Next Gen Tools for Chemical Safety Assessment

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

HUMANE SOCIETY INTERNATIONAL

ZOOM WEBINAR

Regulatory Acceptance and Use of Next-Generation Approaches for Chemical Safety Assessment

July 13, 2022 9:00 EDT / 15:00 CET

Join us for a webinar to learn how state-of-the-art science is being used by corporate and government stakeholders in risk assessment and prioritisation to ensure protection.

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Safety & Environmental Assurance Centre
Protecting People & Planet
Trusted Impactful Innovations designed for Safety & Sustainability

Acknowledgements:
Carl Westmoreland, Gavin Maxwell, Maria Baltazar, Paul Carmichael, Matt Dent, Steve Gutsell, Sarah Hatherell, Predrag Kukic, Hequn Li, Alistair Middleton, Iris Müller, Ramya Rajagopal, Georgia Reynolds, Andrew White & SEAC colleagues + collaborators

Collaborating to modernise the scientific data & tools we use for making safety decisions – 15+ years of research & evaluation

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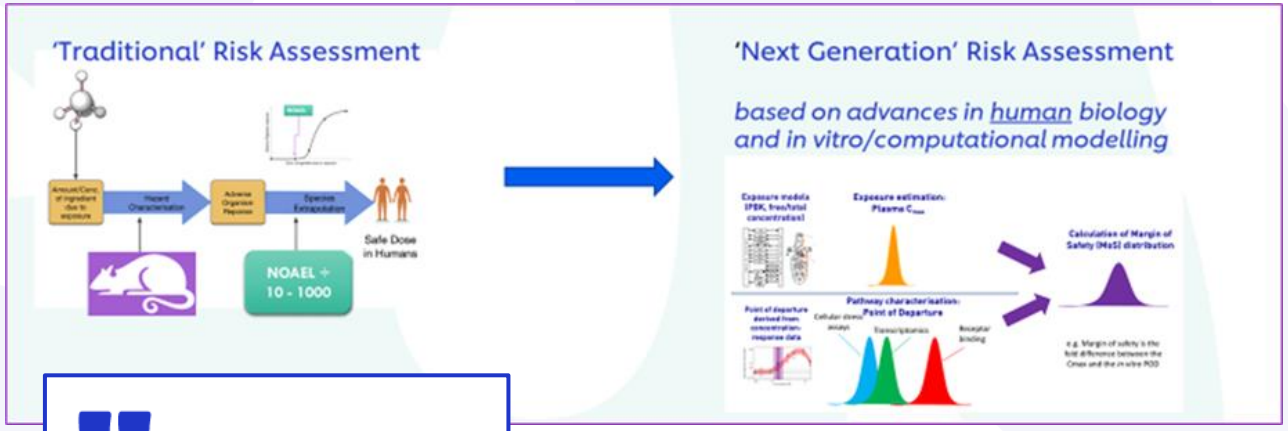
Overview & Background Context

Next Generation Risk Assessment (NGRA) using New Approach Methods (NAMs)

Data are needed for decisions on:

1. safety of **consumers** exposed to chemicals in **products**
2. safety of **workers** exposed to chemicals during product **manufacture**
3. safety of **people & non-human species** if exposed to chemicals in the **environment**



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

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

09/08/2015 | 09:01am EDT

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

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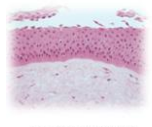
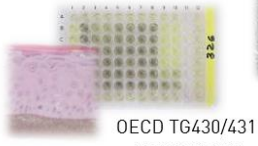
SEAC SAFETY & ENVIRONMENTAL ASSURANCE CENTRE
Scientific Excellence And Collaboration

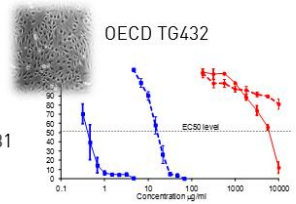
Assessing Consumer Safety of cosmetics ingredients without new animal testing (required by EU Cosmetic Products Regulation, 10+ years experience)

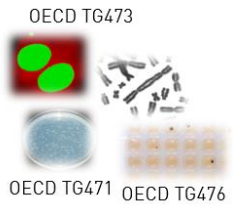
Is the consumer exposure safe? A tiered approach is routine:

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









- **Next Generation Risk Assessment (NGRA)**

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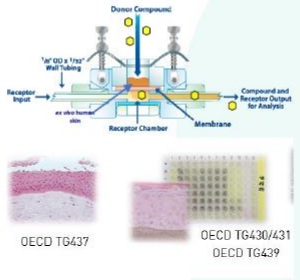
Next Generation Risk Assessment (NGRA)

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

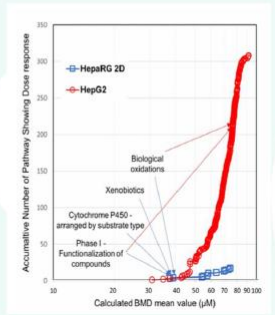
[Safety Homepage « Safety Science in the 21st Century (tt21c.org)]

Next Generation Risk Assessment is highly interdisciplinary

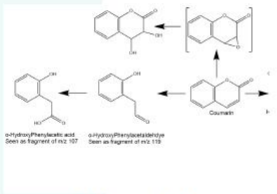
Risk assessment



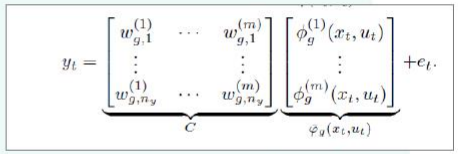
Biology



Bioinformatics



Chemistry



$$y_t = \underbrace{\begin{bmatrix} w_{g,1}^{(1)} & \cdots & w_{g,1}^{(m)} \\ \vdots & & \vdots \\ w_{g,n_y}^{(1)} & \cdots & w_{g,n_y}^{(m)} \end{bmatrix}}_{C} \underbrace{\begin{bmatrix} \phi_g^{(1)}(x_t, u_t) \\ \vdots \\ \phi_g^{(m)}(x_t, u_t) \end{bmatrix}}_{\varphi_g(x_t, u_t)} + e_t.$$

Mathematical and statistical modelling

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

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

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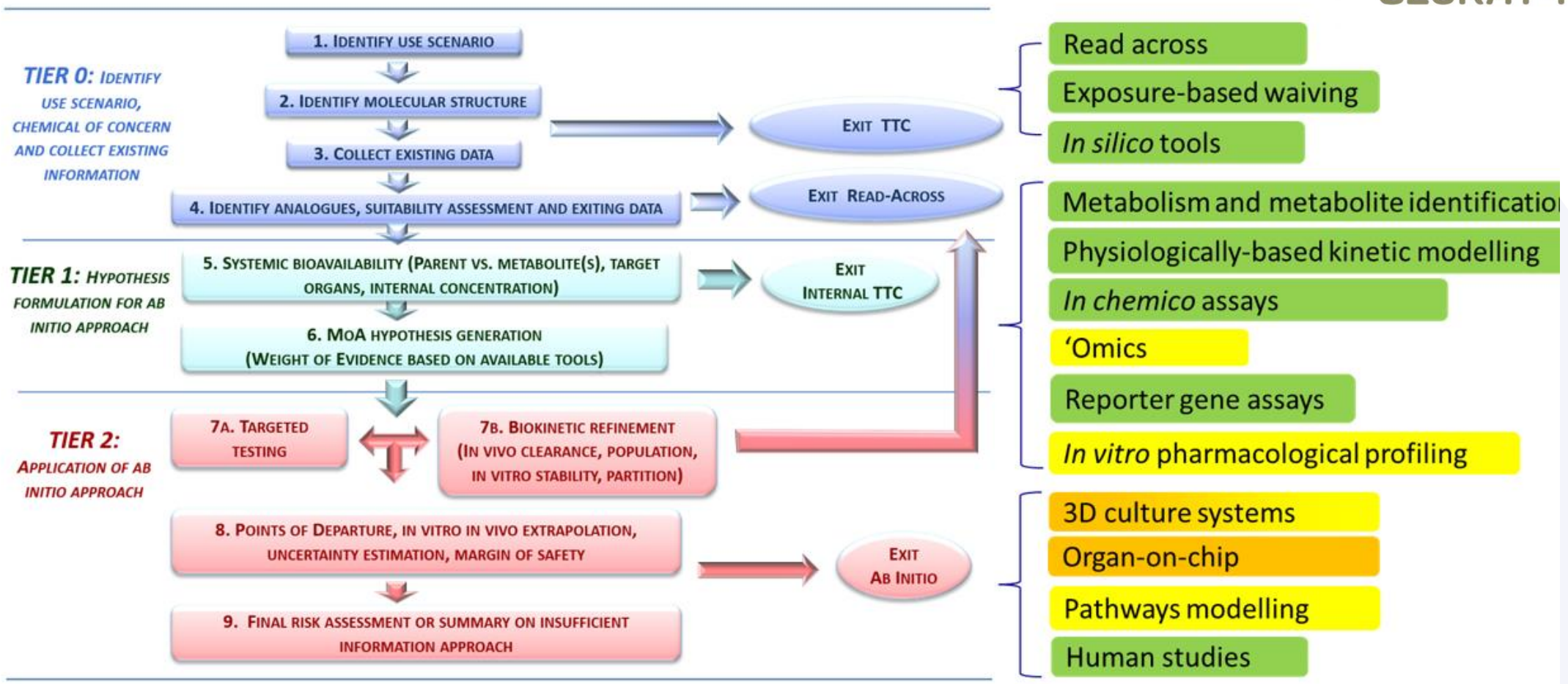
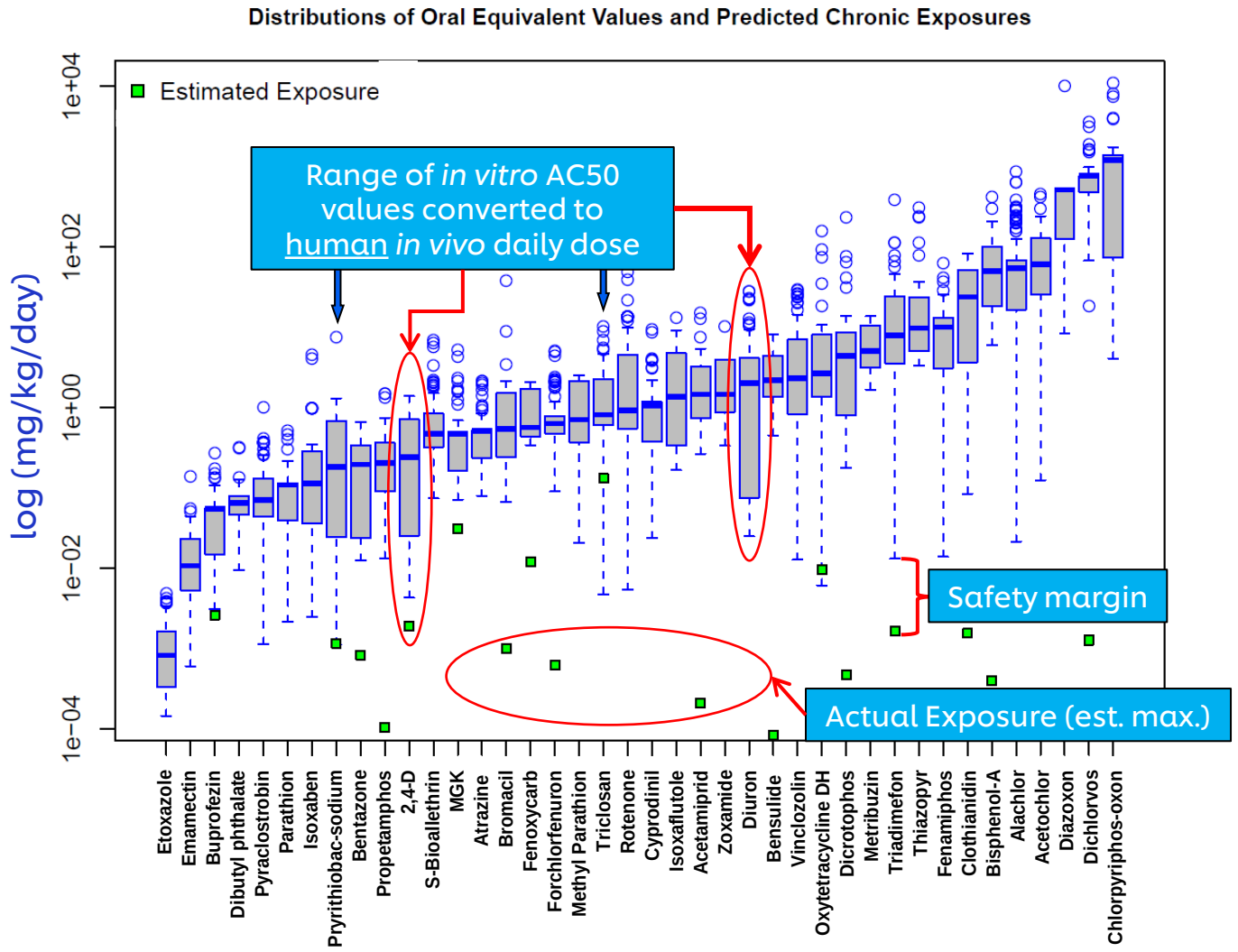
NGRA: tiered testing and human health assessment approach



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

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



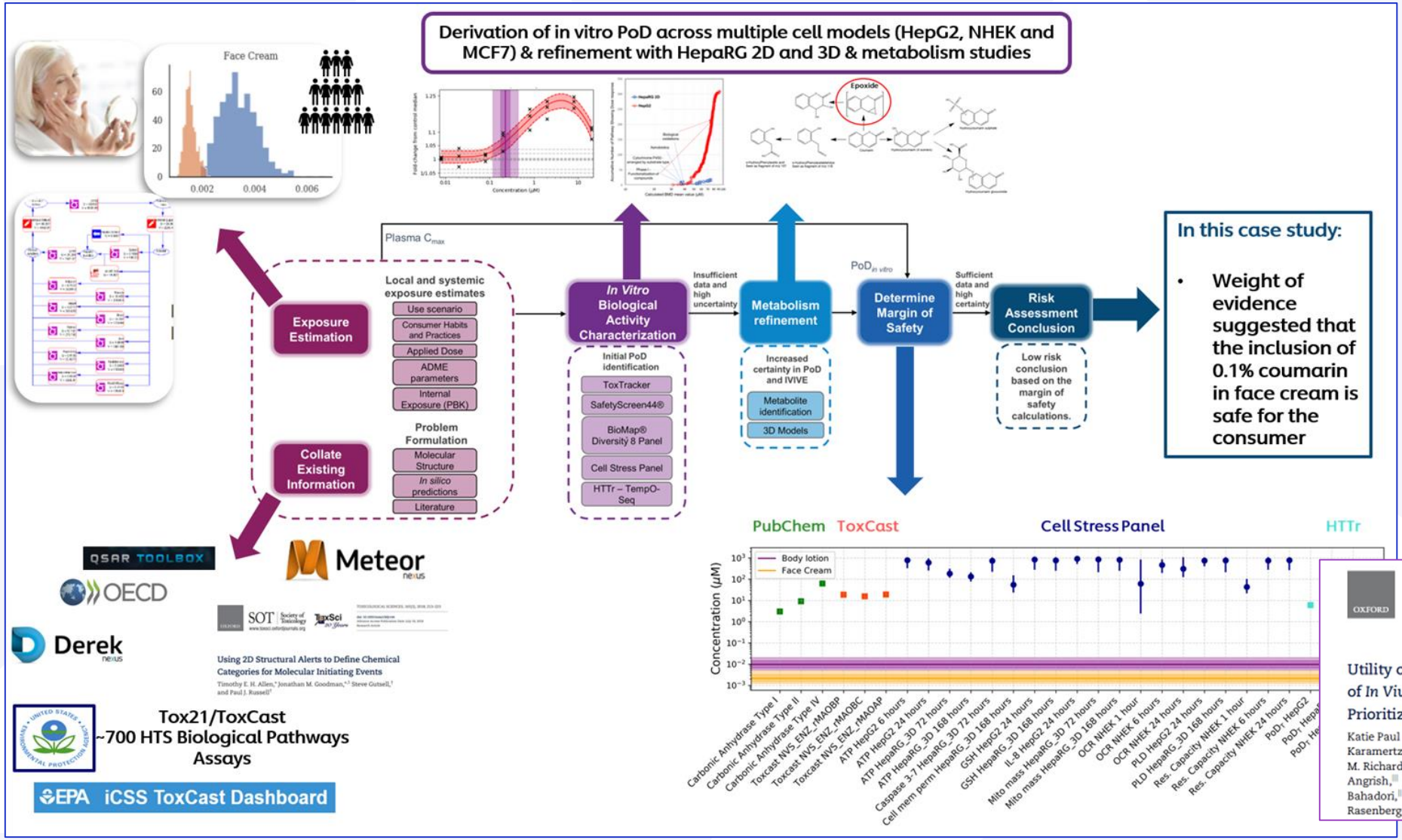
The hypothesis underpinning this NGRA is that **if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.**

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

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

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

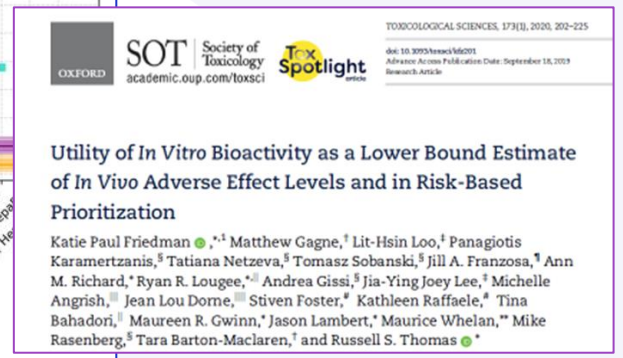
A large toolbox of modern scientific methods (NAMs) is used



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: ***Bioactivity - Exposure Ratio***



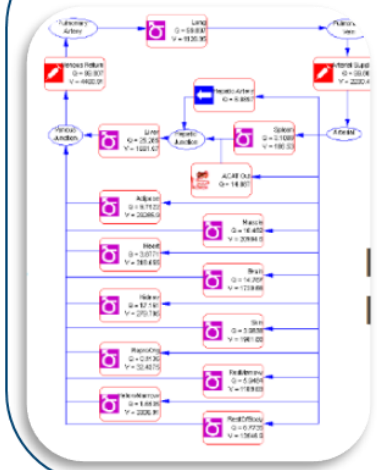
Hatherell *et al* (2020) Toxicological Sciences, **176,** 11-33

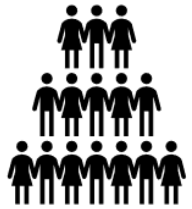
Moxon *et al* (2020) Toxicology in Vitro, **63** 104746

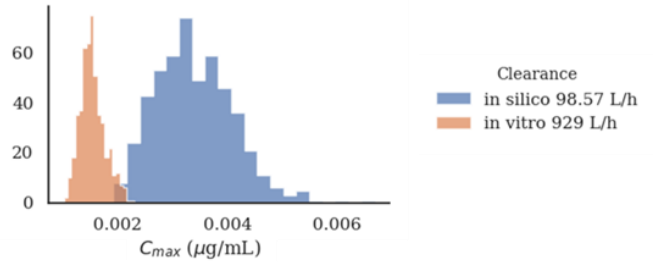
Li *et al* (2022) Toxicol. Appl. Pharmacol., **442** 115992

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

PBK Modelling







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

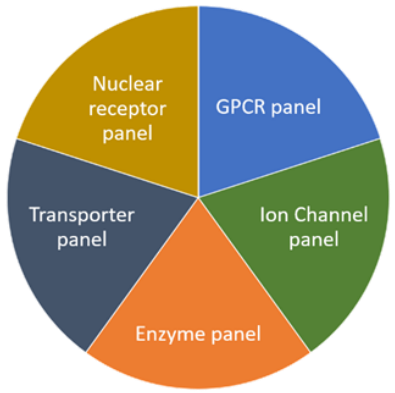
In vitro pharmacological profiling


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

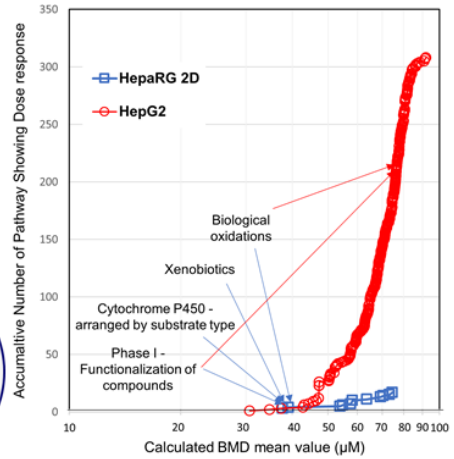


eurofins | Cerep

Transcriptomics

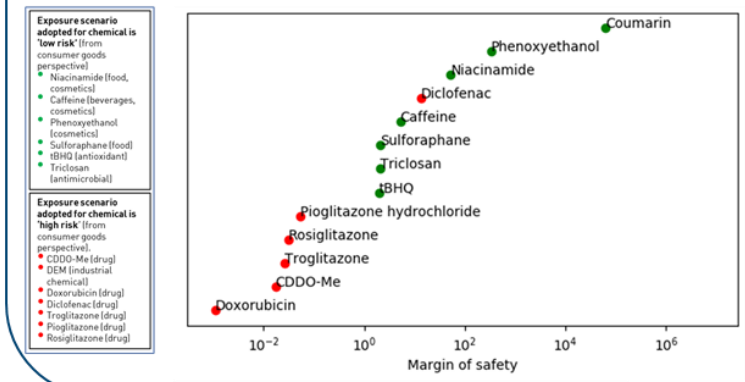
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDexpress 2

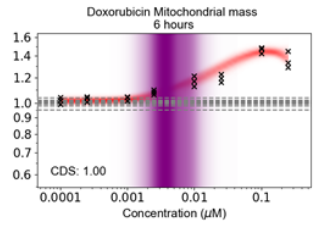


Cellular Stress Pathways

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



cyprotex AN EVOTEC COMPANY



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

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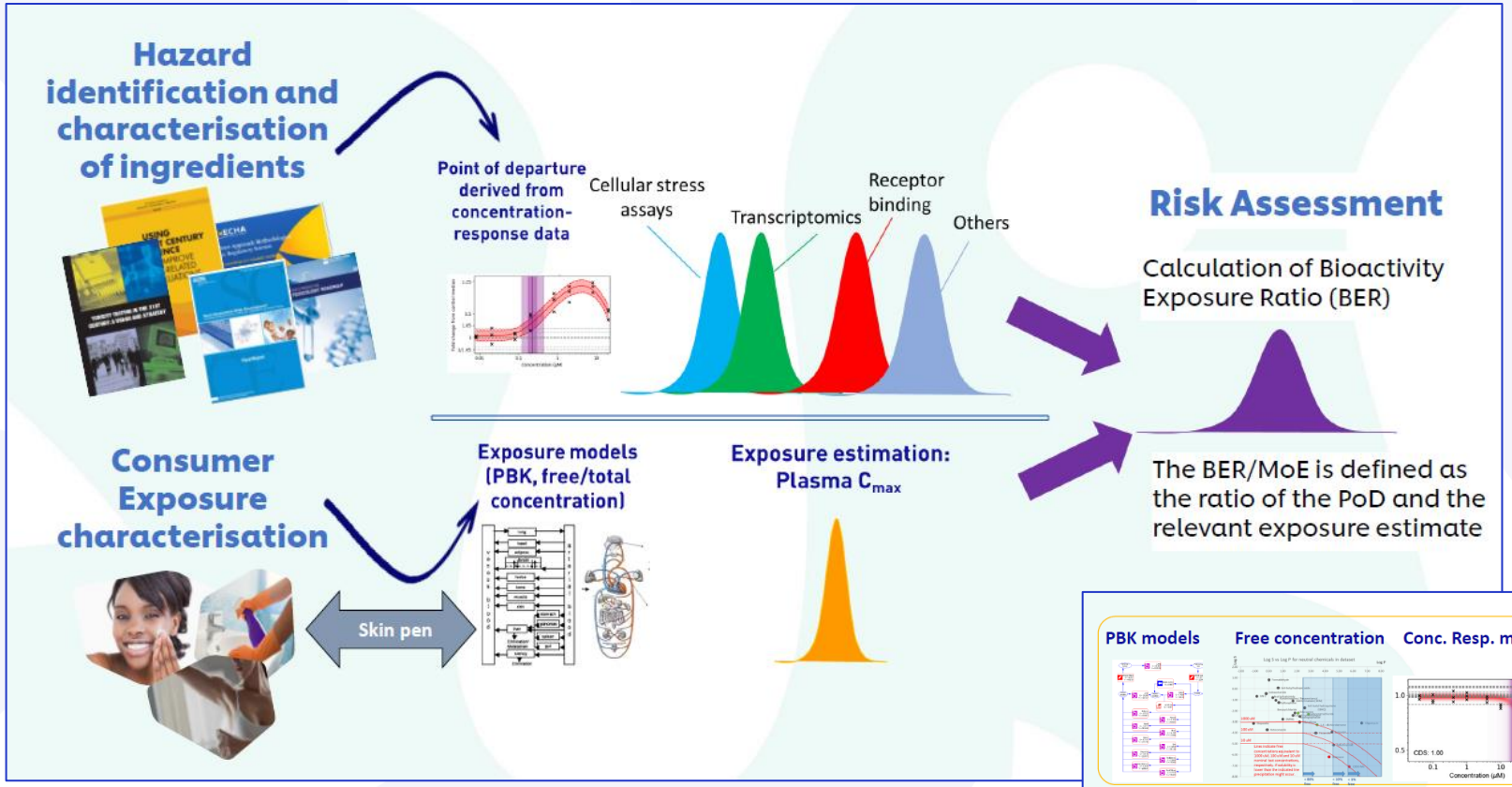
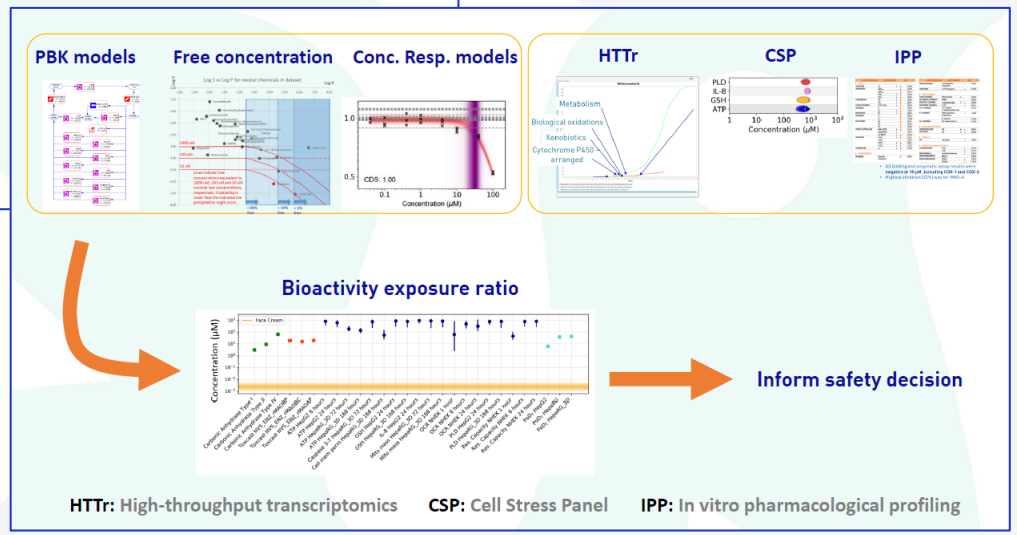
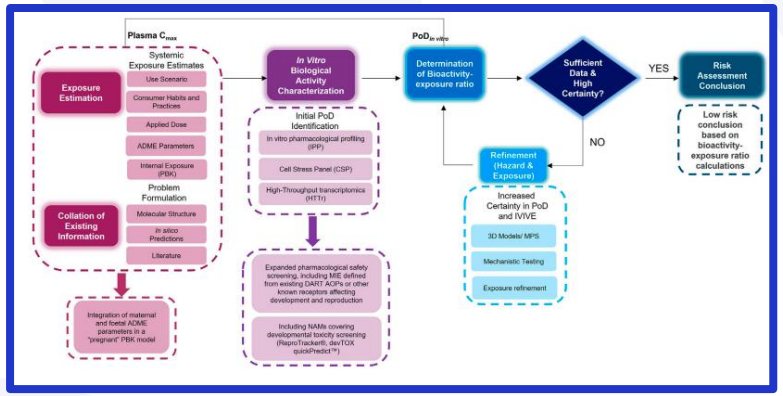
Integrating these approaches to make safety decisions





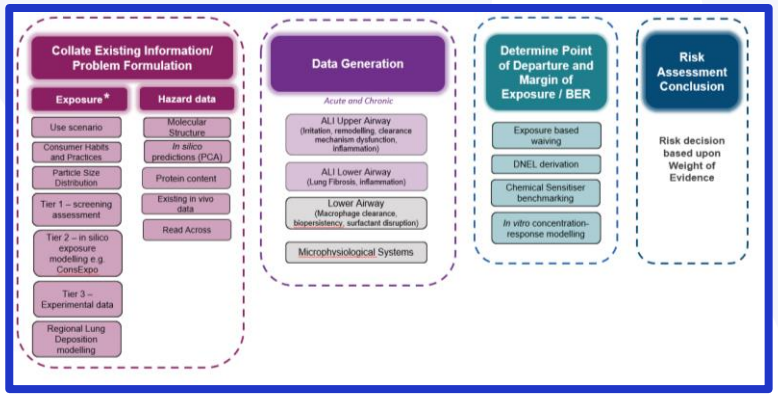
Unilever frameworks for using NAMs for Consumer Safety decisions

Developmental & Reproductive

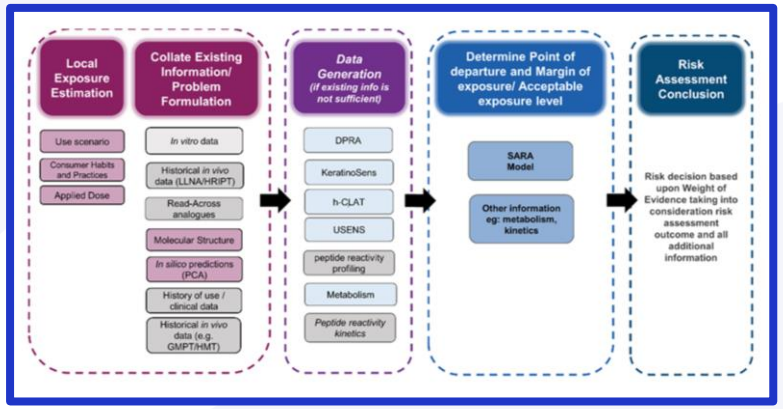


Rajagopal et al (2022) *Frontiers in Toxicology*, doi: 10.3389/ftox.2022.838466

Inhalation

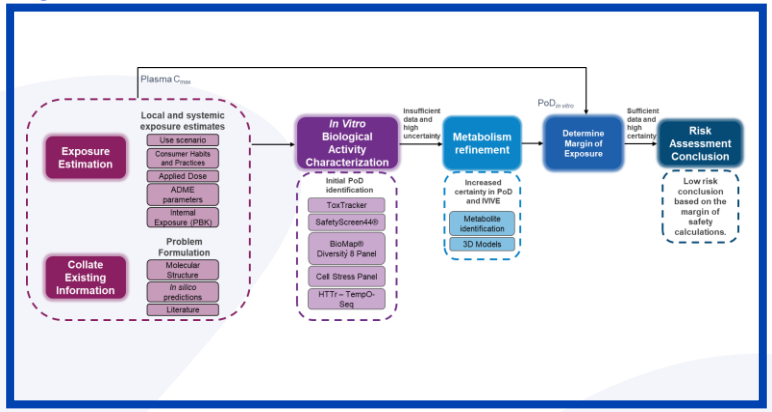


Skin Sensitisation



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

Systemic



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

Ongoing Evaluations - Unilever working with government agencies

EPA United States Environmental Protection Agency

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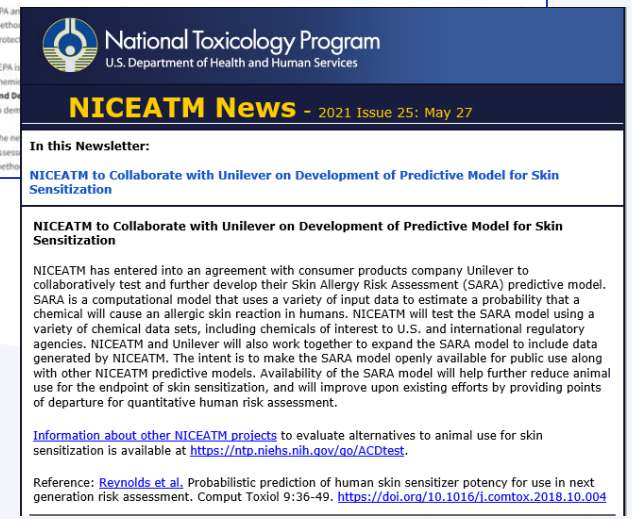
EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment

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 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.



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 animal 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

Evaluating the NAMs Toolbox

Are non-animal systemic safety assessments protective? A toolbox and workflow

Alistair M. Middleton[1*], Joe Reynolds[1], Sophie Cable[1], Maria Teresa Baltazar[1], Hequn Li[1], Samantha Beven[2], Paul L. Carmichael[1], Matthew Philip Dent[1], Sarah Hatherell[1], Jade Houghton[1], Predrag Kukic[1], Mark Liddell[1], Sophie Malcomber[1], Beate Nicol[1], Benjamin Park[2], Hiral Patel[3], Sharon Scott[1], Chris Sparham[1], Paul Walker[1], Andrew White[1]

[1]Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, United Kingdom

[2]Discovery Services, Charles River, Chesterford Research Park, CB10 1XL, United Kingdom

[3]Cyprotex Discovery Ltd, No. 24 Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom.

Toxicological Sciences - accepted for publication

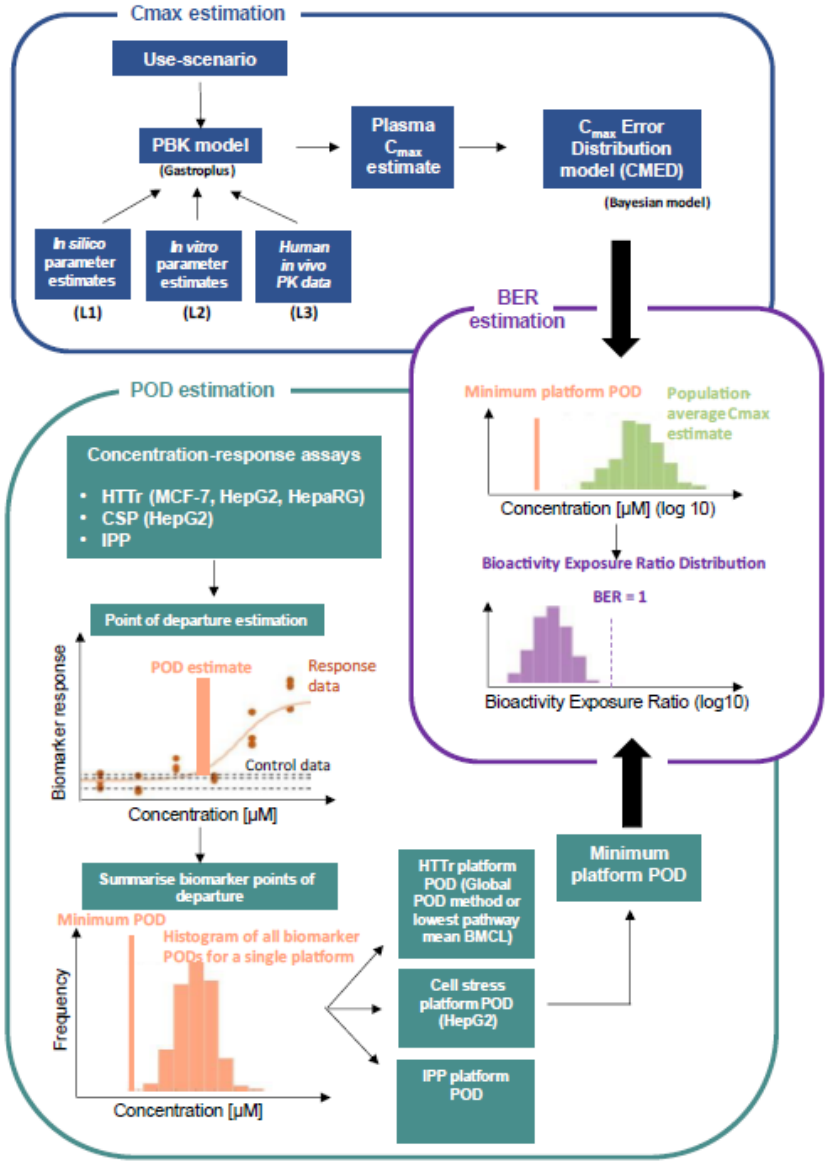
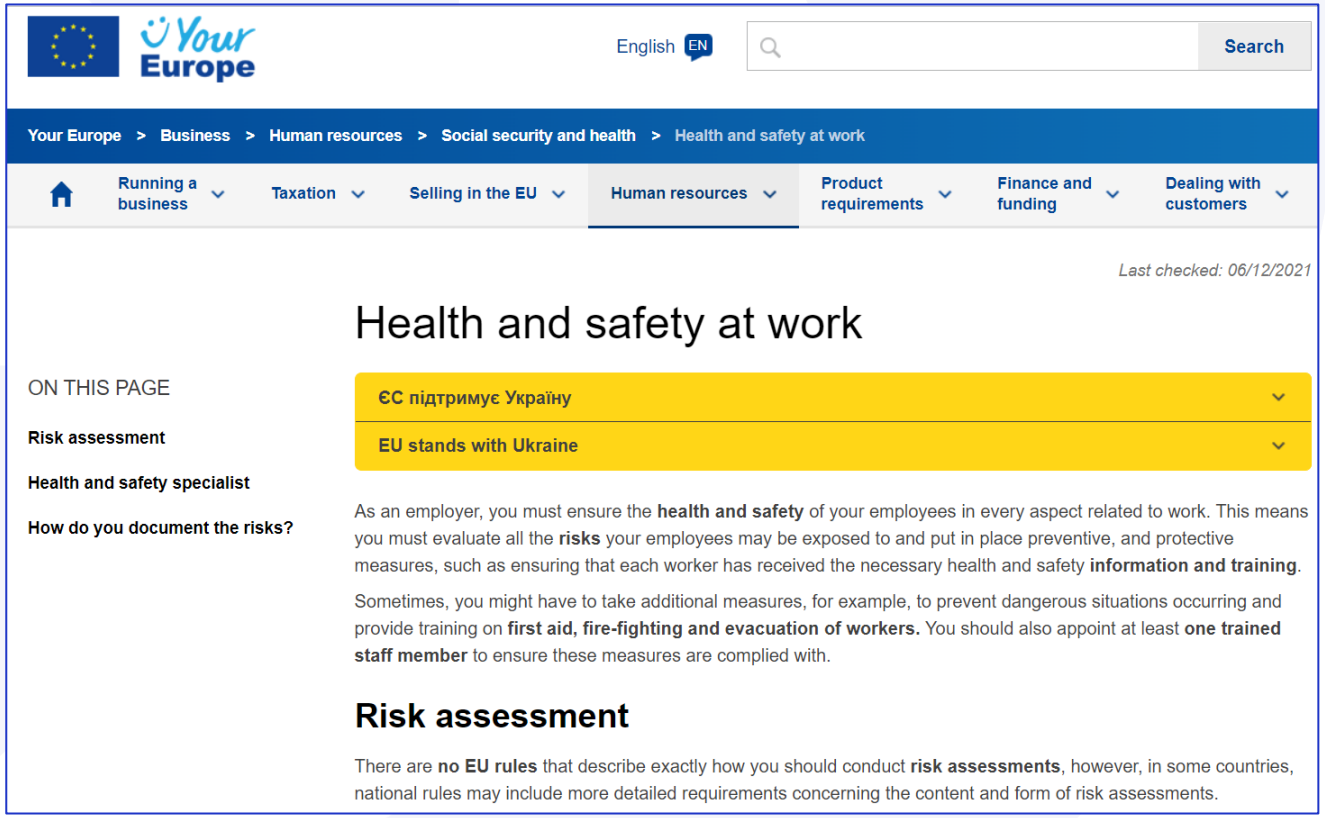


Figure 1: Schematic of the systemic safety toolbox and associated workflow, which comprises three modules: one to estimate the exposure using Physiologically Based Kinetic (PBK) models, another to estimate the point of departure (POD) based on the cell stress panel (CSP), High Throughput Transcriptomics (HTTr) and *in vitro* Pharmacological Profiling (IPP) bioactivity data. The workflow involves combining the outputs from these two modules into the third module to estimate the Bioactivity Exposure Ratio (BER).

Worker Safety is ensured via prevention & protection
– exposure-based risk assessments specific for the activity / local operating set-up



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Last checked: 06/12/2021

Health and safety at work

ON THIS PAGE

- Risk assessment
- Health and safety specialist
- How do you document the risks?

ЄС підтримує Україну

EU stands with Ukraine

As an employer, you must ensure the **health and safety** of your employees in every aspect related to work. This means you must evaluate all the **risks** your employees may be exposed to and put in place preventive, and protective measures, such as ensuring that each worker has received the necessary health and safety **information and training**.

Sometimes, you might have to take additional measures, for example, to prevent dangerous situations occurring and provide training on **first aid, fire-fighting and evacuation of workers.** You should also appoint at least **one trained staff member** to ensure these measures are complied with.

Risk assessment

There are **no EU rules** that describe exactly how you should conduct **risk assessments**, however, in some countries, national rules may include more detailed requirements concerning the content and form of risk assessments.

Under workplace legislation, it is the **employer's duty to carry out a risk assessment and ensure that the workers are protected and provided with information, guidance and training** on the safe use of chemicals in the workplace, based on information derived from the labels and the safety data sheet. The employer also has the right to demand further information from the supplier.

REACH continuously accumulates data on health and safety risks from the use of chemical substances. The **registrant** (the manufacturer or the importer), who has to provide this data to the ECHA, also has to **communicate** this information to the downstream user, by providing an extended safety data sheet with exposure scenarios containing operational conditions and risk management measures for safe use, meant to facilitate the training of workers and the risk assessment procedure. At the same time, the registrant has the right to be informed by the downstream users on the relevance of the proposed risk management measures, in particular if they are inappropriate.

Can we change the types of data generated under REACH so they are based on advanced human-relevant science in place of animal testing?

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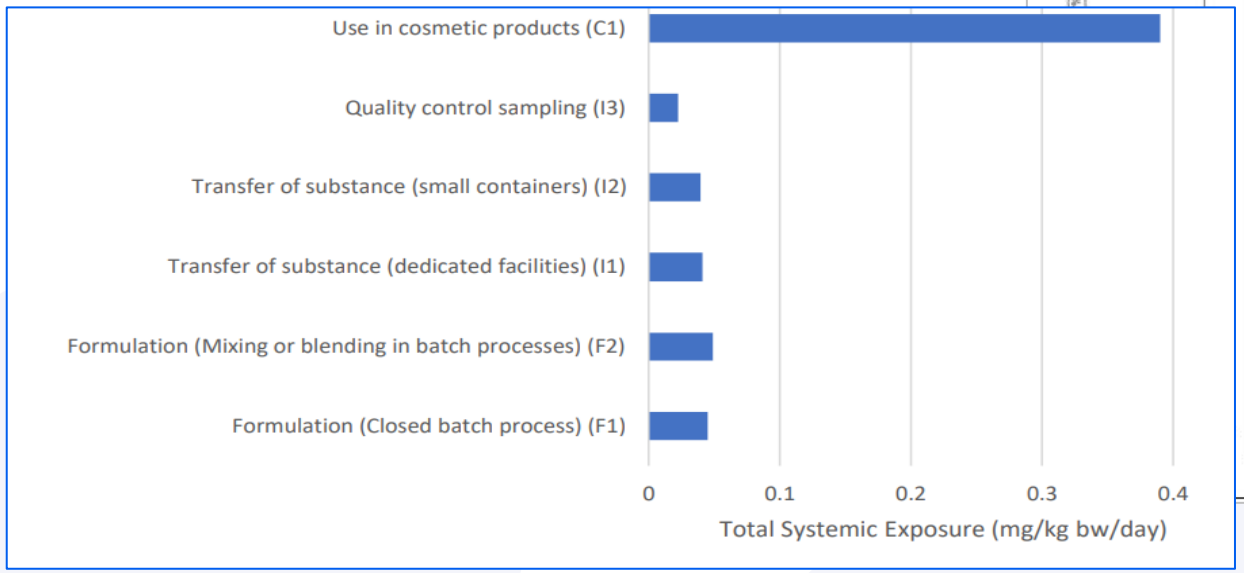
NGRA approaches for Worker Safety decisions

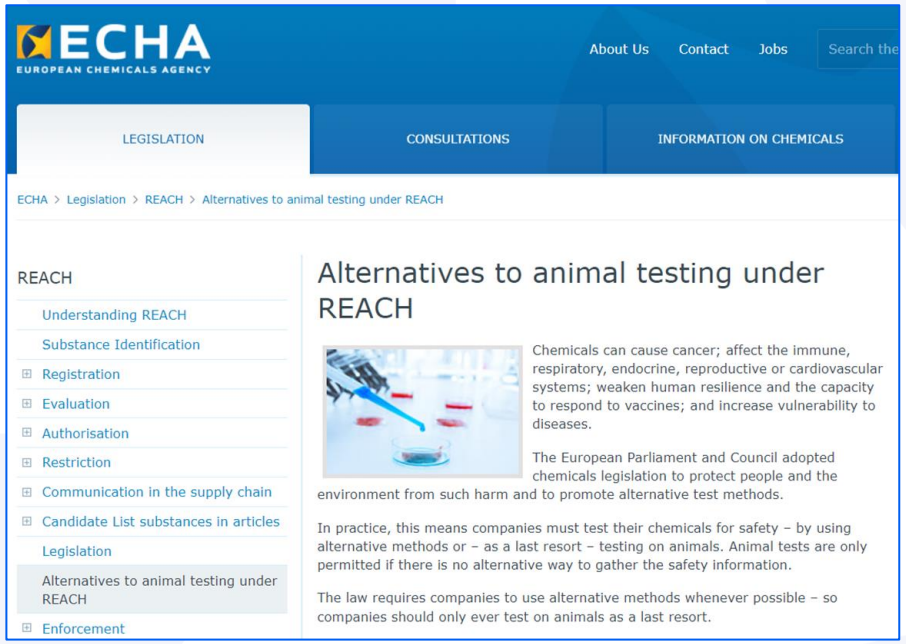
- Understanding worker exposure
  - Routes
  - Levels
  - PPE*, engineering controls, ventilation, etc.
  - ***PBK models for worker exposure***

- NGRA
  - ***Bioactivity – Exposure Ratio (BER) approach for worker exposure***



* PPE = Personal Protective Equipment

Chemical Safety following environmental exposures – EU regulatory approach: protection from harm & use of non-animal tests



- **Closing the Gap** between Modern Safety Science & Regulatory Use of Next Gen Tools
- **Building Confidence** in the use of NAMs being Protective

EU REACH legislation has been in place for 15 years. It was introduced to protect people & the environment from harm and to promote alternative test methods.

Science & technology have advanced hugely since June 2007. Chemicals regulations need to catch up → framework for using best scientific data for safety decisions.

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[4] · Timothy W. Gant[7] · Marcel Leist[8] · Bennard van Ravenzwaay[9]

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Cosmetics

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

By Kacey Culliney

Cosmetics

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

By Kacey Culliney

Adoption of NGRA in cosmetic ingredient safety assessment …

… use of similar approaches for chemicals registration purposes?

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)

ICCR International Cooperation on Cosmetics Regulation

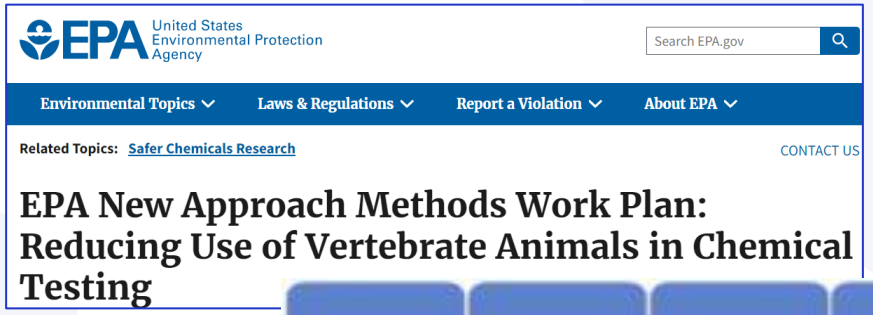
International Cooperation on Cosmetics Regulation (2018)

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]



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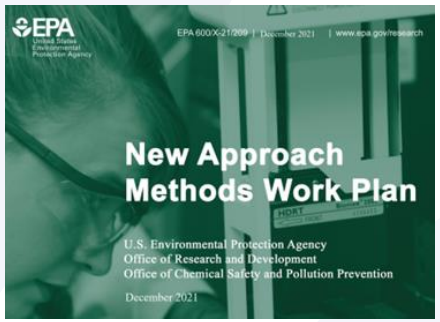
EPA New Approach Methods Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing



Unilever

Stakeholders engaging on use of NAMs for EU chemicals regulations

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

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Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

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

Food for Thought …

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

Paul L. Carmichael[1,2], Maria T. Baltazar[1], Sophie Cable[1], Stella Cochrane[1], Matthew Dent[1], Hequn Li[1], Alistair Middleton[1], Iris Muller[1], Georgia Reynolds[1], Carl Westmoreland[1] and Andrew White[1]
[1]Safety & Environmental Assurance Centre (SEAC), Unilever, Sharnbrook, Bedfordshire, UK; [2]Toxicology, Wageningen University & Research, Wageningen, The Netherlands

anses

Maisons-Alfort, 11 May 2022

PRESS RELEASE

Launch of the European research and innovation PARC programme to improve chemical risk assessment

flash

EPAA Workshop

23 - 24 November 2021, virtual event

epaa
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»

How to accelerate the replacement of animal toxicity testing

Helsinki Chemicals Forum 2022
8-9 June 2022
Stakeholder views on hot topics in chemicals safety

Context

It is agreed that we need to replace animal toxicity testing and many regulations encourage avoiding it. But the tests are still widely used. They can be time-consuming, costly and are not always accurate in predicting chemical effects in humans. While new approach methods (NAMs) are becoming available, implementing them has been a relatively slow process. Regulatory authorities are looking for assurance that these alternative test methods protect human health as efficiently/ effectively as the animal models they replace. But how can confidence be achieved and how can we speed up their adoption by decision makers?

Moderator: Patience Browne, principal administrator, Hazard Assessment and Pesticides Programmes, Environmental Directorate, OECD

Panelists:

Gavin Maxwell, EPAA industry co-chair and safety science leader, Unilever Safety & Environmental Assurance Centre (SEAC)

Ofelia Bercaru, director – prioritisation and integration, Echa

Tara Barton-Maclaren, research manager, Healthy Environments and Consumer Safety Branch, Health Canada/ Government of Canada

Marina Pereira, senior strategist – regulatory policy, research and toxicology, Humane Society International

Maurice Whelan, head of Chemical Safety and Alternative Methods Unit, European Commission

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