Next Generation Risk Assessment: What do we need from validation?

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Safety & Environmental Assurance Centre, Unilever

23rd August 2021

Our products must be safe

Can we make robust, reproducible decisions on these people's safety?

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

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

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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

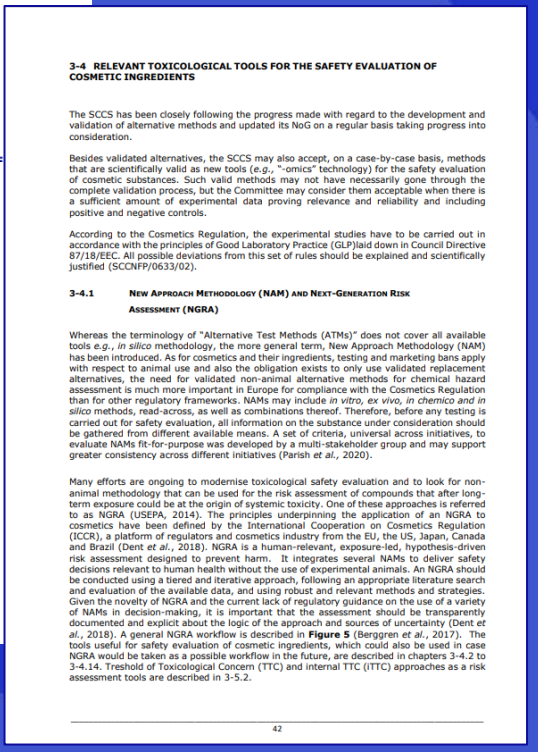
Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 11TH REVISION

Scientific Committees on Consumer Safety and 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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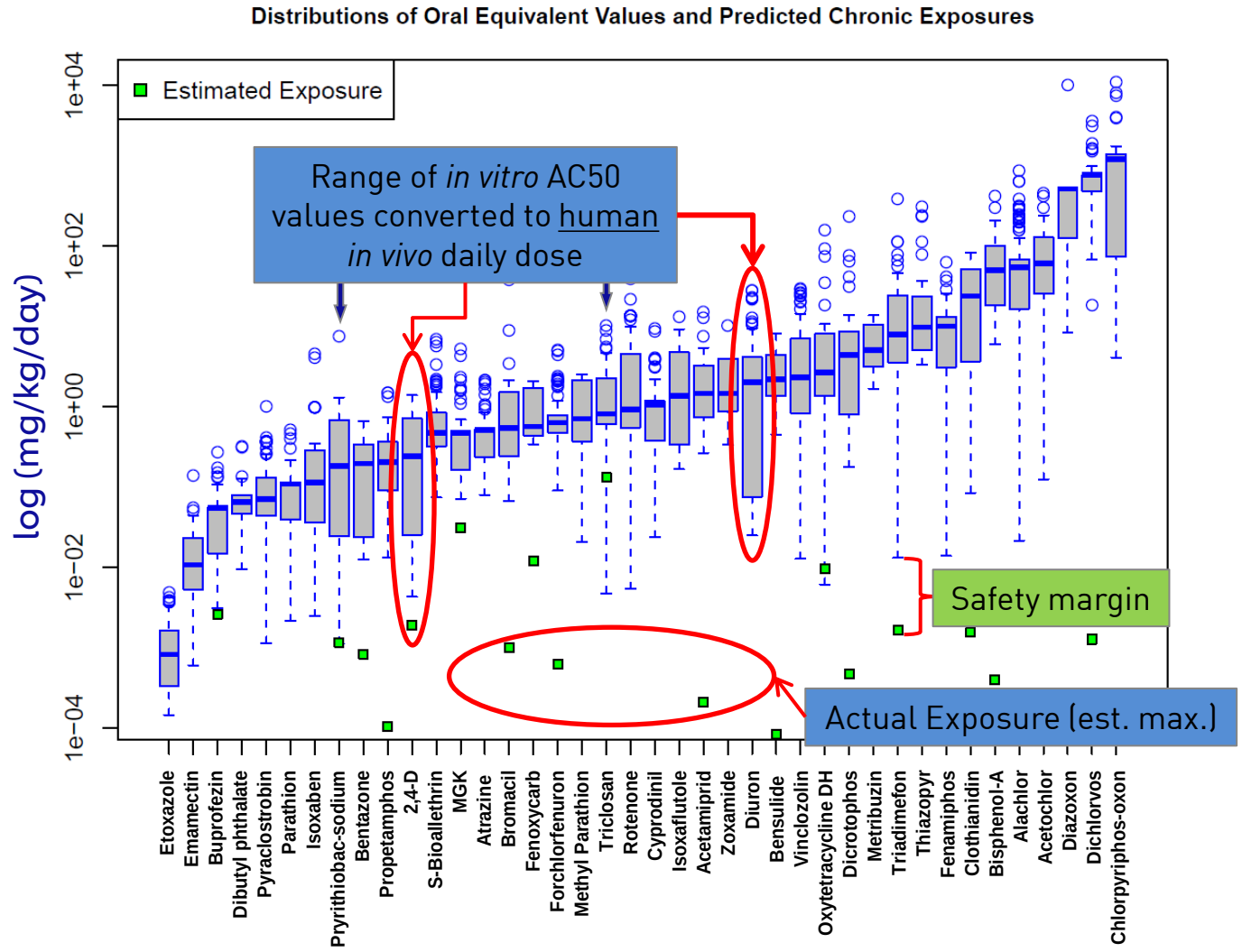
ICCR International Cooperation on Cosmetics Regulation

International Cooperation on Cosmetics Regulation (2018)

European Commission

European Commission: Scientific Committee on Consumer Safety (2021)

A fundamental principle of NGRA: 'Protection not prediction'



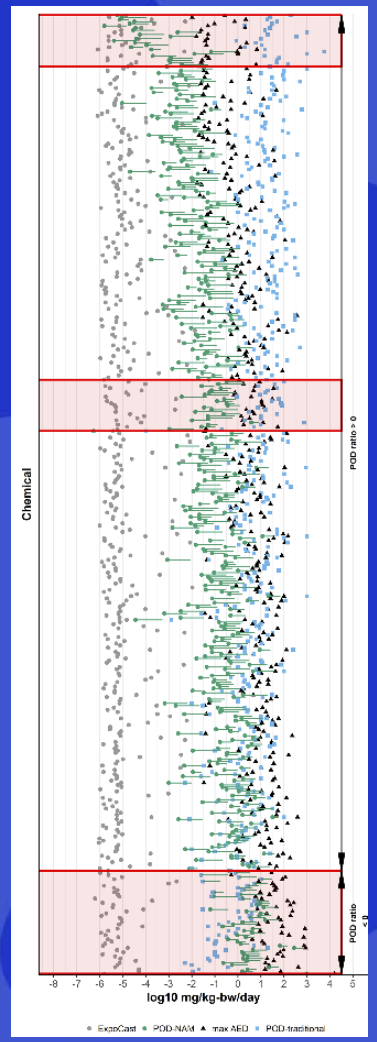
The hypothesis underpinning this type of NGRA is that if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.

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

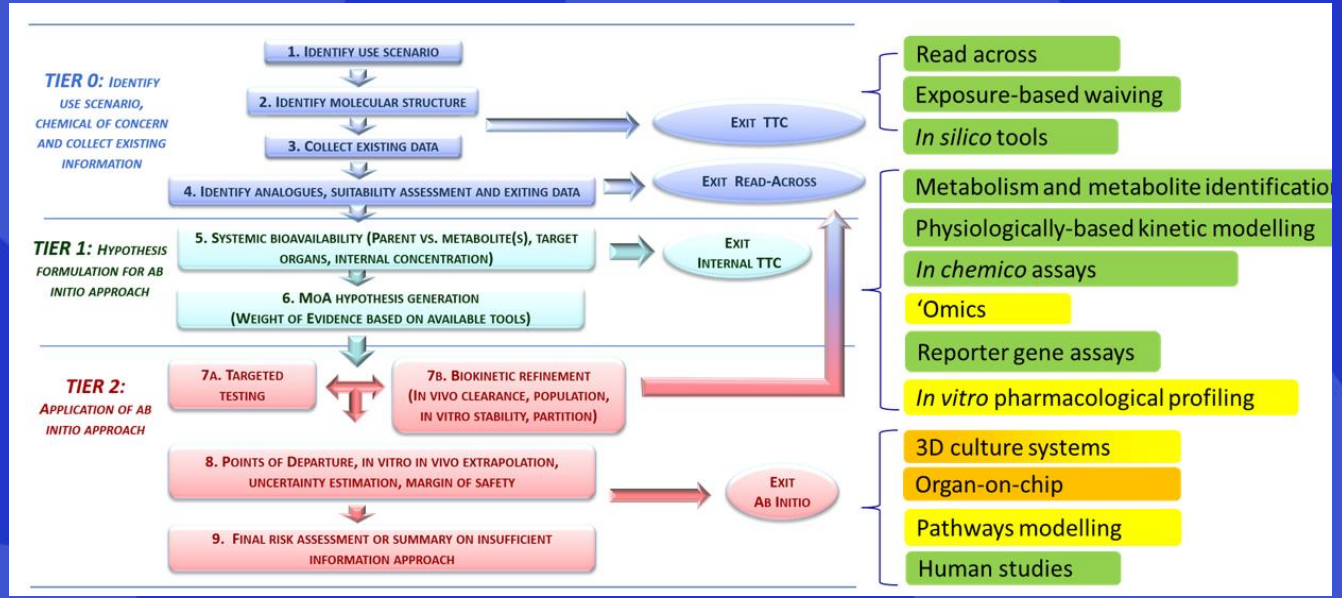
Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

In Vitro Bioactivity to Determine Margins of Safety



"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". APCRA, 2020

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT



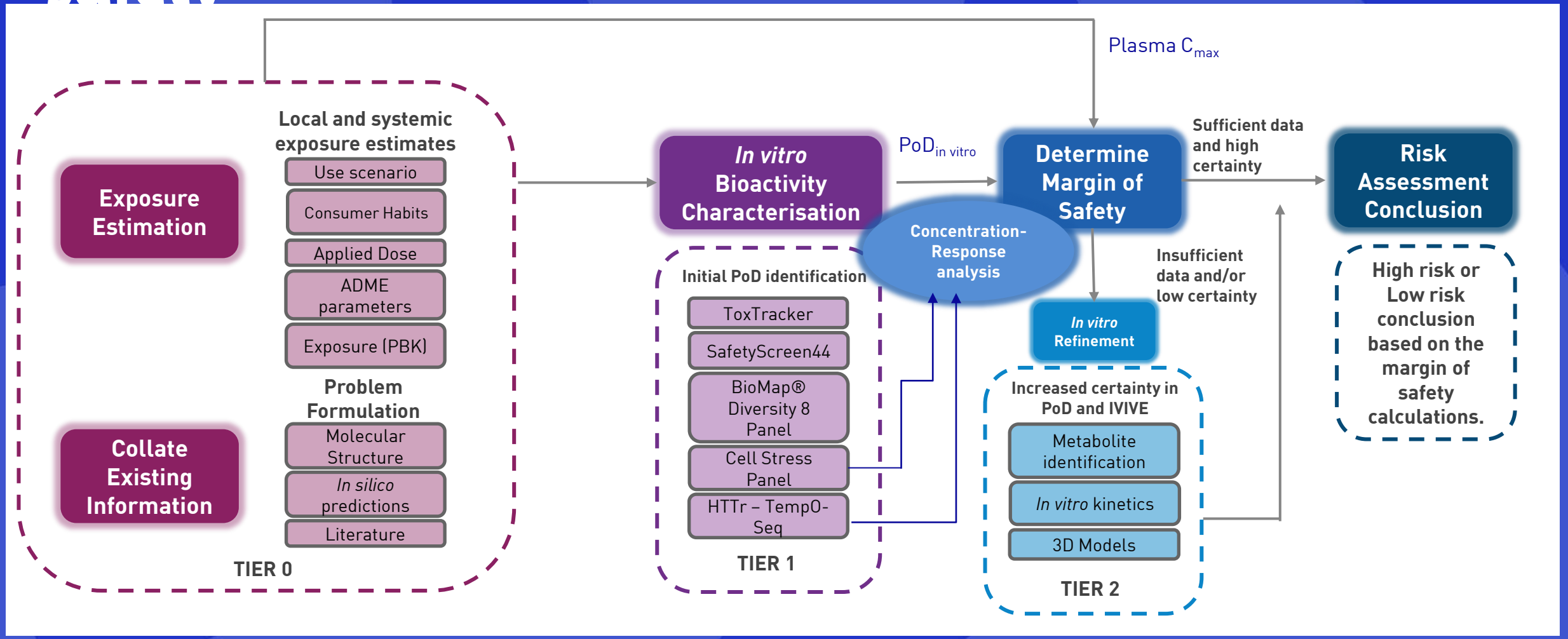
EUTOXRISK

SEURAT-1

Paul Friedman *et al* (2020) Toxicological Sciences, **173**, 202-225

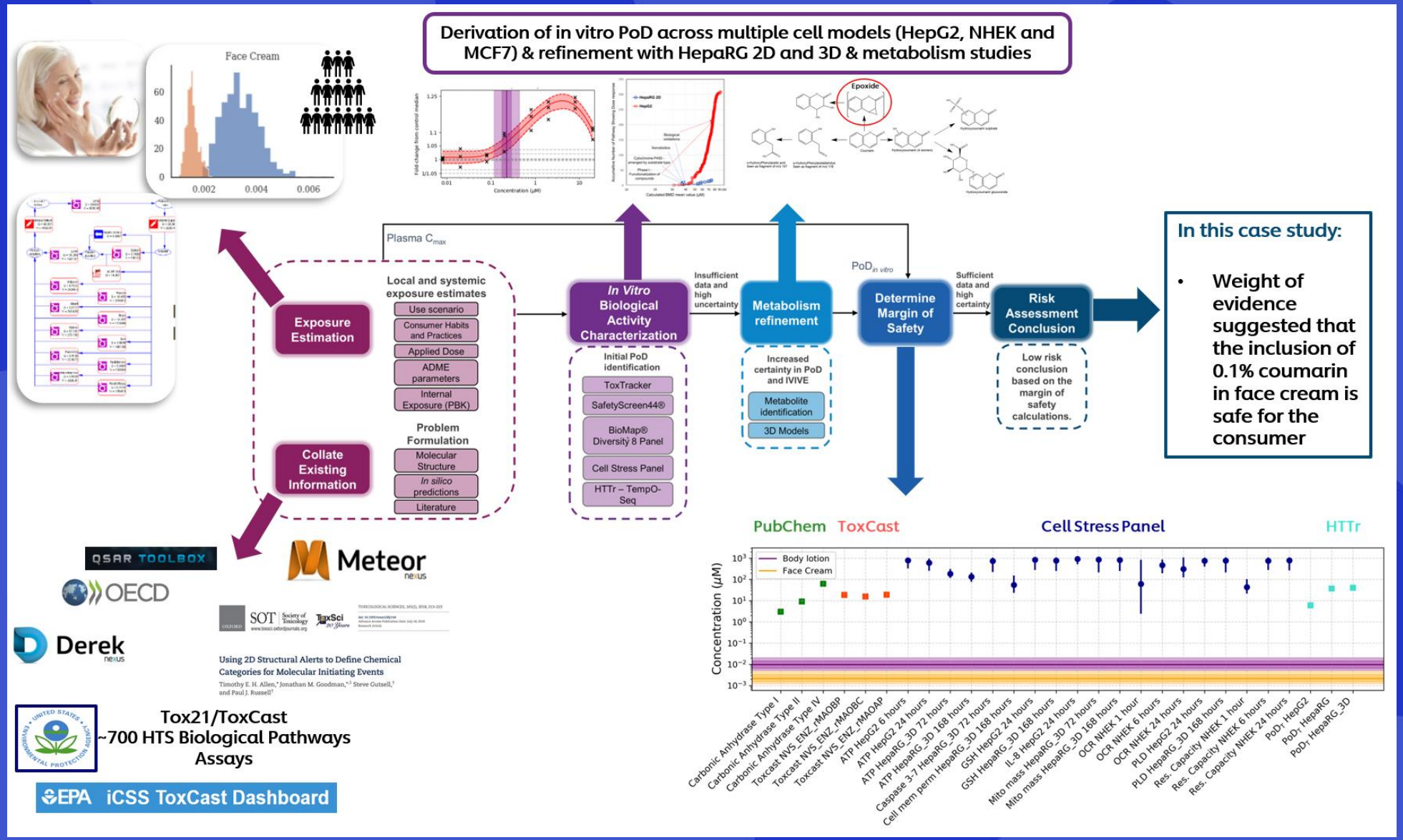
Berggren *et al* (2017) Computational Toxicology **4**, 31-44

NGRA Framework: Decision-making on consumer safety



Baltazar *et al* (2020) Toxicological Sciences, 236-252

A large toolbox of methods is used



Exposure tools to inform level of systemic exposure

Bioactivity tools to provide Points of Departure

Not a prescriptive set of tools, but driven by the risk assessment question

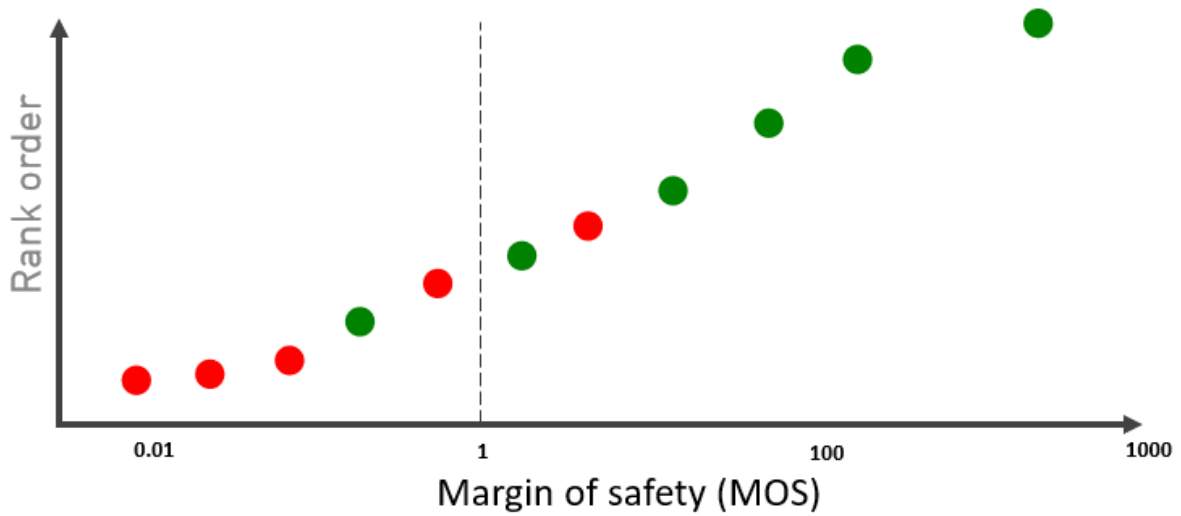
Hatherell *et al* (2020) Toxicological Sciences, **176,** 11-33

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

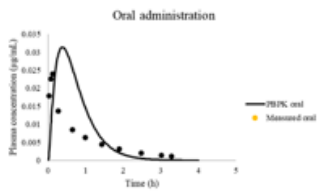
Evaluating the toolset for risk assessment: A data-driven approach

Chemical exposures scenarios

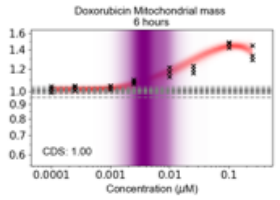
- 'Low' risk (from consumer goods perspective) – e.g. foods, cosmetics
- 'High' risk (from consumer goods perspective) – e.g. drugs



Define typical use-case scenarios benchmark chemical-exposures



PBK models of systemic exposure



Calculate the PoDs

Calculate the margin of safety

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

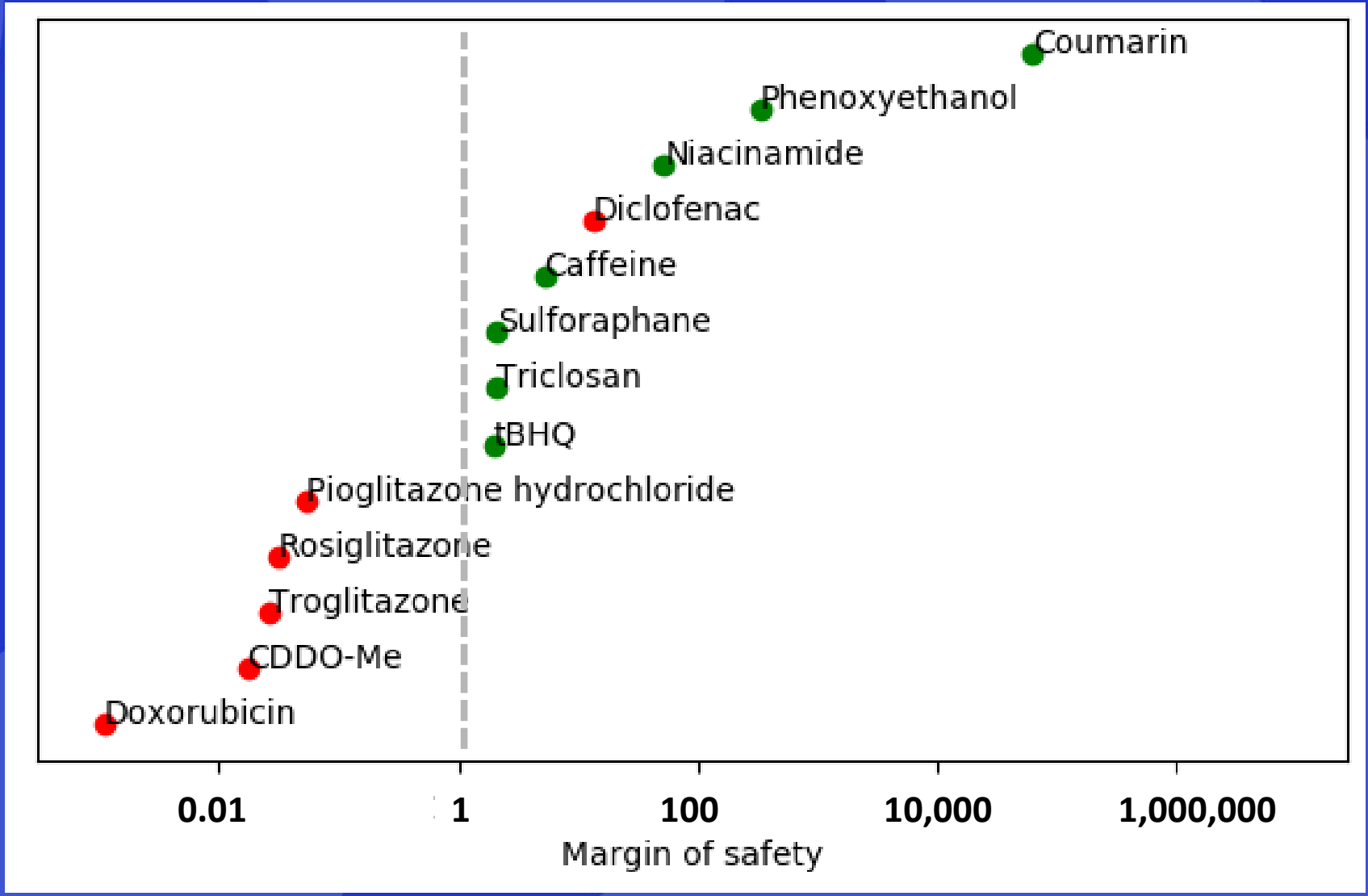
Margins of Safety for Different Chemical/Exposure Scenarios

Exposure scenario adopted for chemical is 'low risk' (from consumer goods perspective)

- Niacinamide (food, cosmetics)
- Caffeine (beverages, cosmetics)
- Phenoxyethanol (cosmetics)
- Sulforaphane (food)
- tBHQ (antioxidant)
- Triclosan (antimicrobial)

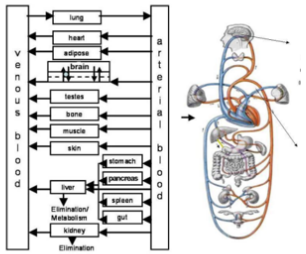
Exposure scenario adopted for chemical is 'high risk' (from consumer goods perspective).

- CDDO-Me (drug)
- DEM (industrial chemical)
- Doxorubicin (drug)
- Diclofenac (drug)
- Troglitazone (drug)
- Pioglitazone (drug)
- Rosiglitazone (drug)

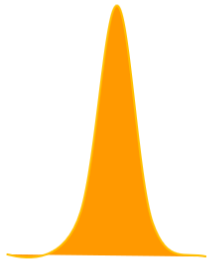


Uncertainty and the Margin of Safety

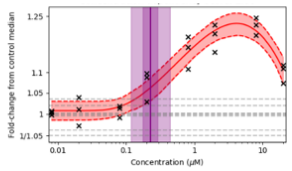
Exposure models (PBK, free/total concentration)



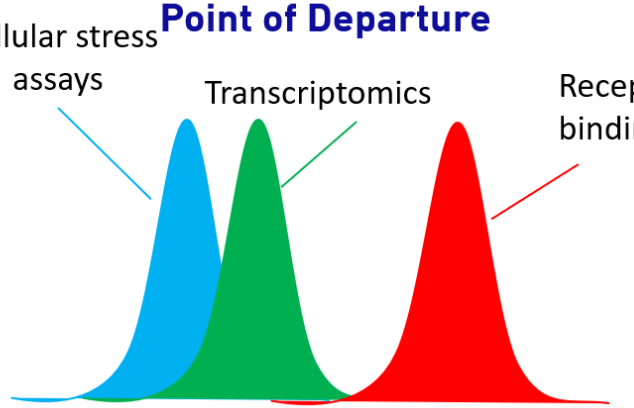
Exposure estimation: Plasma C_{max}



Point of departure derived from concentration-response data



Pathway characterisation: Point of Departure

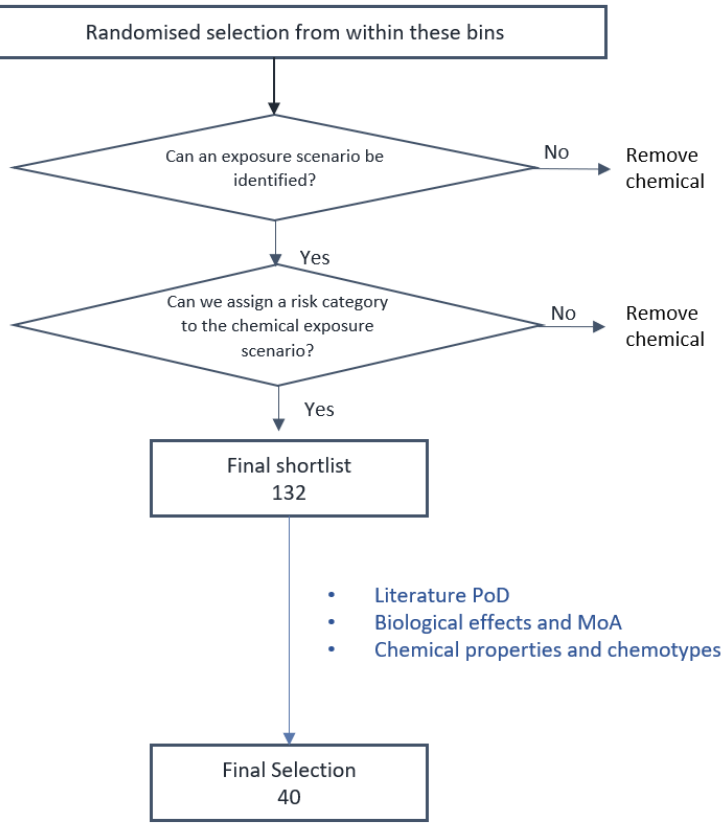


Calculation of Margin of Safety (MoS) distribution

e.g. Margin of safety is the fold difference between the Cmax and the *in vitro* POD

Ongoing evaluation of the toolset

Chemical	Product type	Level	Route	Cmax (µM) prediction	Risk class
Thalidomide	Tablet - drug	400 mg	Oral	121	High
Paraquat Dichloride	Accidental ingestion of pesticide	35 mg/kg/day	Oral	300	High
Valproic acid	Tablet or syrup - drug	1000 mg	Oral	361	HIgh
Butylated hydroxytoluene	Body Lotion	0.50%	Dermal	0.0031	Low
Oxybenzone	Sunscreen	6%	Dermal	1.1	Low
Hexylresorcinol	Throat Lozenge	2.4 mg	Oral	0.23	Low
Hexylresorcinol	Face Serum	0.40%	Dermal	0.05	Low
Caffeine	Food & drink		Oral	52	Low
Coumarin	-	0.1 mg/kg bw/day	Oral	0.01	Low
Doxorubicin HCl	Drug	60mg/m^2	Intravenous	1	High
Niacinamide	Food & drink	12.5 mg/kg bw/day	Oral	163	Low
Sulforaphane	Food & drink	4.1-9.2 mg/day	Oral	0.07	Low
Rosiglitazone	Drug	8 mg	Oral	1	High
Etc					
Etc					
Etc					



cyprotex eurofins Stemina BIOMARKER DISCOVERY

BioClavis ToxTracker® AO charles river

Maximise synergy with other, ongoing evaluation activities including:

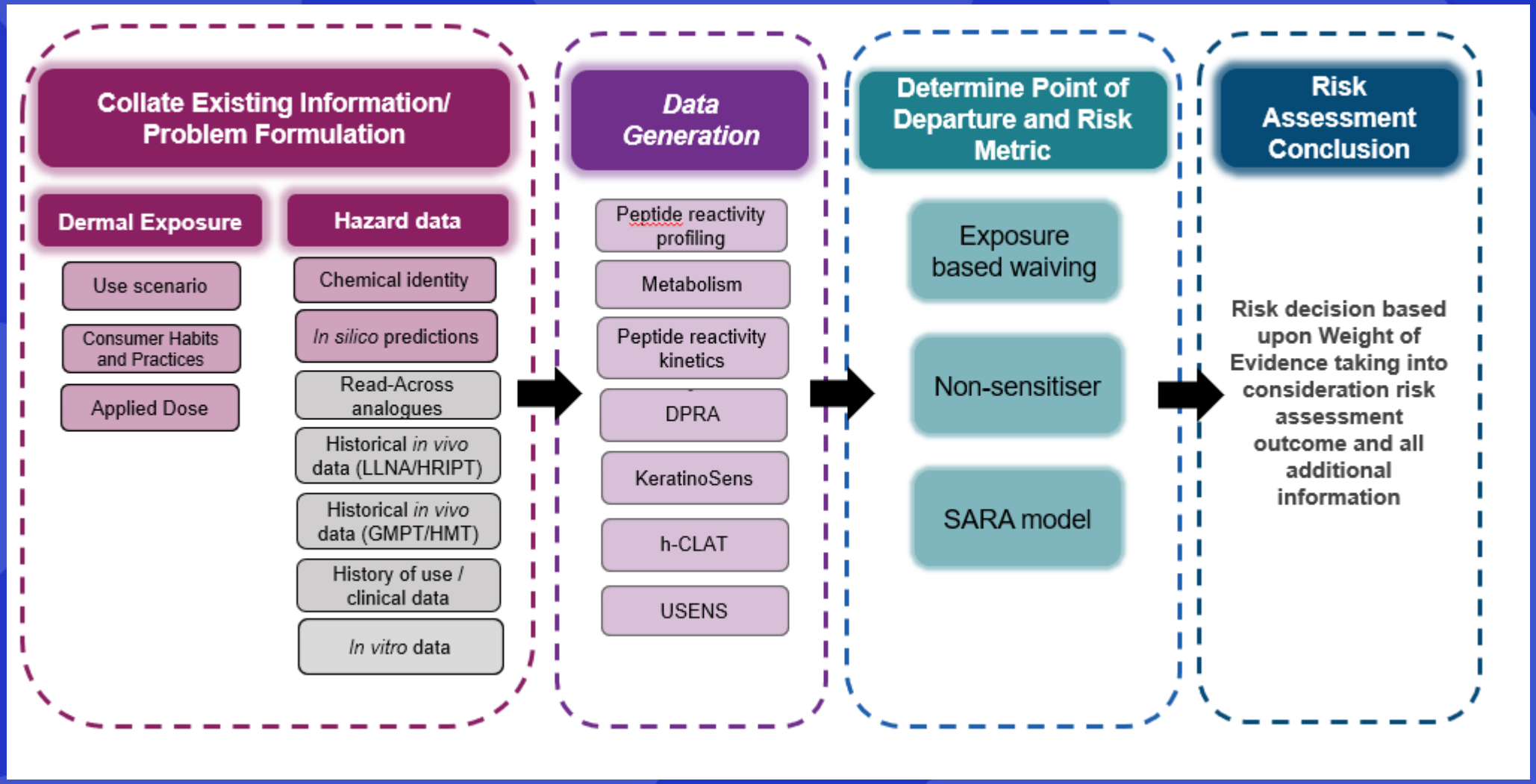
EUTOXRISK

RISK HUNT3R

Cosmetics Europe
the personal care association

EPA United States Environmental Protection Agency

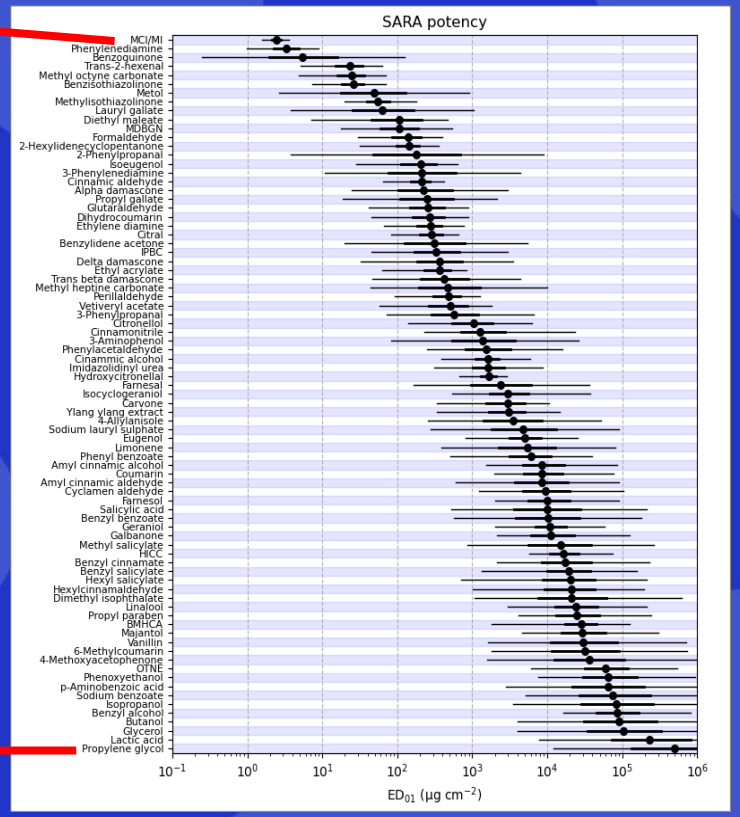
Application of NGRA Framework for skin allergy



Gilmour N *et al,* Regul. Toxicol. Pharmacol., submitted
Reynolds G *et al*, Regul. Toxicol. Pharmacol., submitted

SARA Defined Approach and use of benchmark information

MCI/MI



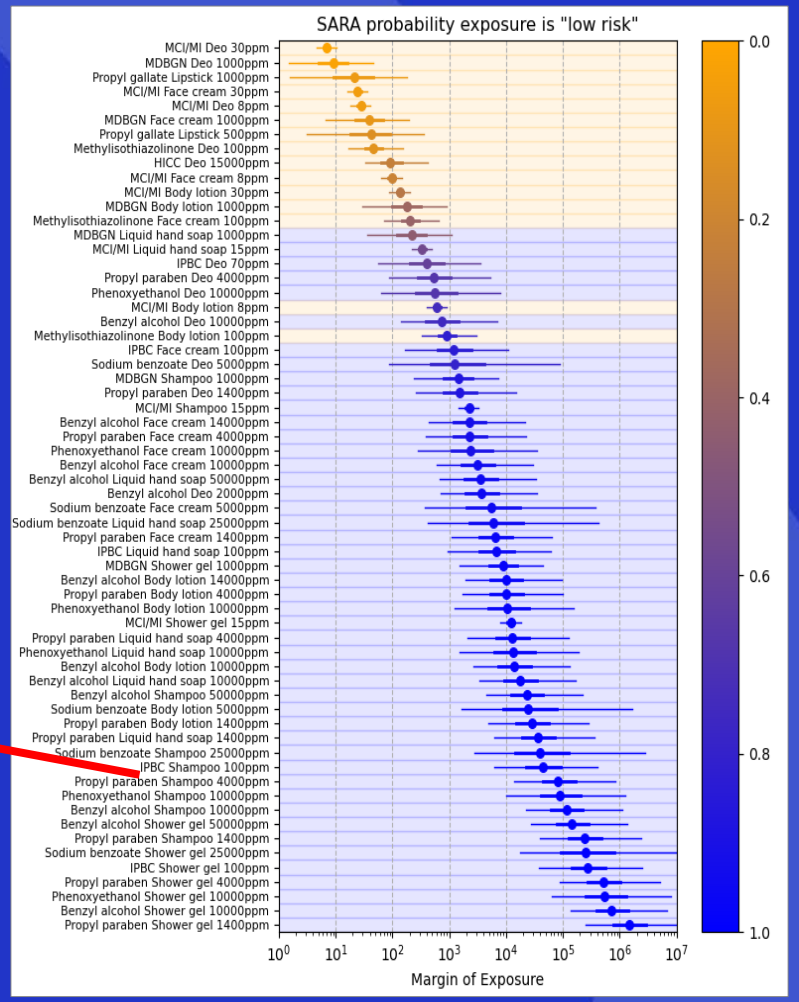
Propylene glycol

Point of departure (PoD) metric calculated: dose with a 1% chance of human skin sensitisation (termed ED01)

Reynolds *et al* (2019) Comp Toxicol, **9**, 36-49

e.g.

IPBC Shampoo 100ppm



Margin of Exposure and probability that exposure is 'low risk'

Gilmour N *et al,* Regul. Toxicol. Pharmacol., submitted
Reynolds J & Gilmour N *et al,* Regul. Toxicol. Pharmacol., submitted
Reynolds G *et al*, Regul. Toxicol. Pharmacol., submitted

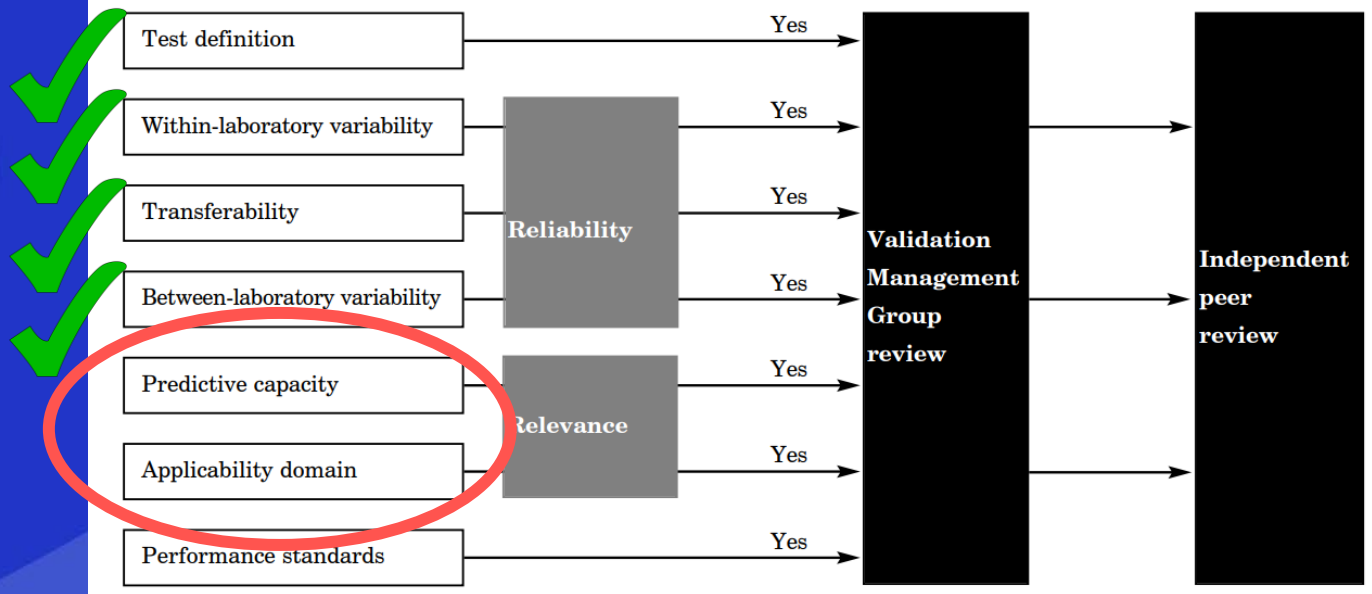
NGRA – Aspects of validation when not trying to predict the results of animal test

- NGRA is exposure-led, hypothesis driven, and requires clear articulation of the risk assessment question
- A tiered approach to decision-making is central to NGRA, use the tools that are as complex as necessary to make the decision. Move to more complex tools if more data is needed
- Progress has been possible with a change in mindset (‘protection not prediction’)
- Science keeps moving – the tools for NGRA decision-making will not remain static. We must ensure that we continue to harness new science and all new exposure and bioactivity tools add value to the decision-making process

NGRA – Aspects of validation when not trying to predict the results of animal test

- Need to ensure quality/robustness of non-standard (non TG) assays and computational approaches used in NGRA (role of GLP, reporting frameworks etc)
- Aspects of reproducibility and transferability are part of standard approaches to validation (e.g. modular approach to validation)

Figure 1: The modular approach for applying the ECVAM principles on test validity



A "yes" indicates that the appropriate information for the module is adequate for entrance into the peer-review process. All seven modules have to be satisfactorily completed, as judged by the Validation Management Group, before a method can enter the peer-review process.

ECVAM = European Centre for the Validation of Alternative Methods.

xref OECD TG428: Skin penetration *in vitro* method

Hartung *et al* (2004) ATLA, **32**, 462-472

NGRA – Thoughts on predictive capacity

- NGRA aims to be protective of human health at defined exposures
  - Prediction models need to include both bioactivity and levels of exposure
  - Evaluation of NGRA needs to be in the context of how to combine (often many different) estimates of exposure and bioactivity to give reproducible decisions on safety with transparent measurement of uncertainty
  - For evaluation of this approach there is a need for
    - Well curated chemical/exposure scenarios that have documented history of safety/ non-safety in humans

    or

    - Chemical/exposure scenarios in humans that are recognised from historical risk assessments as being safe/non-safe

- NGRA does not aim to predict the results of hazard ID tests in animals
  - Therefore prediction models relating to GHS categories etc are inappropriate

- There is a need to increase confidence amongst many risk assessors with the use of mathematical approaches in NGRA used to combined different types of *in vitro* data (PBK modelling, PoD modelling etc)

- A proactive evaluation of MoS derived with NGRA for defined chemical/exposure scenarios will add to the growing information on the degree of protection provided by risk assessments based on human exposure and biology rather than on trying to predict high dose effects in animal

Acknowledgements

Nora Aptula
Maja Alexic
Maria Baltazar
Trina Barritt
Sophie Cable
Paul Carmichael
Richard Cubberley
Tom Cull
Matt Dent
Ellen Edwards
Julia Fentem
Nicola 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
Tom Moxon
Iris Muller
Alexis Nathanail
Beate Nicol
Ruth Pendlington
Sam Piechota
Ramya Rajagopal
Fiona Reynolds
Georgia Reynolds
Joe Reynolds
Annabel Rigarlsford
Paul Russell
Andy Scott
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Sandrine Spriggs
Charlotte Thorpe
Erica Vit
Andy White
Sam Windebank

#UseScienceNotAnimals