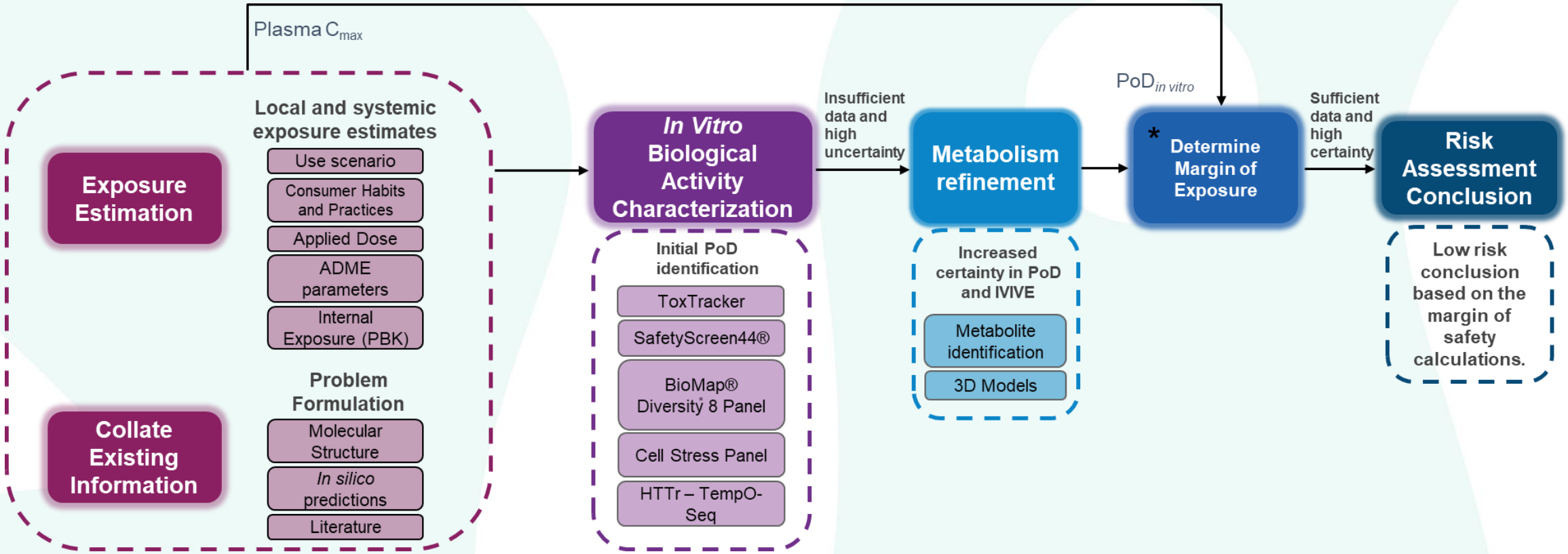
SEURAT-1 NGRA Framework



Berggren *et al* (2017) Computational Toxicology **4**, 31-44

NGRA: case study workflow for systemic effects



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

*or Bioactivity exposure ratio (BER)

Physiologically-based Kinetic (PBK) Modelling

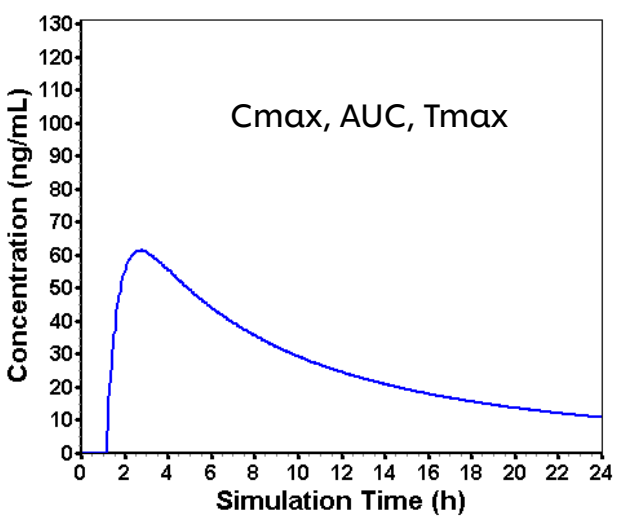
Input

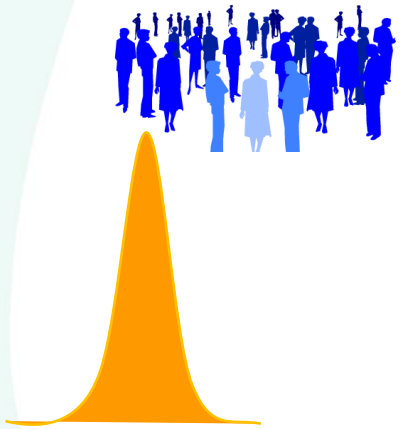
ADME properties

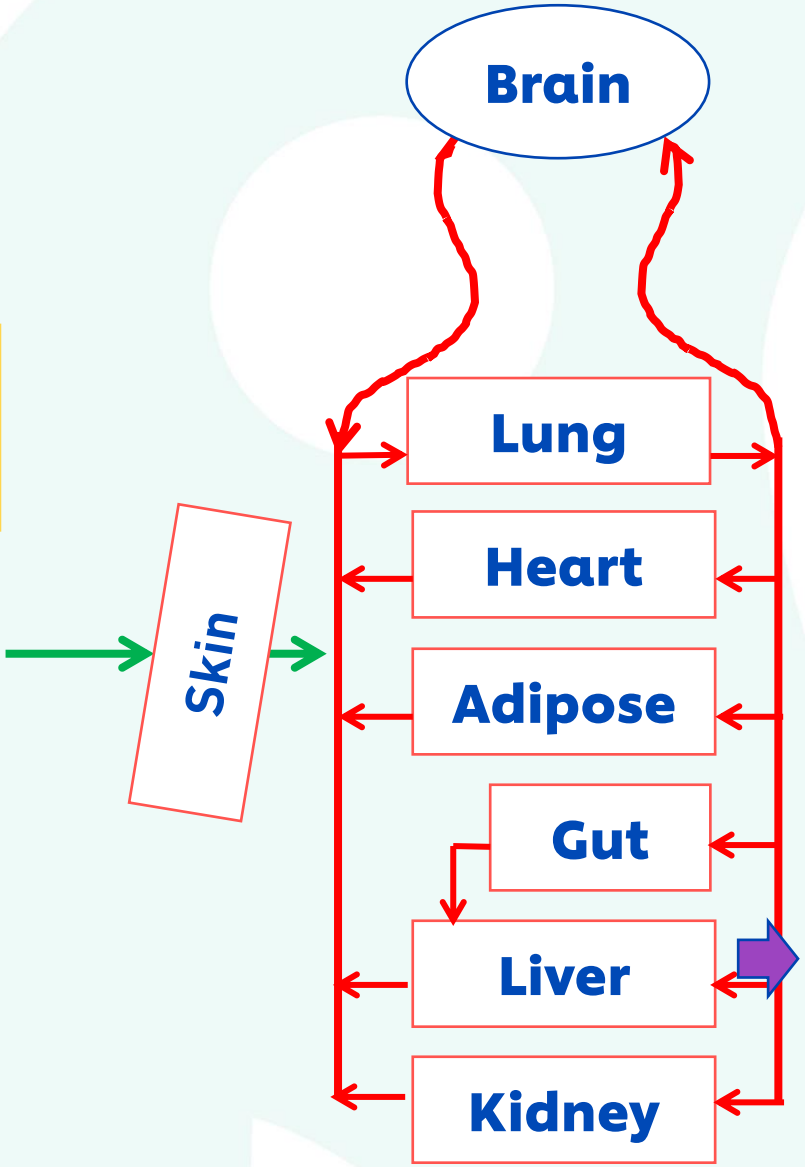
Absorption, Distribution, Metabolism, Excretion

- Physiological parameters (e.g. body weight, blood flow rates, tissue volume)
- Physico-chemical parameters (e.g. LogP, Fup, tissue/plasma partition coefficients)
- Kinetic parameters (e.g. dermal absorption, hepatic metabolism, renal excretion)
- Product use information (e.g. dose, frequency, site area, formulation)

Output



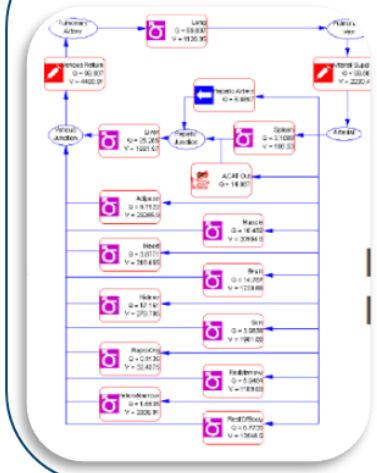


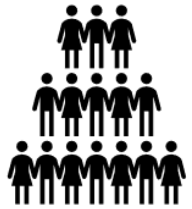


Li *et al* (2022) *Toxicology and Applied Pharmacology*, **442**, 115992

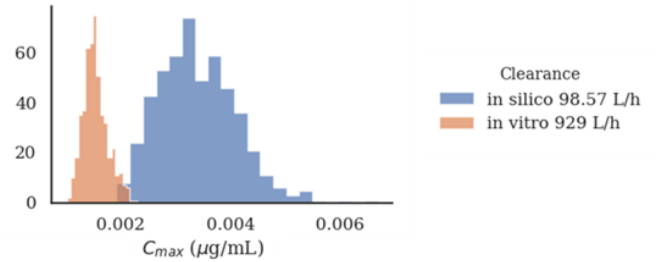
Key tools in our NGRA approach for systemic effects

PBK Modelling





Face Cream



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

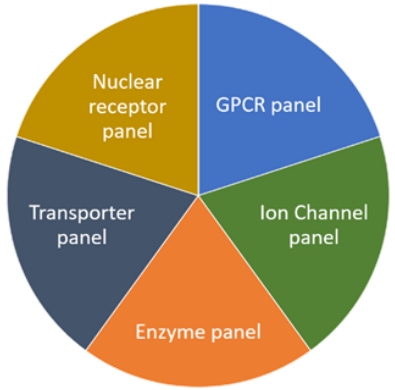
In vitro pharmacological profiling

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

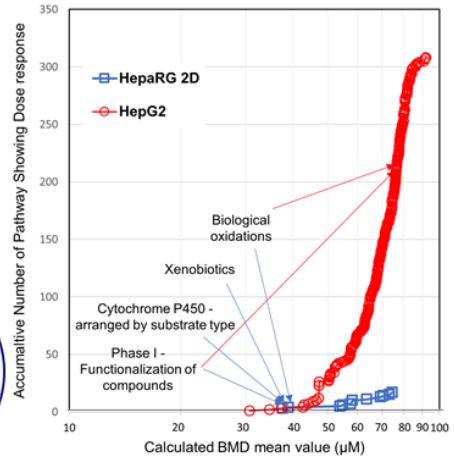


eurofins | Cerep

Transcriptomics

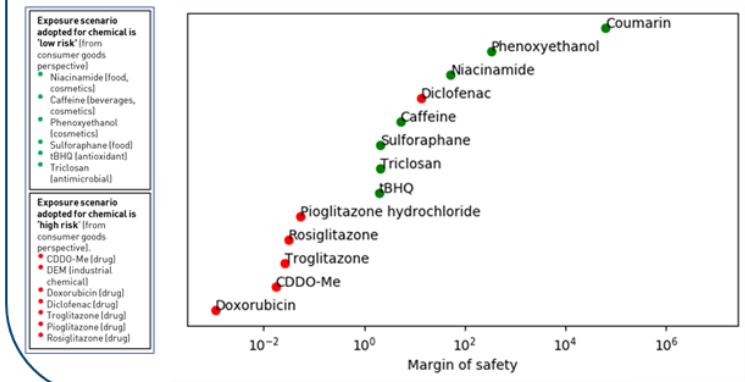
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDExpress 2

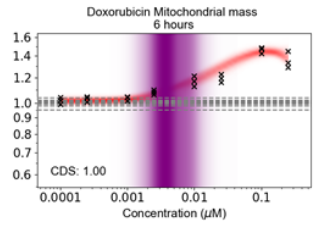


Cellular Stress Pathways

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



cyprotex AN EVOTEC COMPANY



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

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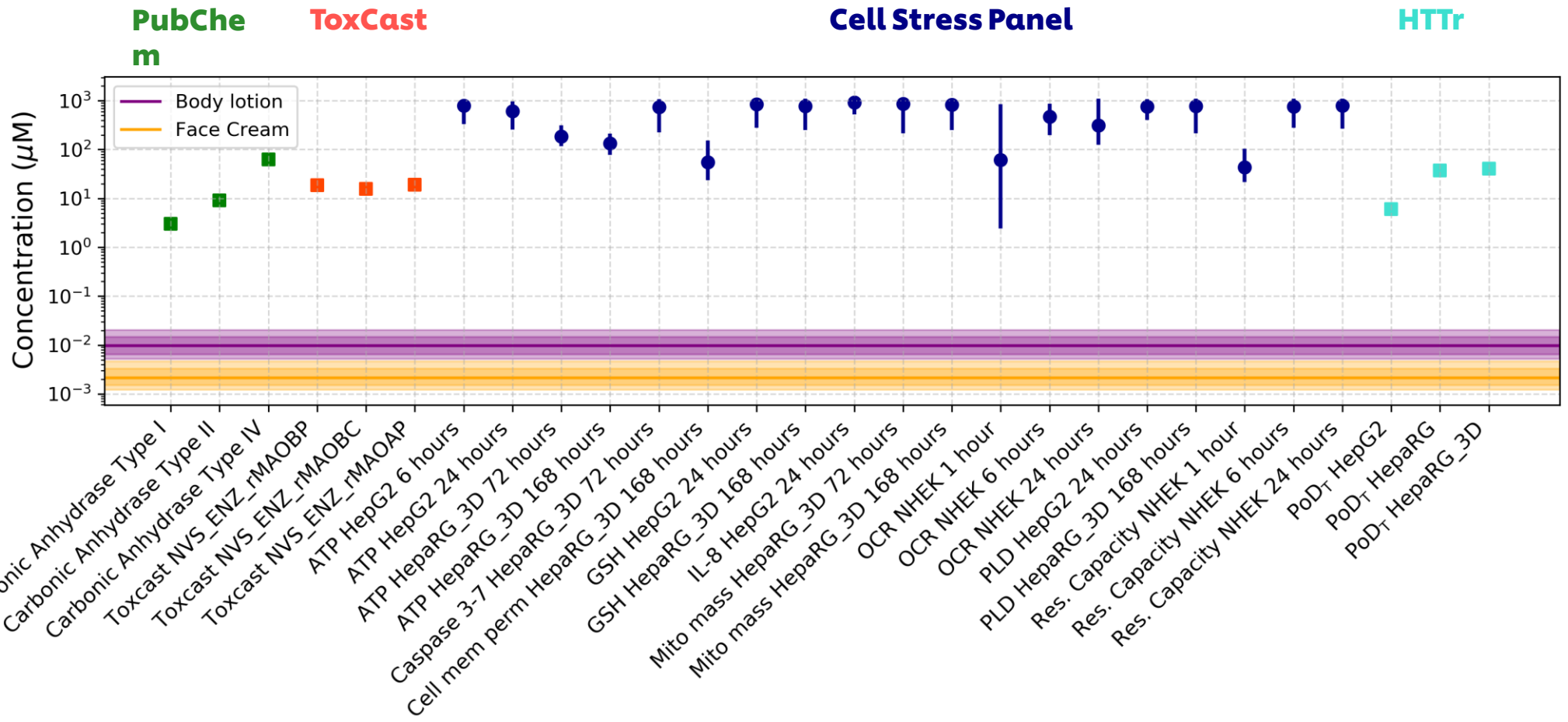
Exposure and PoD are plotted and used to derive a Bioactivity-Exposure Ratio (MoE/BER)



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

APCRA approach to evaluate the integration of exposure and bioactivity

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

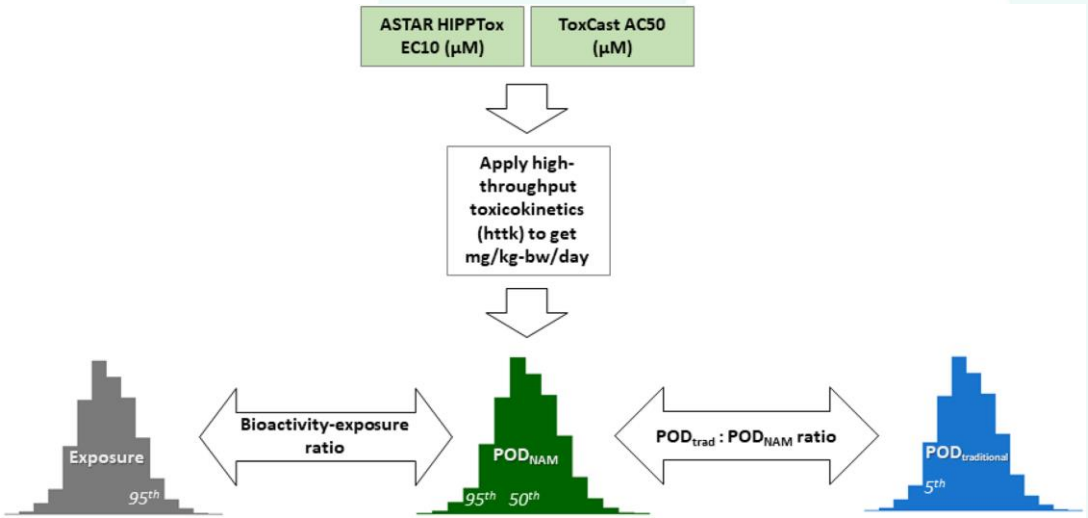
TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225

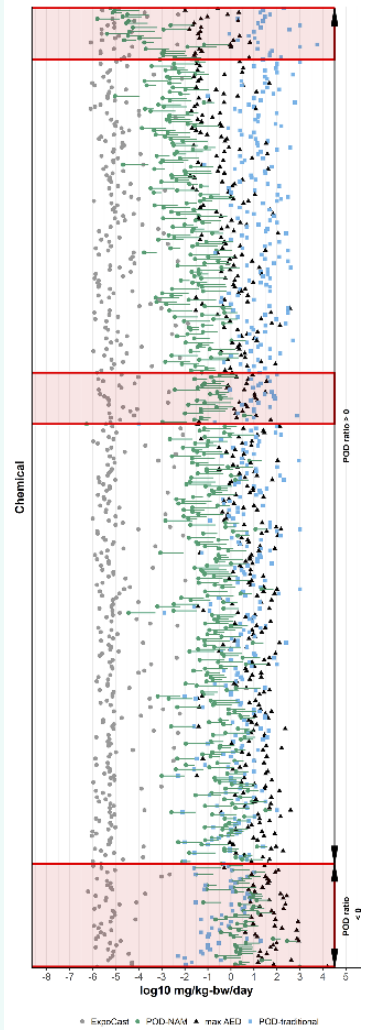
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

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 *

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT





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

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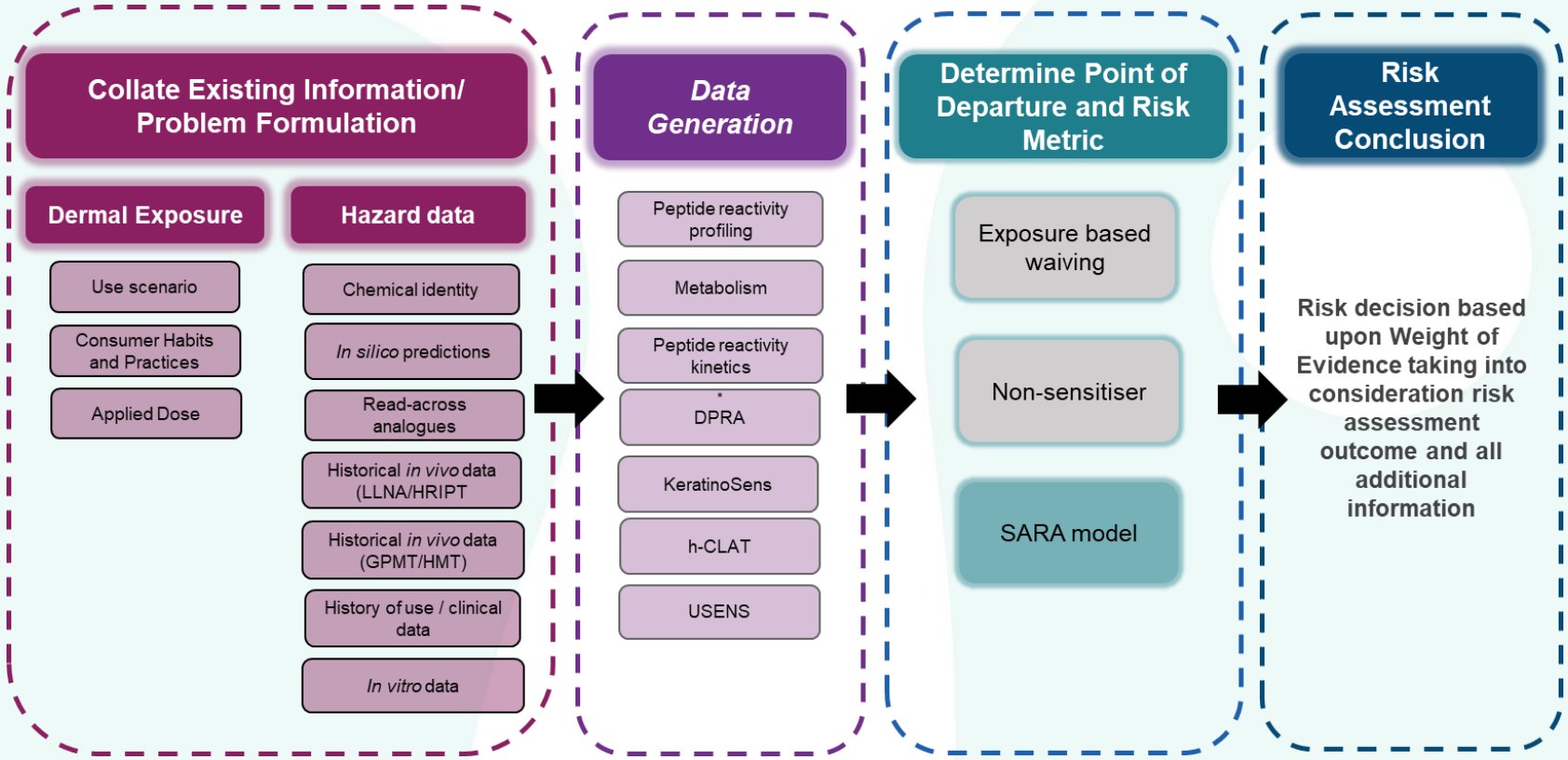
Next Generation Risk Assessment (NGRA) Framework for Skin Allergy

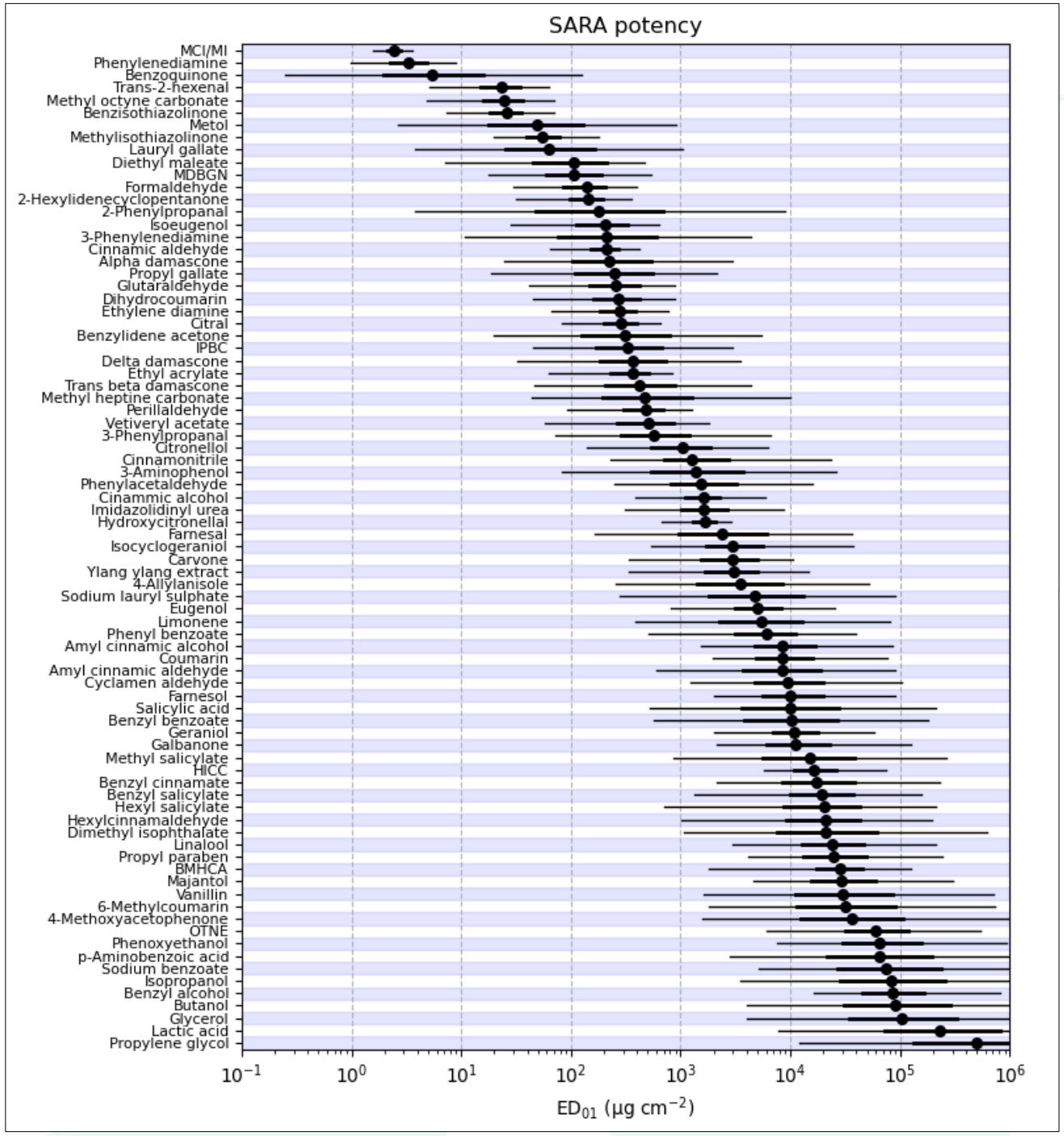


- NGRA framework for skin allergy based upon the ICCR principles and SEURAT-1 frameworks for systemic tox
- WoE based upon all available information, accommodate range of consumer product exposure scenarios and provide a quantitative point of departure and risk metric → Skin Allergy Risk Assessment (SARA) Model.

Reynolds et al (2021) *Reg Tox Pharmacol*, **127**, December 2021, 105075
Gilmour et at (2022) Reg Tox Pharmacol **131**, June 2022, 105159

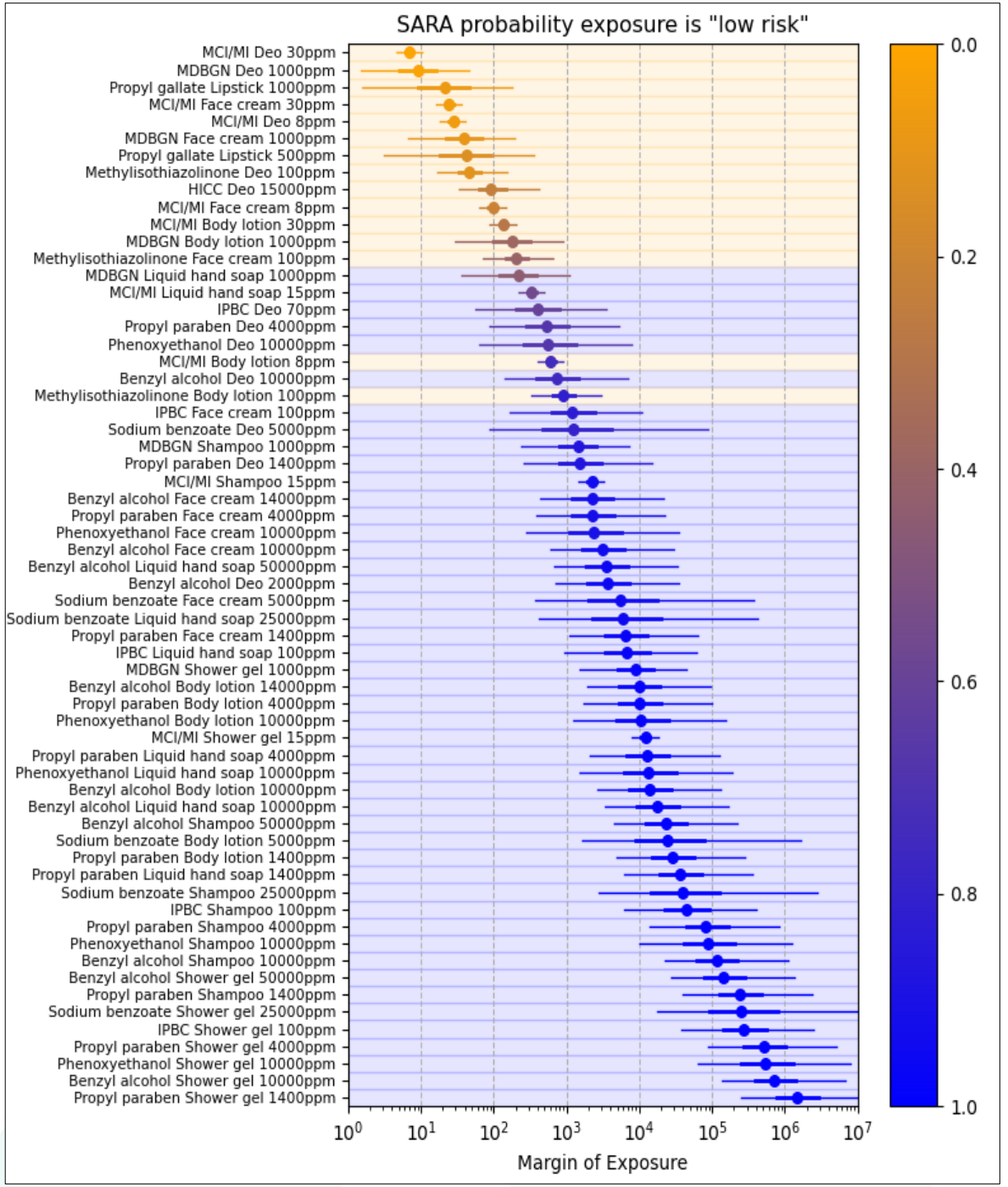
SARA Defined Approach

- The point of departure (PoD) metric is a dose with a 1% chance of human skin sensitisation (termed ED_{01}).
- The SARA dataset contains 81 chemicals.
- The model accounts for variability in the DPRA, KeratinoSens™, h-CLAT and U-Sens
- The model has been expanded to incorporate benchmark exposure information.



Expansion of SARA model to use benchmark exposure information

- Model expanded to incorporate benchmark exposure information as an additional input alongside historic *in vivo* and NAM data.
- After fitting the model, and given some exposure scenario of interest, the model can calculate the *SARA risk metric*, defined as the probability that the exposure is low risk for human skin sensitisation induction.



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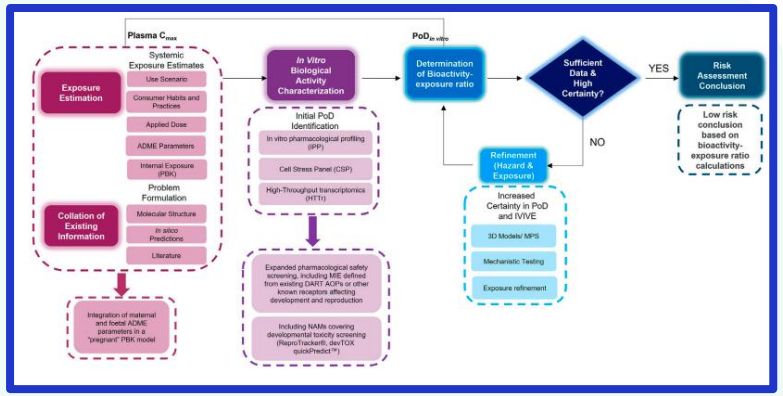
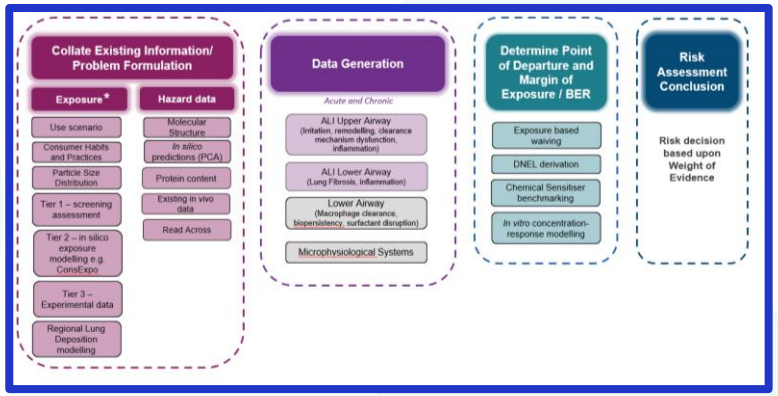
Frameworks for using NAMs to make safety decisions

Developmental & Reproductive

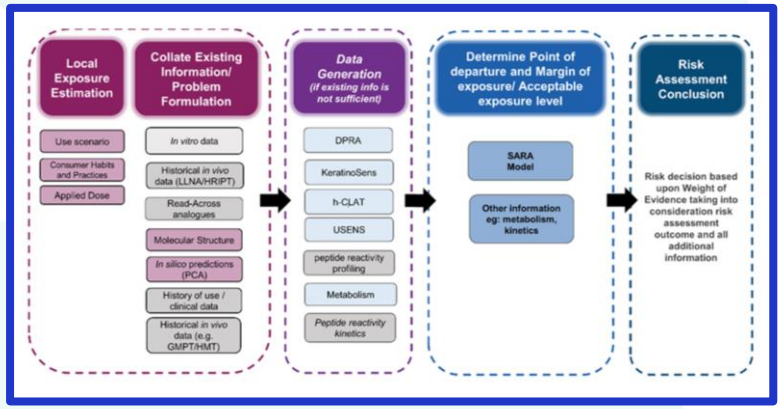


Rajagopal et al (2022) *Frontiers in Toxicology*, doi: 10.3389/ftox.2022.838466

Inhalation

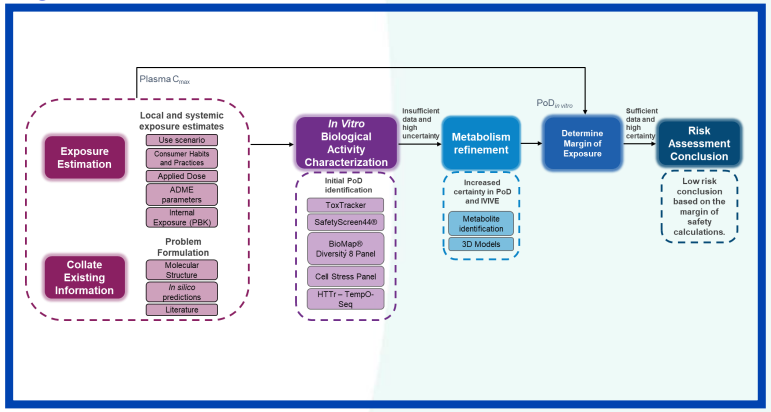


Skin Sensitisation



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

Systemic



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

Ongoing Evaluations

Working with regulators/ government agencies

EPA United States Environmental Protection Agency

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

August 19, 2021

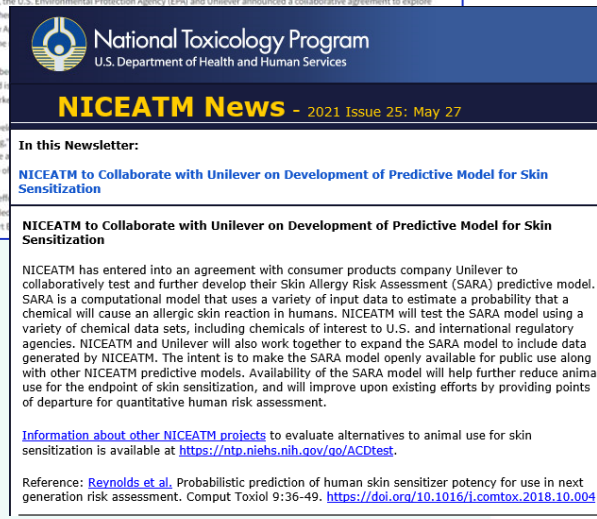
Contact Information
EPA Press Office (press@epa.gov)

WASHINGTON – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess che... Unilever regarding New A... to reduce reliance on the...

EPA and Unilever have ba... Methods Work Plan and i... protect consumers, work...

"EPA is a pioneer in deve... chemical toxicity testing,"... and Development. "We a... to demonstrate the use o...

The new collaborative eff... assessments are intende... methods and to support t...



National Toxicology Program
U.S. Department of Health and Human Services

NICEATM News - 2021 Issue 25: May 27

In this Newsletter:

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce anima use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

Information about other NICEATM projects to evaluate alternatives to animal use for skin sensitization is available at https://ntp.niehs.nih.gov/go/ACDtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. Comput Toxiol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004

Animal Testing and EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

Regulation (EC) No 1907/2006

- These same types of toxicity are also relevant to EU REACH registrations, where animal testing must only be undertaken as 'a last resort'
  - Article 25: '*In order to avoid animal testing, testing on vertebrate animals for the purposes of this regulation shall be undertaken only as a last resort*'

- Annex XI of UK REACH lists 'adaptations' to waive animal testing (including use of QSAR, *in vitro* methods, weight-of-evidence approaches etc.)
  - More opportunities for use of NAMs?
    - Need for Flexibility and good scientific dialogue
    - Need to develop criteria for acceptance of NAMs in EU Chemicals legislation

- Longer-term evolution of EU REACH. Ongoing public consultation around the revision of EU REACH

Recognition of NGRA in cosmetic safety assessment…

… Using similar approaches for chemical registration?

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

ABSTRACT

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

Scientific Committee on Consumer Safety (2021)

International Cooperation on Cosmetics Regulation (2018)

Archives of Toxicology (2022) 96:743–766
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]

flash

EPAA Workshop

23 - 24 November 2021, virtual event

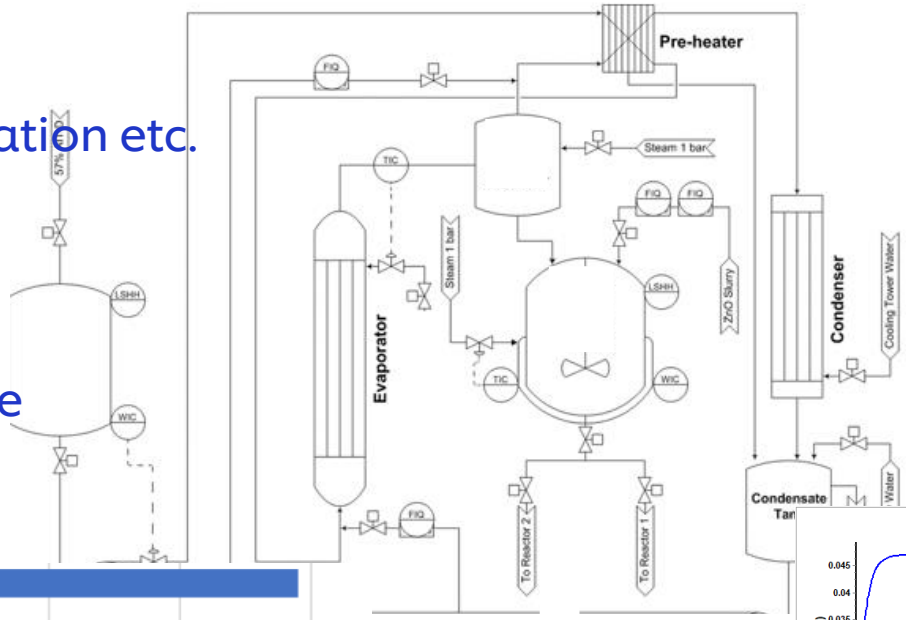
The European Partnership for Alternative Approaches to Animal Testing

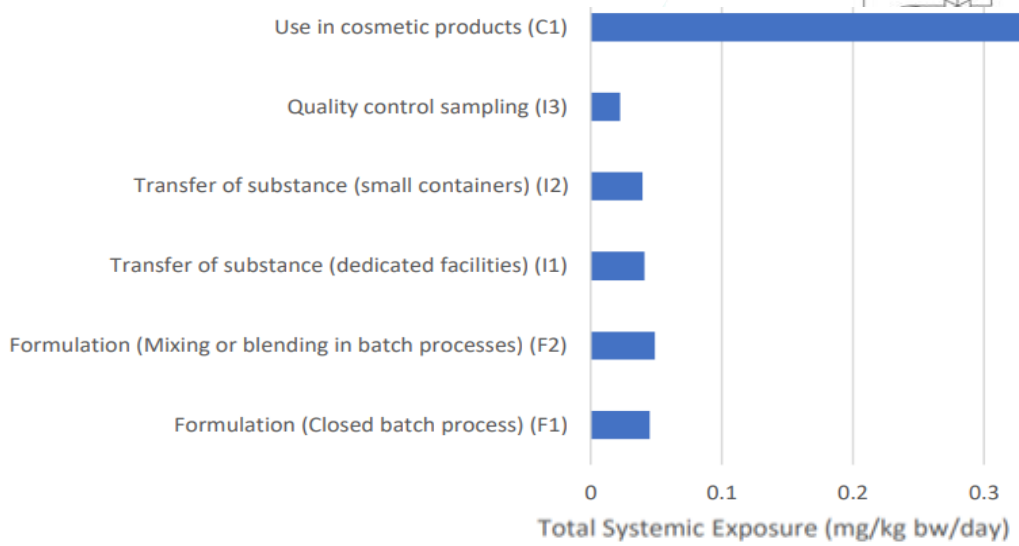
Deep-Dive Workshop on «Use of New Approach Methodologies (NAMs) in Regulatory Decisions for Chemical Safety»

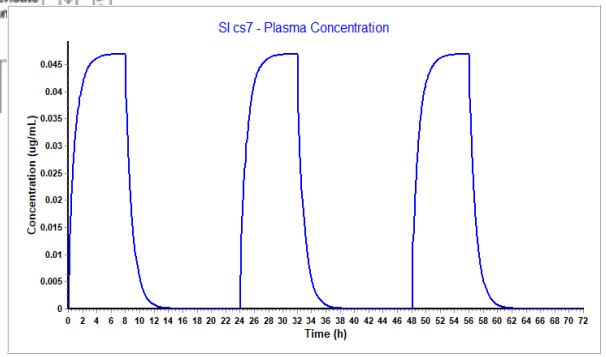
NGRA and Worker Safety

- Understanding worker exposure
  - Routes
  - Levels of exposure
  - PPE*, engineering controls, ventilation etc.
  - PBK for worker exposure

- NGRA
  - BER approach for worker exposure







	Dosage Form	Dose [mg]	TD Dose Vol [ml]	Start [h]	End [h]	Physiology or .cat file	PBPK Physiology or .pbk file
	IV: Infusion	8.68	0	0	8	Human - Physiological - Fed	HumAmeFemPreg1GA30Y0_75.58kg_28.
	IV: Infusion	8.68	0	24	32	Human - Physiological - Fed	HumAmeFemPreg1GA30Y0_75.58kg_28.
	IV: Infusion	8.68	0	48	56	Human - Physiological - Fed	HumAmeFemPreg1GA30Y0_75.58kg_28.
	IV: Infusion	8.68	0	72	80	Human - Physiological - Fed	HumAmeFemPreg1GA30Y0_75.58kg_28.
	IV: Infusion	8.68	0	120	128	Human - Physiological - Fed	HumAmeFemPreg1GA30Y0_75.58kg_28.
*							

* PPE = Personal protective equipment

Acknowledgements

Nora Aptula
Maja Aleksic
Maria Baltazar
Trina Barritt
Danilo Basili
Sophie Cable
Paul Carmichael
Tom Cull
Matt Dent
Ellen Edwards
Julia Fentem
Nicky Gilmour
Steve Gutsell
Sarah Hatherell
Jade Houghton
Lucy Ingram
Predrag Kukic
Hequn Li
Mark Liddell
Keeley Mahwing
Sophie Malcomber
Deborah Martin
Gavin Maxwell
Alistair Middleton
Iris Muller
Beate Nicol
Claire Peart
Ruth Pendlington
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Sharon Scott
Nikol Simecek
Wendy Simpson
Chris Sparham
Sandrine Spriggs
Charlotte Thorpe
Erica Vit
Andy White
Sam Windebank

Unilever