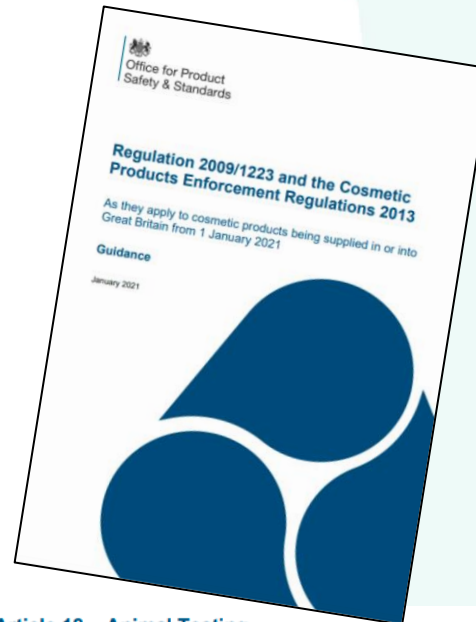


Considering worker and consumer safety

Carl Westmoreland

17th March 2022

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



Global Animal Test Policy

Article 18 – Animal Testing

74 Cosmetic products are not permitted on the GB market if the product's ingredients, combination of ingredients or final formulation have been the subject of animal testing used to prove their safety for the purposes of this Regulation. However, historic animal testing data from animal testing that took place before such testing was banned at EU level may still be used in order to meet the requirements of the Regulation.

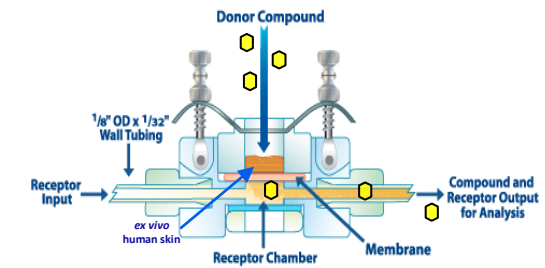
Assuring consumer safety without animal testing: Maximising use of existing information and non-animal approaches

- All our risk assessments are exposure-led

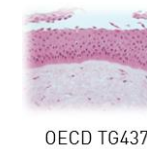


Table 2: Estimated daily exposure levels for different cosmetic product types according to Cosmetics Europe data (SCCNFP/0321/00; Hall et al., 2007, 2011).

Product type	Estimated daily amount applied	Relative amount applied (mg/kg bw/d)	Retention factor ¹	Calculated daily exposure (µg/d)	Calculated relative daily exposure (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67 g	279.20	0.01	0.19	2.79
Hand wash soap ²	20.00 g	-	0.01	0.20 ³	3.33
Hair care					
Shampoo	10.46 g	150.49	0.01	0.11	1.51
Hair conditioner ²	3.92 g	-	0.01	0.04	0.60
Hair styling products	4.00 g	57.40	0.1	0.40	5.74



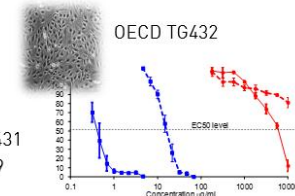
- Use all available safety data on the ingredient
 - Clinical, epidemiological, animal (if dates permit), *in vitro* etc
- Exposure-based waiving approaches (e.g. TTC, DST, Inhalation TTC)
- in silico* predictions
- History of safe use
- Read across
- Use of existing OECD *in vitro* approaches
- Next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



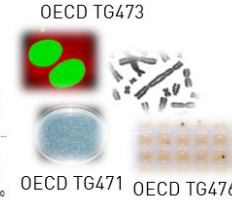
OECD TG437



OECD TG430/431
OECD TG439



OECD TG432



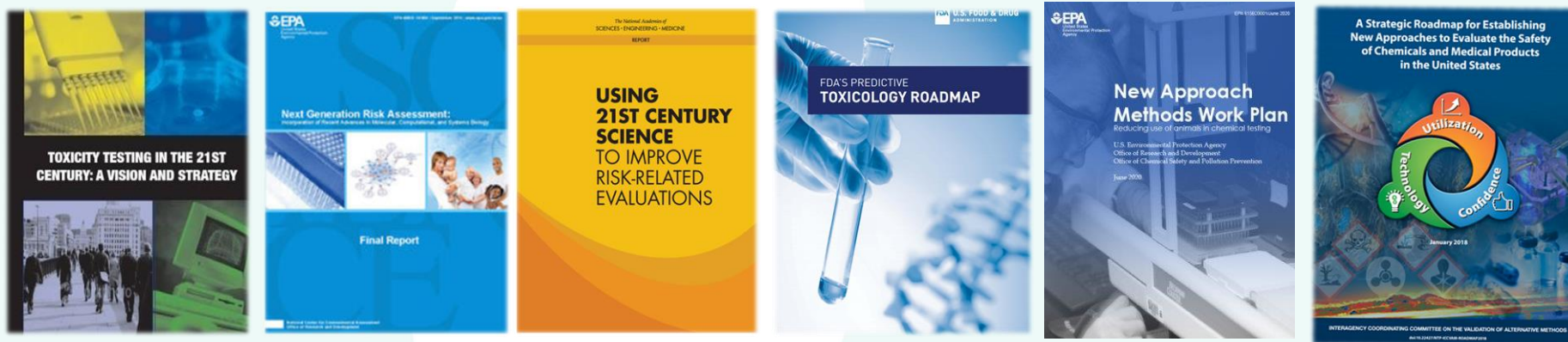
OECD TG473

OECD TG471

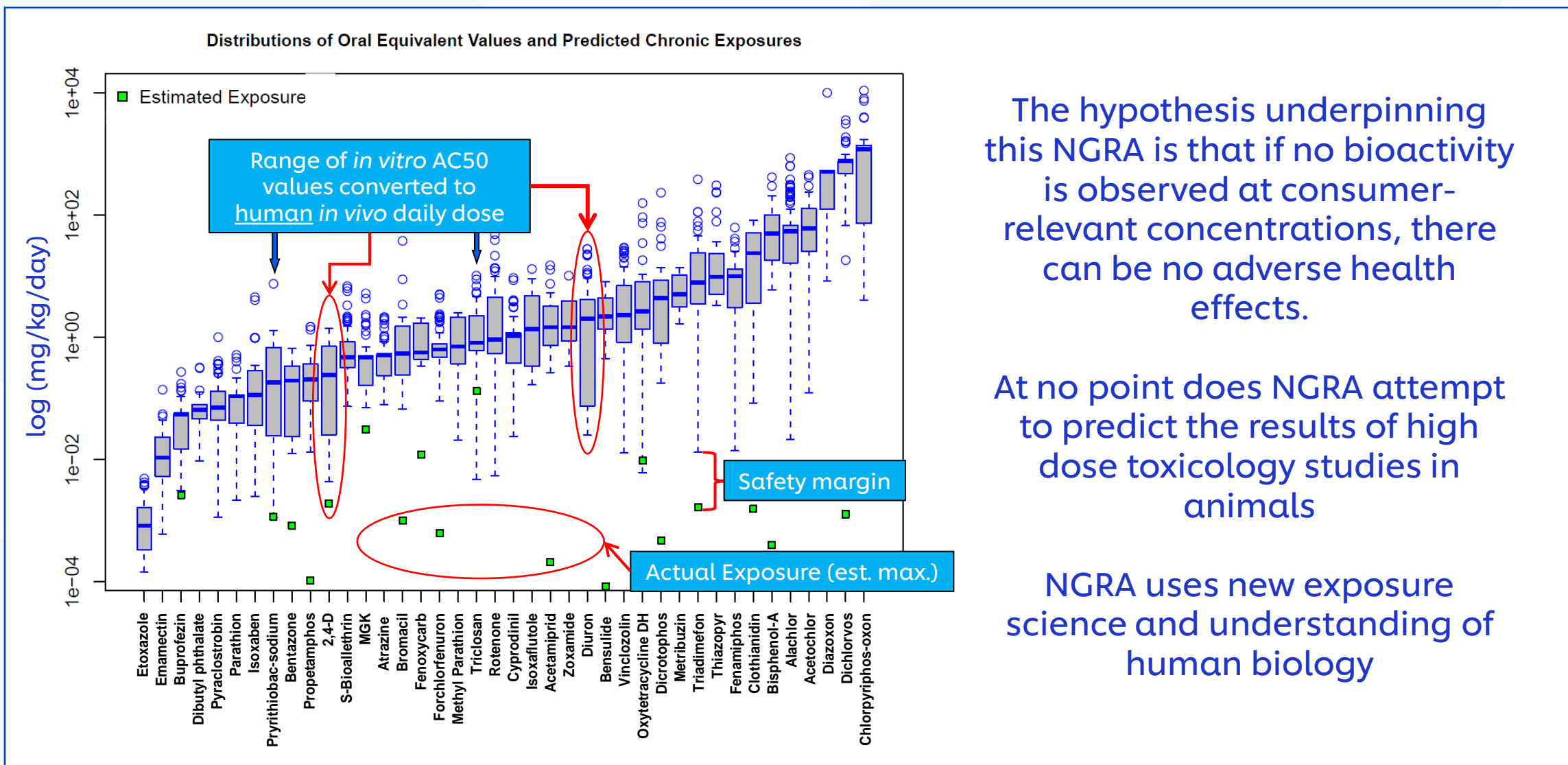
OECD TG476

Next Generation Risk Assessment (NGRA)

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



NGRA: Protection not prediction



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

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

NGRA uses new exposure science and understanding of human biology



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

Computational Toxicology 7 (2018) 20–26

Contents lists available at ScienceDirect

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Computational Toxicology

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

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

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ⁿ Cosmetics Europe, Avenue Herrmann Debrux 40, 1160 Auderghem, Belgium
^o Health Canada (HC), Consumer Product Safety Directorate, Healthy Environments and Consumer Safety Branch, 369 Laurier Ave. W., Ottawa, ON K1A 0K9, Canada
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ARTICLE INFO

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



International Cooperation on Cosmetics Regulation (2018)



European Commission: Scientific Committee on Consumer Safety (2021)

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

in Consumer Safety
in 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/0533/02).

3-4.1 NEW APPROACH METHODOLOGY (NAM) AND NEXT-GENERATION RISK ASSESSMENT (NGRA)

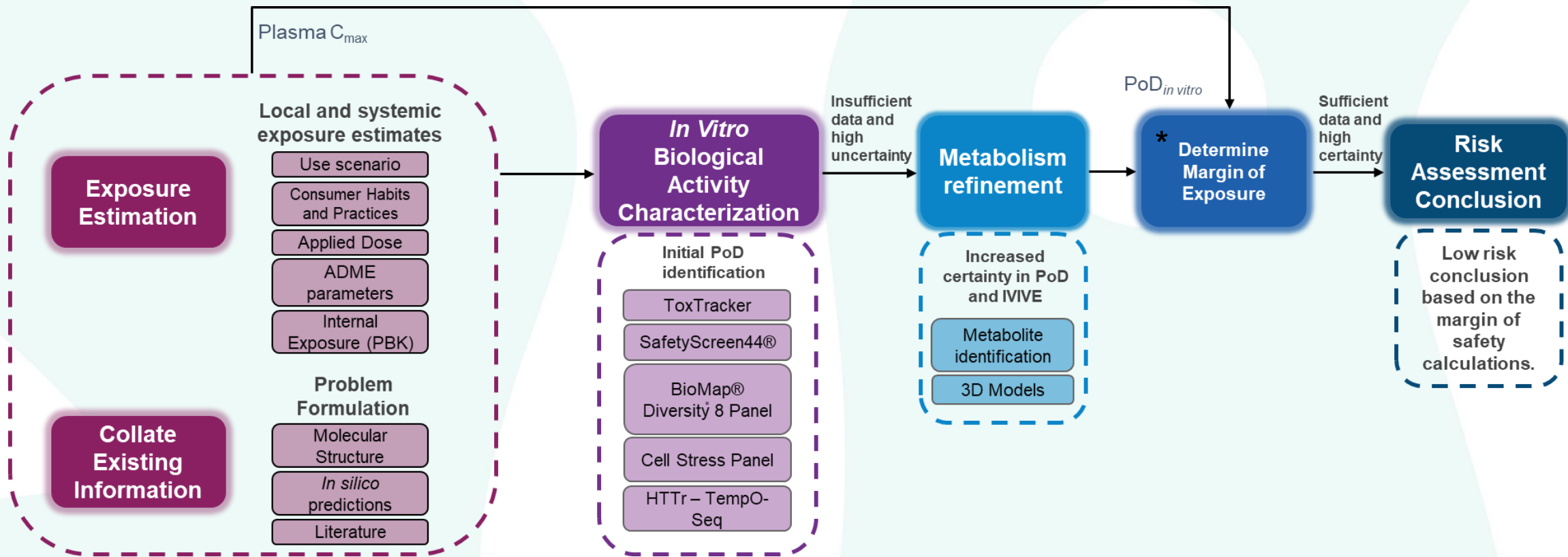
Whereas the terminology of "Alternative Test Methods (ATMs)" does not cover all available tools e.g., *in silico* methodology, the more general term, New Approach Methodology (NAM) has been introduced. As for cosmetics and their ingredients, testing and marketing bans apply with respect to animal use 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. Threshold of Toxicological Concern (TTC) and internal TTC (iTTC) approaches as a risk assessment tools are described in 3-5.2.

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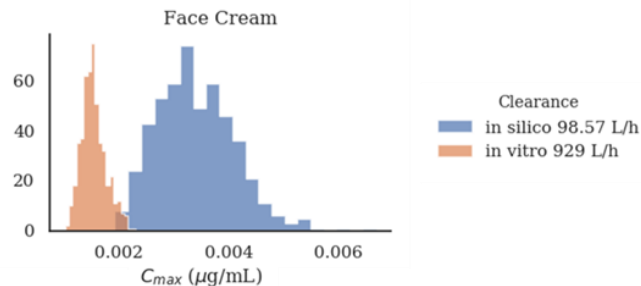
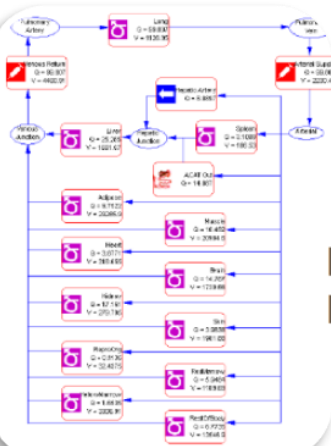


NGRA: case study workflow for systemic effects



Key tools in our NGRA approach for systemic effects

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 Brown, Andrew J. Brown, Jacques Hamon, Wolfgang Juratnik, Arun Sridhar, Gareth Waldron and Steven Whitehead

Abstract: *In vitro* pharmacological profiling is increasingly being used earlier in the drug discovery process to identify undesirable off-target activity profiles that could hinder or halt the development of candidate drugs or even lead to market withdrawal if discovered after a drug is approved. Here, for the first time, the rationale, strategies and methodologies for *in vitro* pharmacological profiling at four major pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Novartis and Pfizer) are presented and illustrated with examples of their impact on the drug discovery process. We hope that this will enable other companies and academic institutions to benefit from this knowledge and consider joining us in our collaborative knowledge sharing.

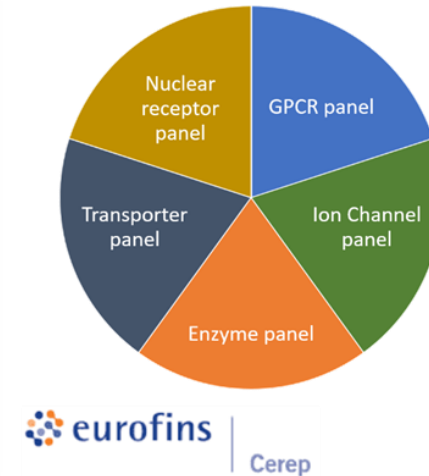
Decreasing the high attrition rate in the drug discovery and development process is a primary goal of the pharmaceutical industry. One of the main challenges in achieving this goal is striking an appropriate balance between drug efficacy and potential adverse effects as early as possible in order to reduce safety-related attrition, particularly in the more expensive late stages of clinical development. Gaining better understanding of the safety profile of drug candidates early in the process is also crucial for reducing the likelihood of safety issues leading to the withdrawal of approved drugs, or even leading to their market withdrawal, having to incur the associated substantial and irreversible costs.

target (or targets), whose secondary effects are due to interactions with targets other than the primary target (or targets) that is off-target interactions. Off-target interactions are often the cause of ADRs in animal models or clinical studies, and so careful characterization and identification of secondary pharmacology profiles of drug candidates early in the drug discovery process might help to reduce the incidence of type A ADRs.

In vitro pharmacological profiling involves the screening of compounds against a broad range of targets (receptors, ion channels, enzymes and transporters) that are distinct from the intended

safety testing of drug candidates and are designed to prevent serious ADRs from occurring in clinical studies. The *in vitro* pharmacology assay that is absolutely required by regulatory authorities is that measures the effects of new chemical entities on the ion channel of hERG (hERG1) or hERG2 (hERG2), also known as KCNH2. The mechanism by which blockade of hERG can elicit potentially fatal cardiac arrhythmias (torsades de pointes) following a prolongation of the QT interval is well characterized^{1,2}, and the seriousness of this ADR is one reason why this assay is a mandatory regulatory requirement. Receptor binding studies are also recommended as the first tier approach for the assessment of the dependence potential of novel chemical entities³. However, current regulatory guidance does not describe which targets should constitute an *in vitro* pharmacological profiling panel and does not indicate at what stage of the discovery process in which *in vitro* pharmacological profiling should occur. Nevertheless, the general need for most pharmaceutical companies to perform this testing early in drug discovery to reduce attrition and to facilitate better prediction of ADRs in the later stages of drug discovery and development.

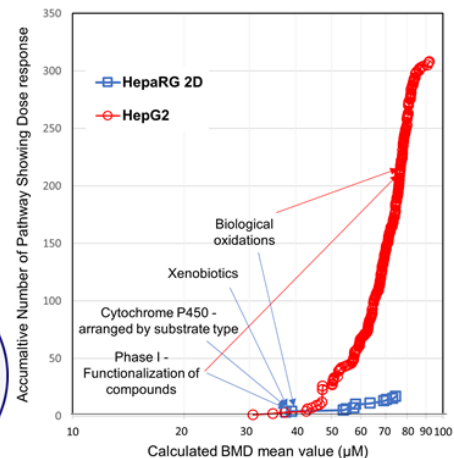
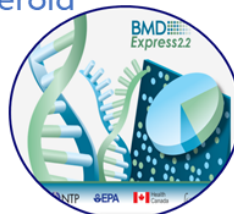
Here, for the first time, four major pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Novartis and Pfizer) share their knowledge and experience of the innovative application of existing screening technologies to detect off-target interactions of compounds. The objective of this article is to describe the rationale and main strategies for the use of *in vitro* pharmacological profiling to discuss their products and to



Transcriptomics

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

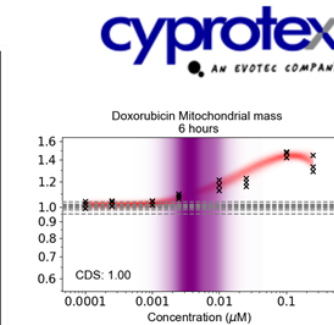
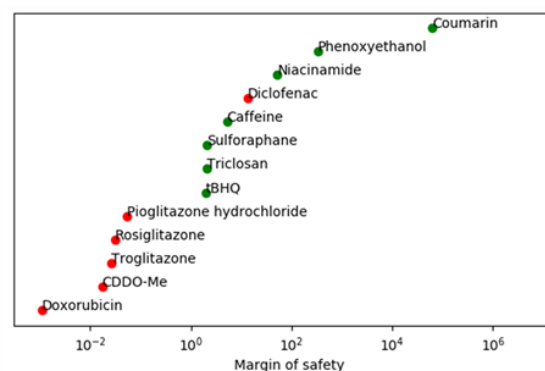
BMDexpress 2



Cellular Stress Pathways

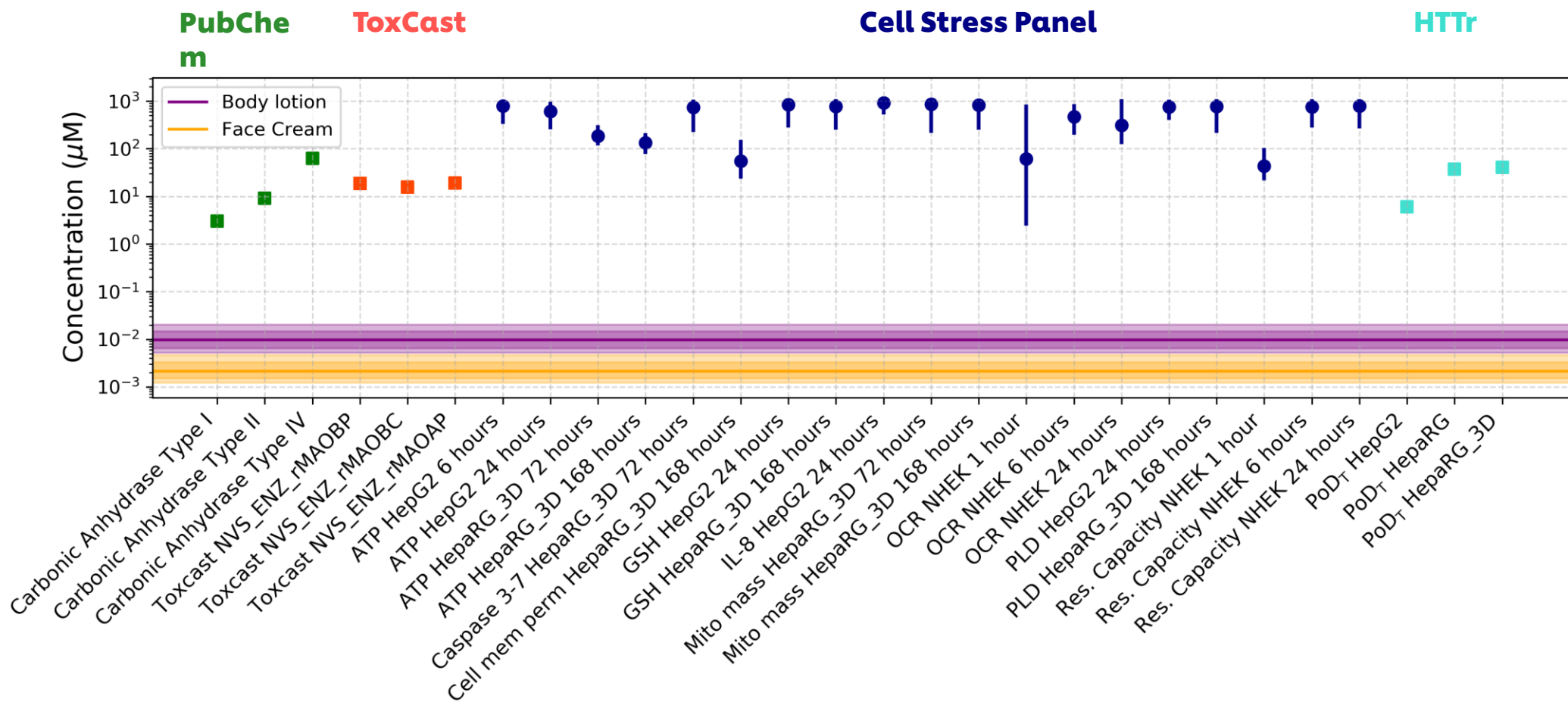
13 chemicals, 36 Biomarkers; 3 Timepoints; 8 Concentrations; ~10 Stress Pathways

- Exposure scenario adopted for chemical is 'low risk'** (from consumer goods perspective)
- Niacinamide (food, cosmetics)
 - Caffeine (beverages, cosmetics)
 - Phenoxethanol (cosmetics)
 - Sulfonaphane (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)



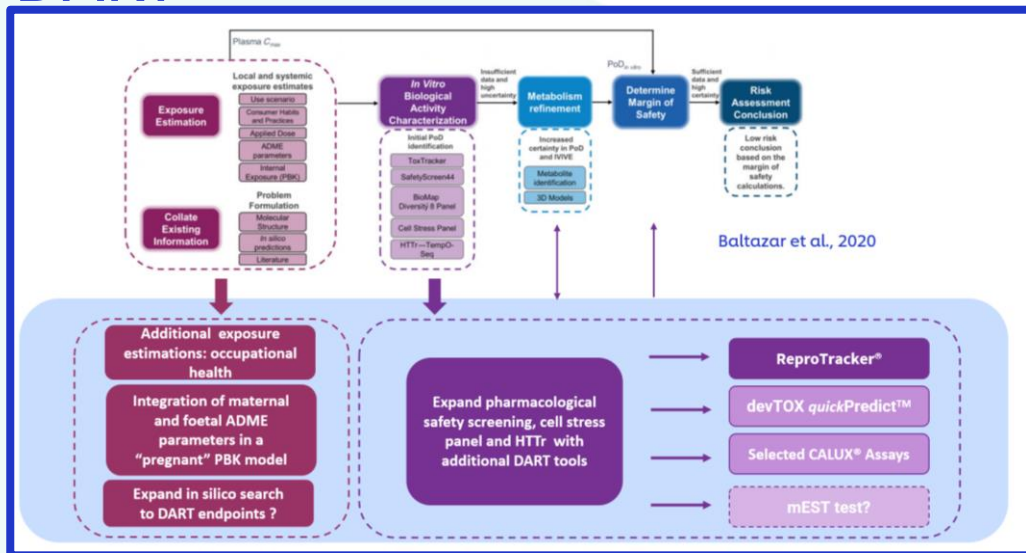
Toxicol Sci (2020), 176, 11-33

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

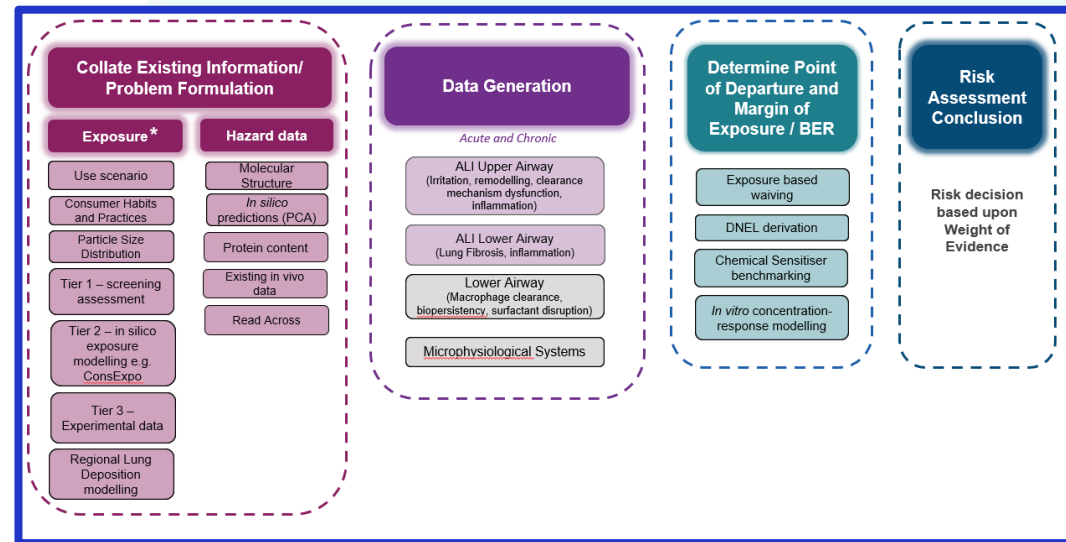


Other NGRA approaches for human health

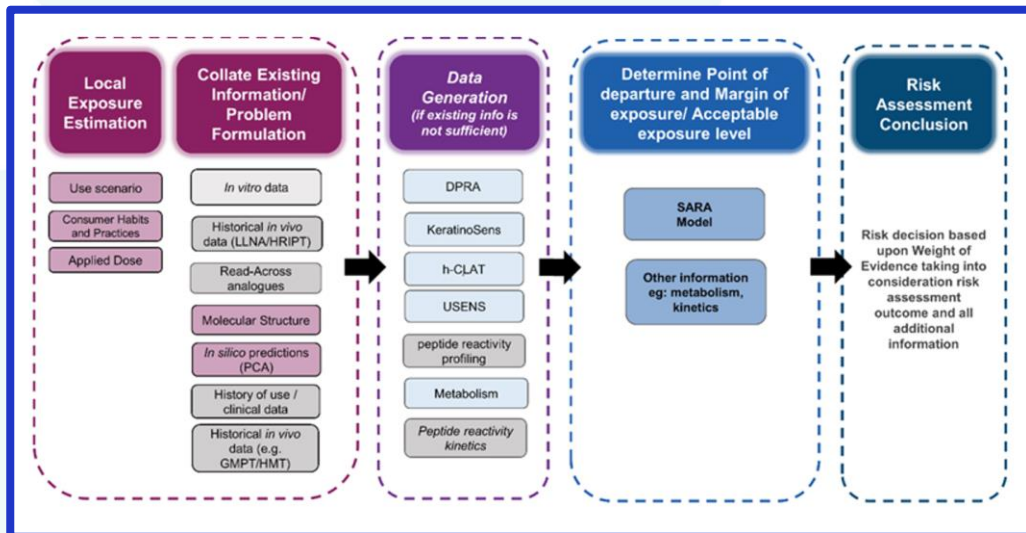
DART



Inhalation



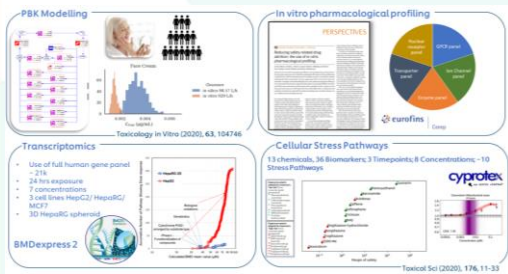
Skin Sensitisation



Why can non-animal science be accepted for consumer safety, but not for worker safety?*

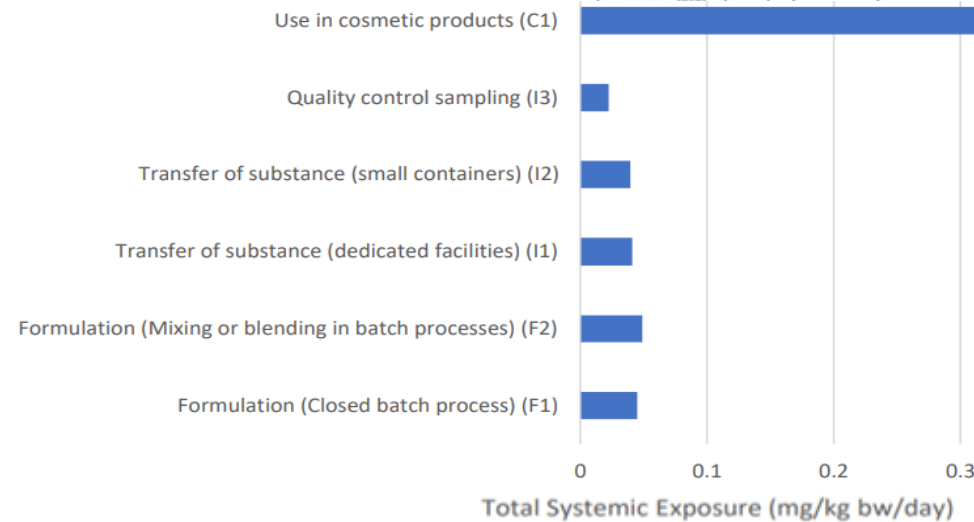
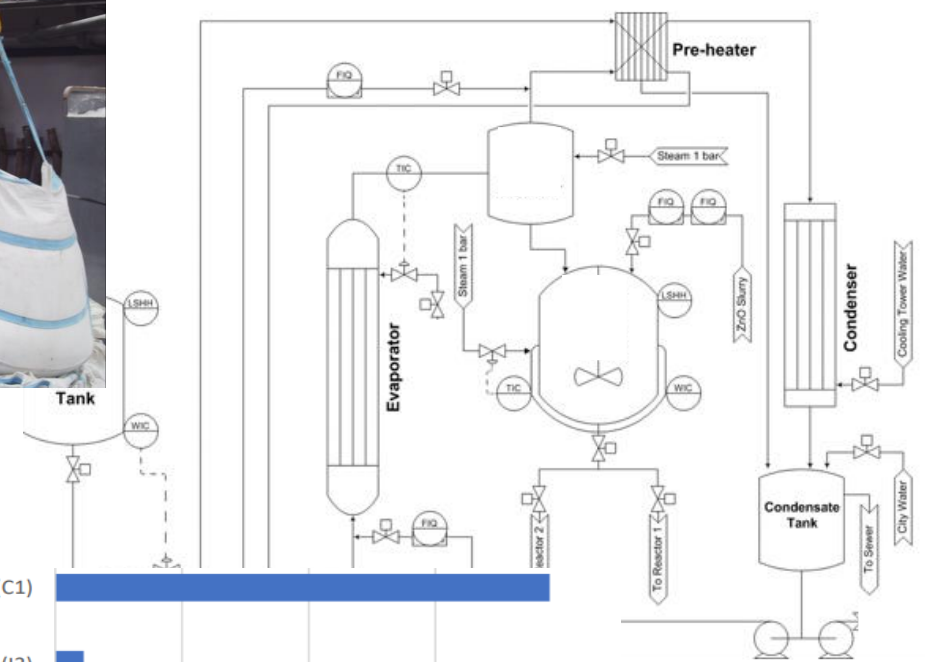
- Understanding worker exposure
 - Routes
 - Levels of exposure
 - Factory automation procedures, containment measures, local extract ventilation, PPE
- NGRA for worker safety
 - BER approach for worker exposure
 - Potentially different PBK models for worker exposure
 - Same biological data on ingredients

Cosmetic-Only Ingredients



CONSUMER SAFETY

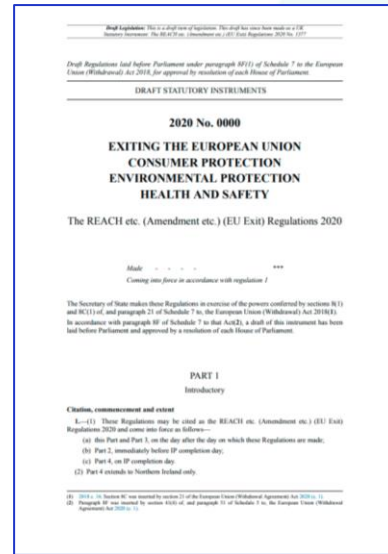
WORKER SAFETY



Recognising NAMs in Chemical Registration: What needs to happen?



Scientific Committee on Consumer Safety (2021)



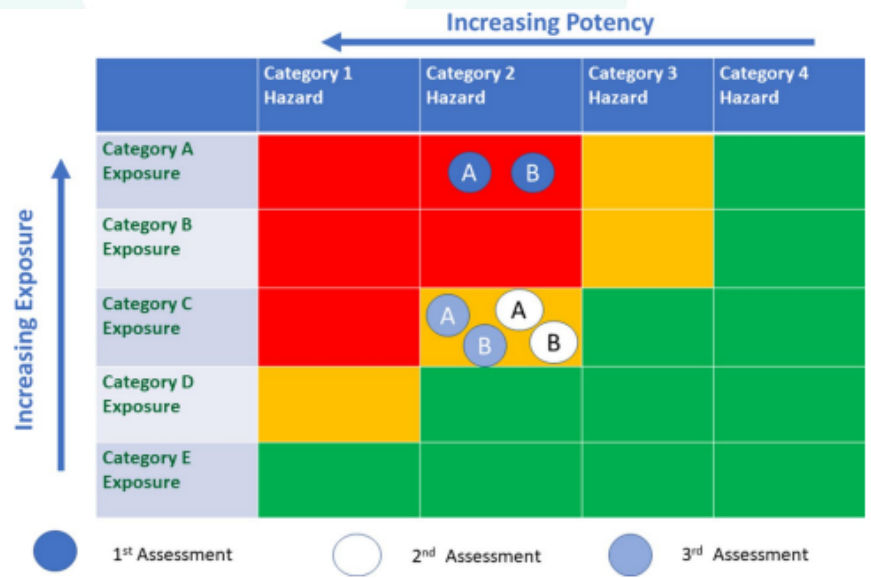
Tiered, iterative approach for hazard and exposure

Hazard
In silico
In vitro
In vivo

Exposure
TTC

Limit doses

(animal testing is transparently 'a last resort')



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