Next Generation Risk Assessment
An Industry Perspective

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Unilever

We make many of the world's favourite brands

Our products must be safe

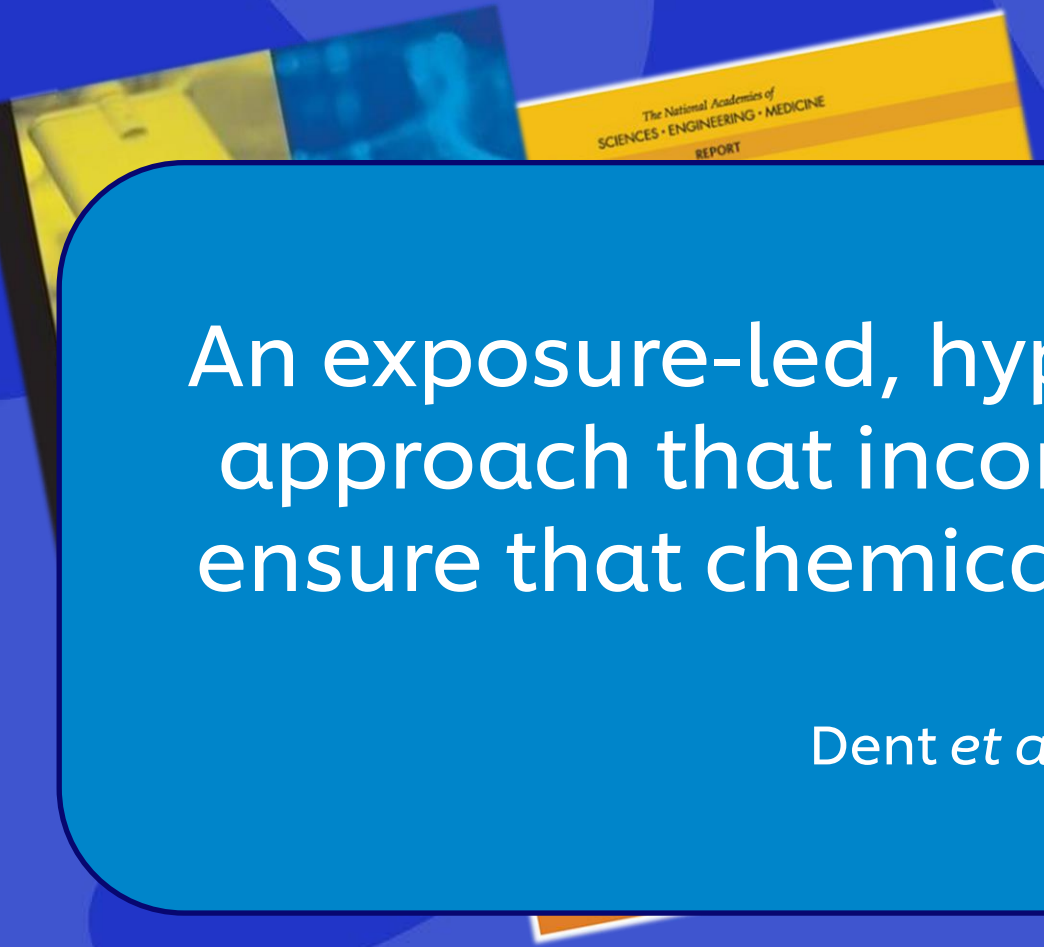
Can we make decisions on these people's safety?

The decisions we make about the safety of our products are for our consumers and workers all around the globe

Making safety decisions without generating data in animals

- Many of our consumers do not want to buy products associated with animal testing
- Many of our brands are ‘PETA-approved’
- Our safety assessments use a variety of non-animal approaches from QSARs/read across and ‘traditional’ in vitro approaches to Next Generation Risk Assessment (NGRA)

What is NGRA?

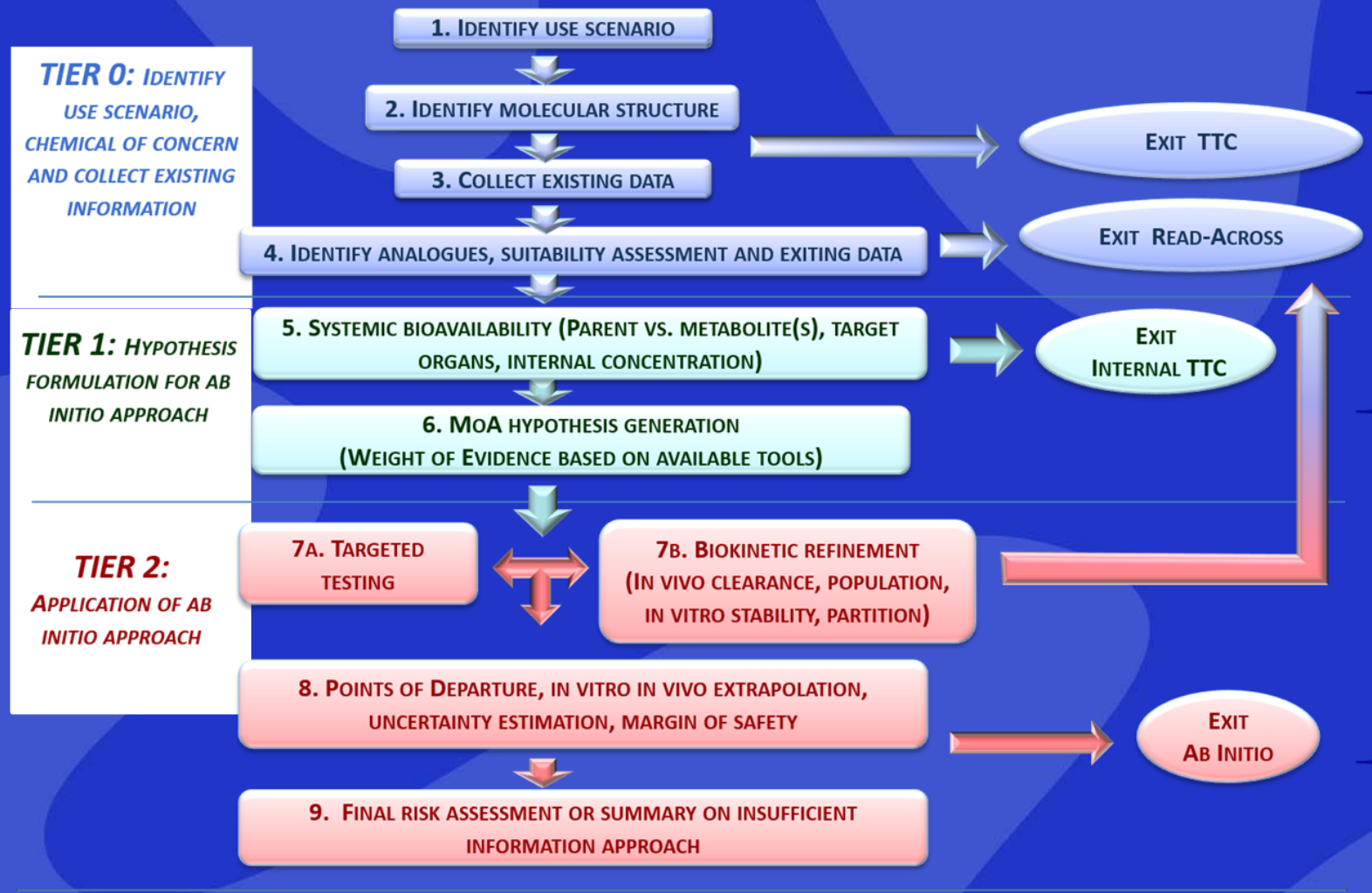


An exposure-led, hypothesis-driven risk assessment approach that incorporates one or more NAM*s to ensure that chemical exposures do not cause harm

Dent *et al* (2018) *Comp Tox* **7**, 20-26

*NAM = New Approach Methodology

Next Generation Risk Assessment (NGRA)



- Read across
- Exposure-based waiving
- *In silico* tools
- Metabolism and metabolite identification
- Physiologically-based kinetic modelling
- *In chemico* assays
- 'Omics
- Reporter gene assays
- *In vitro* pharmacological profiling
- 3D culture systems
- Organ-on-chip
- Pathways modelling
- Human studies

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

Recognition of NGRA in cosmetic safety assessment

Computational Toxicology 7 (2018) 20–26

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

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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 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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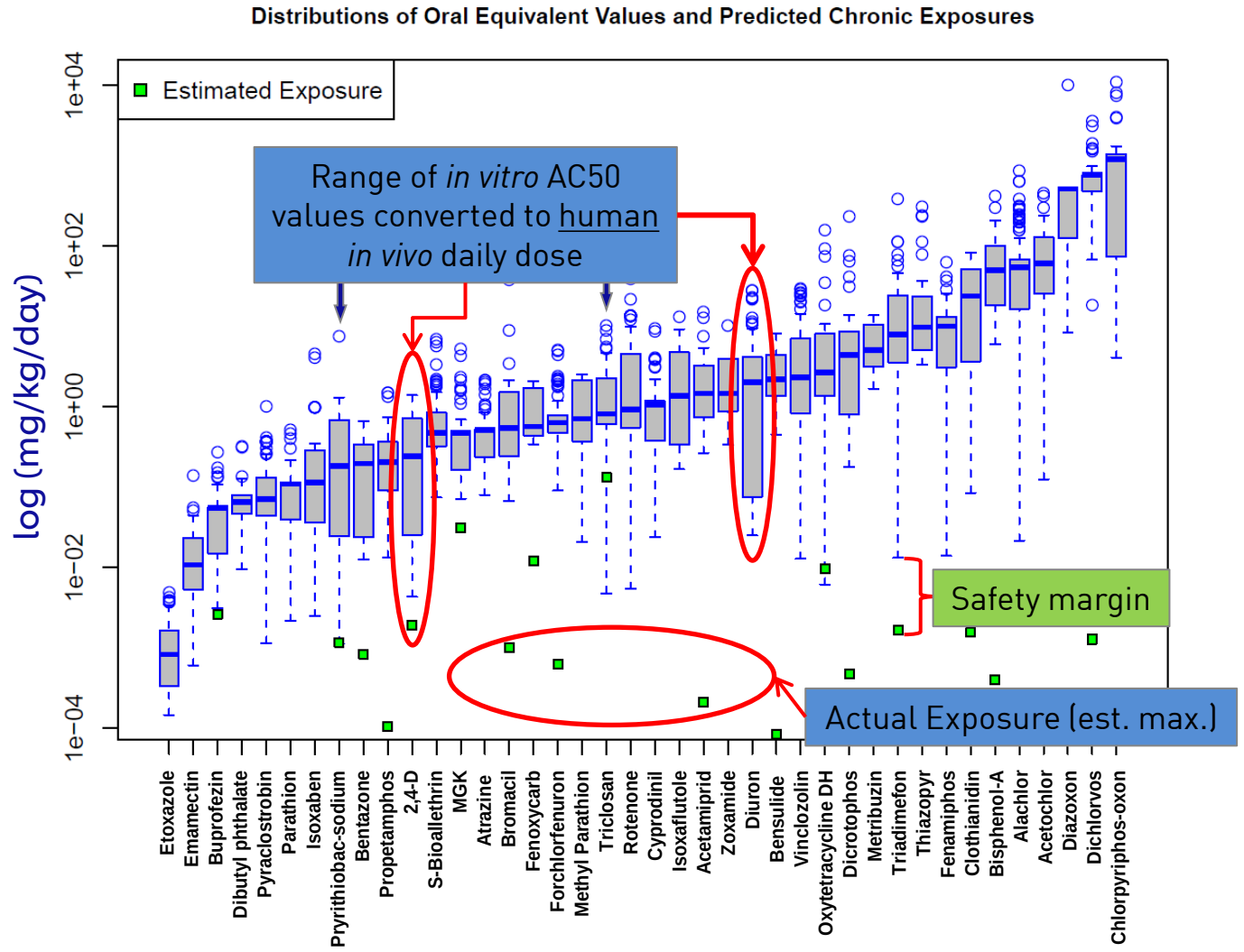
ICCR International Cooperation on Cosmetics Regulation

International Cooperation on Cosmetics Regulation (2018)

European Commission

European Commission: Scientific Committee on Consumer Safety (2021)

A fundamental principle of NGRA: 'Protection not prediction



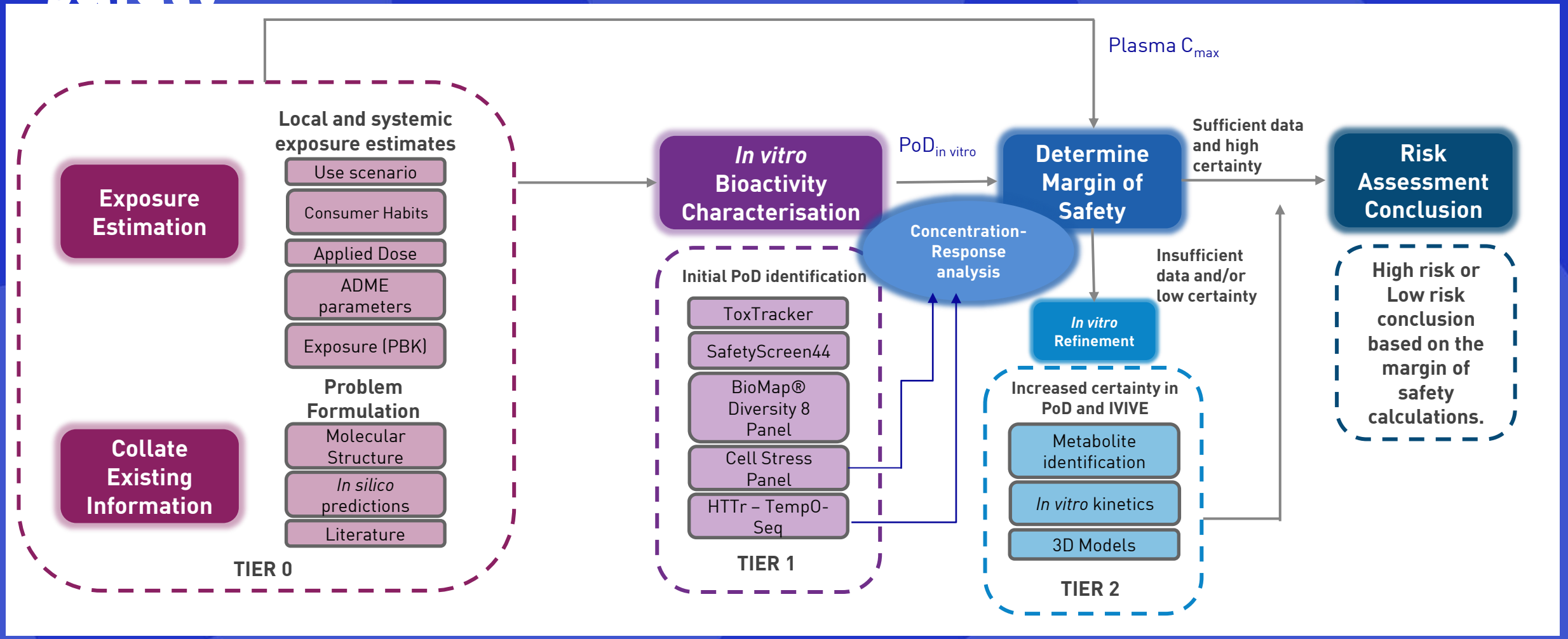
The hypothesis underpinning this type of NGRA is that if there is no bioactivity observed at consumer-relevant concentrations, there can be no adverse health effects.

At no point does NGRA attempt to predict the results of high dose toxicology studies in animals that were first used in the 1960s

NGRA uses new exposure science and understanding of human biology

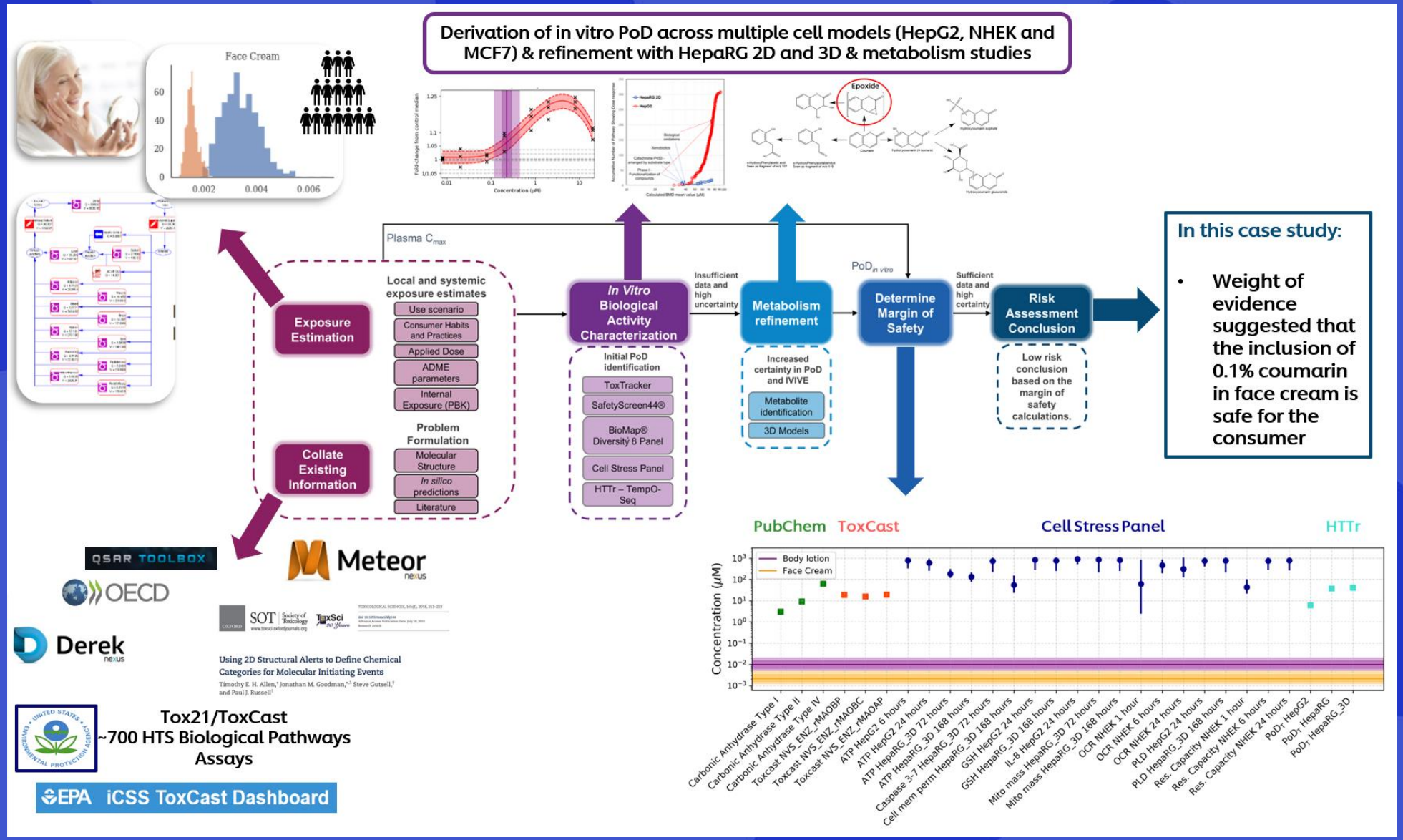
Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological.Sciences , **117**, 348-358

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

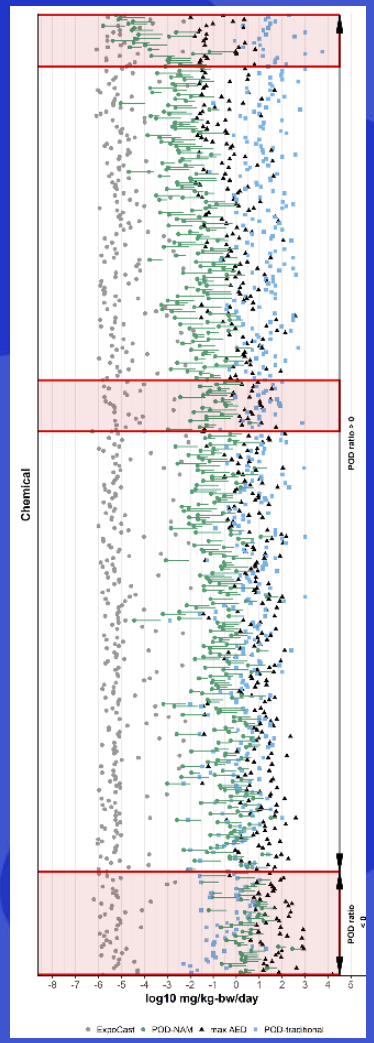
NGRA for risk assessment

Non-animal safety assessments for cosmetics have moved from '*might be possible in theory*' to '*case studies to evaluate*'

- 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
- Importance of characterising uncertainty to allow informed decision-making
- Need to ensure quality/robustness of the non-standard (non-TG) work

The approaches and challenges are not cosmetic-specific, how can different sectors learn together?

USE OF THE SAME APPROACHES FOR CHEMICALS REGISTRATION?



OXFORD
SOT Society of Toxicology
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Tox Spotlight article

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Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

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APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

"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

USE OF THE SAME APPROACHES FOR CHEMICALS REGISTRATION?

"Today's memo directs the agency to aggressively reduce animal testing, including reducing mammal study requests and funding 30% by 2025 and completely eliminating them by 2035"

EPA Administrator, 2019

Speaking at an 18 May virtual forum organised by the Green Chemistry and Commerce Council (GC3), Dr Hansen said we're currently 40 years away from being able to effectively predict toxicity of chemicals, but with focused investment and regulatory needs driving the work, this could be reduced to 20 years.

ECHA, Executive Director, 2021

What is needed to accelerate the uptake of NAMs and the principles of NGRA for use in the EU Chemicals Regulation?

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