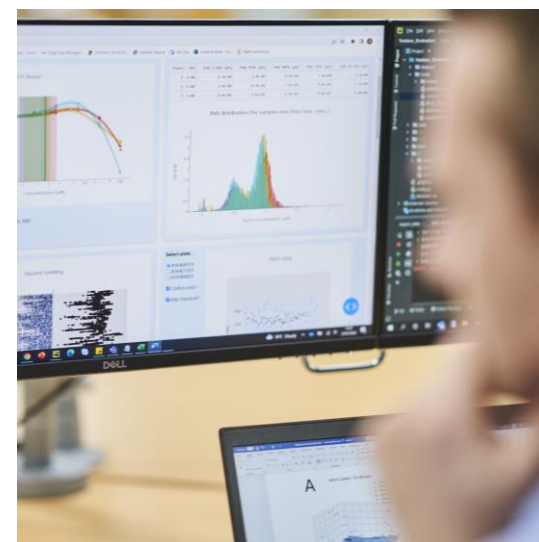
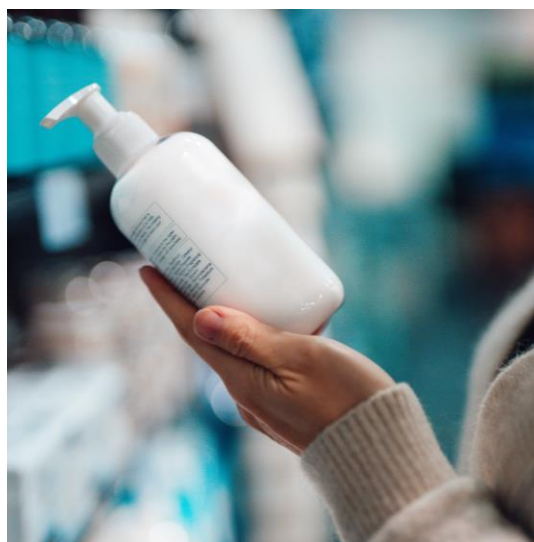


Current Progress with NAMs in Next Generation Risk Assessment (NGRA) and opportunities in chemical registration

Carl Westmoreland



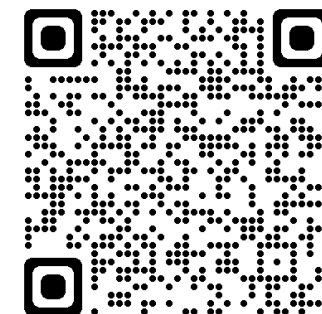
Unilever's Safety & Environmental Assurance Centre (SEAC)

Our purpose: to **protect people & the environment**

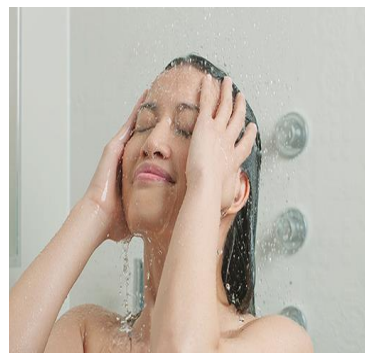
Around the world, 3.4 billion people use a Unilever product every day. **We want our consumers to be confident that our products are safe.**

In collaboration with our partners, SEAC scientists help ensure **Unilever's innovations are safe & sustainable without animal testing.**

We engage with all stakeholders to build shared understanding and promote trust in **our scientific evidence-based approach to decision-making.**



All Unilever products must be safe for humans and the environment



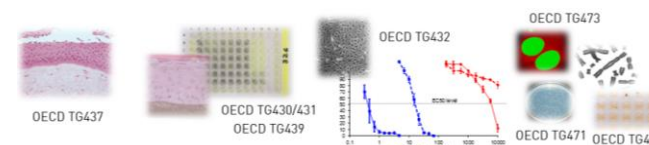
Assuring safety without animal testing: Maximising use of existing information and non-animal approaches

EXPOSURE

- All risk assessments start by understanding levels of consumer exposure

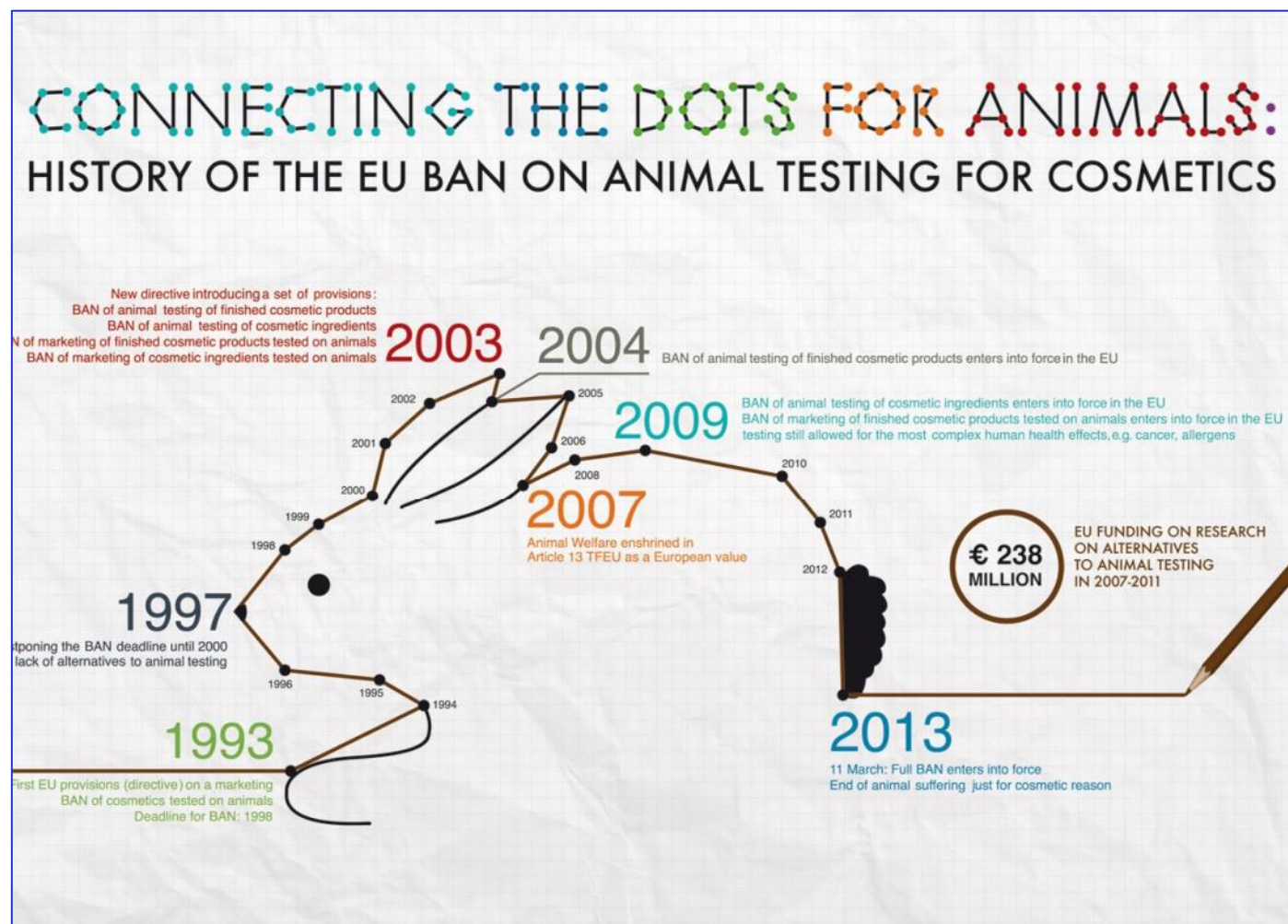
INGREDIENT-SPECIFIC BIOACTIVITY DATA

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



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

>10 years of assuring safety without animal testing



What is next generation risk assessment (NGRA)?

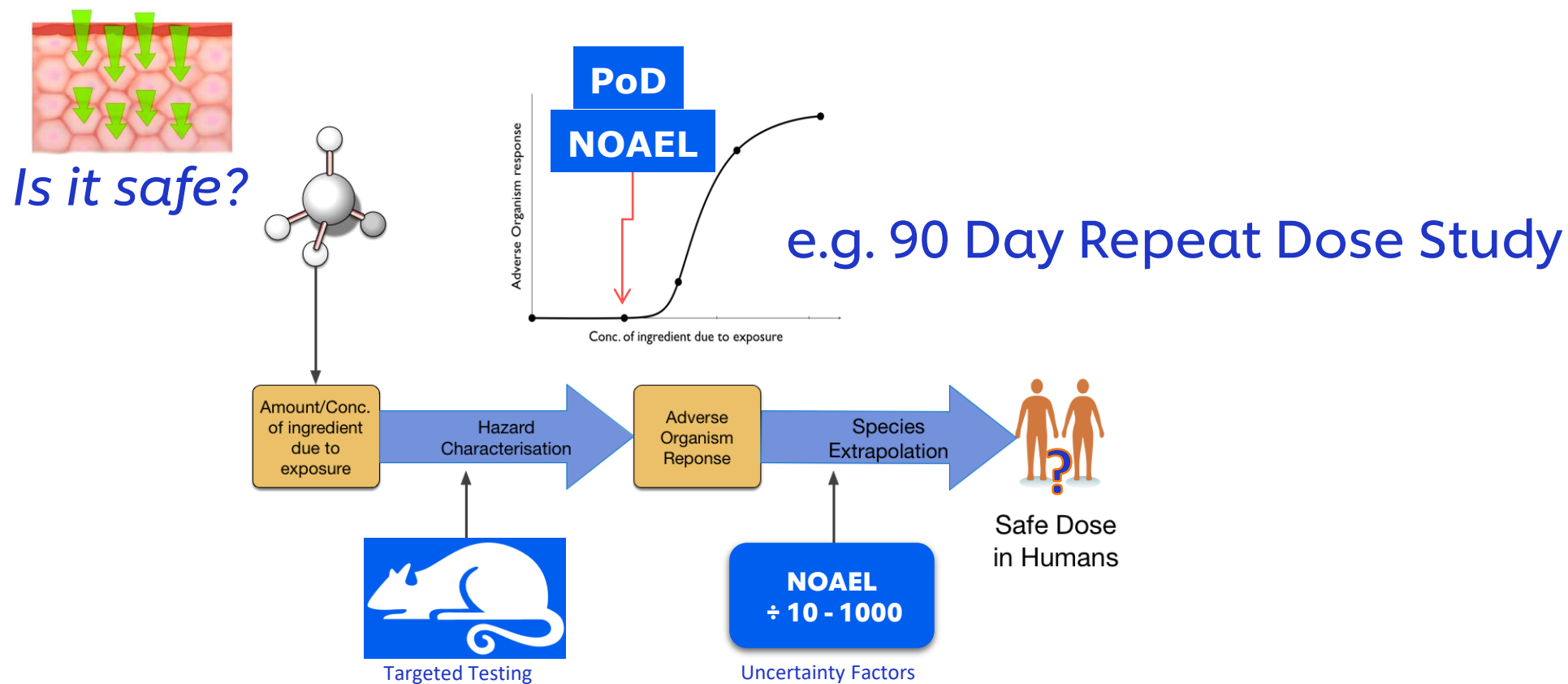


What is next generation risk assessment (NGRA)?

“An exposure-led, hypothesis driven risk assessment approach that incorporates one or more NAMs to ensure that chemical exposures do not cause harm to consumers”

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

Why is NGRA important? The Systemic Challenge

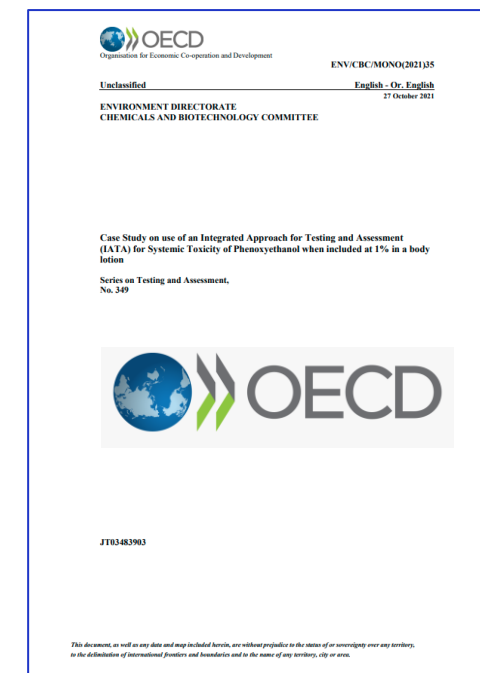
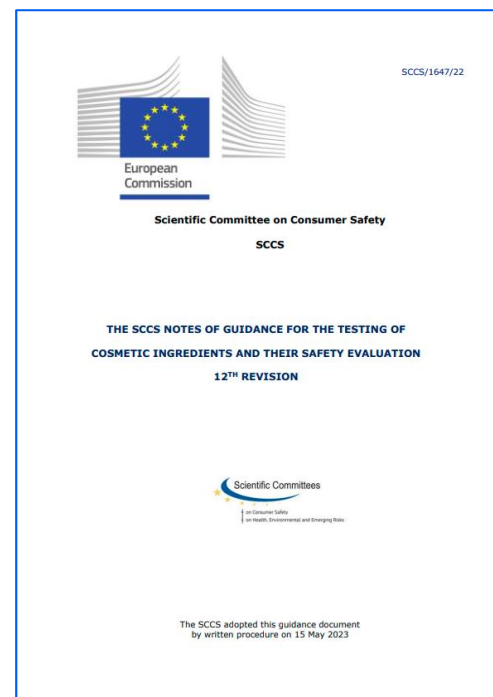


A new non-animal paradigm is needed...

...but replacement of animal test data is not the answer

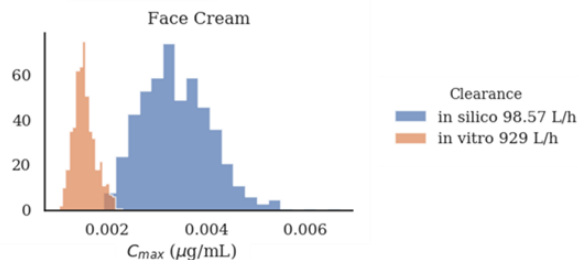
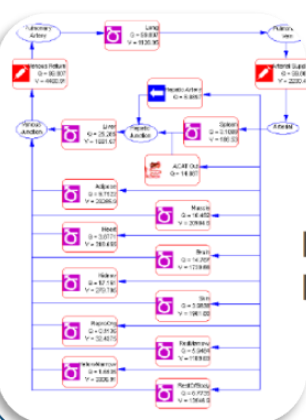
Tiered, exposure-led NGRA means we can make robust safety decisions

- Increasing recognition that *in vitro* bioactivity can inform decision making (e.g. Health Canada, EU SCCS)



Key tools in our NGRA approaches for Systemic Toxicity: Exposure and Bioactivity (First Tier Tools)

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 Blower, Andrew J. Blower, Jacques Hamon, Wolfgang Junold, Anur Srivastava, Gareth Wadsworth and Steven Whitebread

Abstract | *In vitro* pharmacological profiling is increasingly being used earlier in the drug discovery process to identify predictable 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 (Amgen, 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 in our collaborative knowledge sharing.

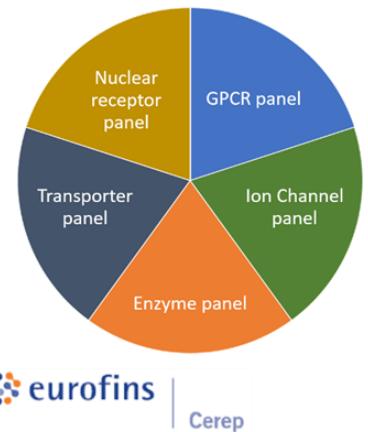
Decreasing the high attrition rate in the drug discovery process is a primary goal of the pharmaceutical industry. One of the main challenges in achieving this goal is striking an appropriate balance between drug efficacy and potential adverse effects. It is early possible to reduce safety-related attrition, particularly in the later stages of drug development. Gaining a 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 drugs, or even leading to their market withdrawal, having the potential to reduce attrition and enhance the success of drug candidates.

target (or targets), whereas 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 adverse effects in clinical studies, and so careful characterisation 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 adverse effects from occurring in clinical studies. The only *in vitro* pharmacology assay that is absolutely required by regulatory authorities to test the effects of new chemical entities on the basic contractile force of smooth muscle is the rat aortic strip assay. This assay is also recommended as a mandatory regulatory requirement. Except for binding studies, *in vitro* pharmacological profiling should occur throughout the general level for most pharmaceutical companies to prevent 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.

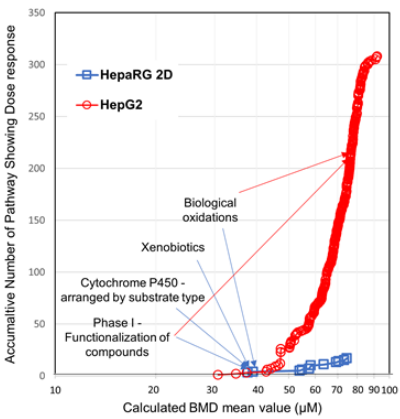
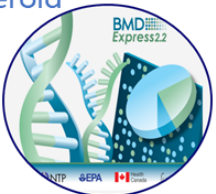
Here, for the first time, four major pharmaceutical companies (Amgen, GlaxoSmithKline, Novartis and Pfizer) share their knowledge and experiences of the innovative application of existing screening technologies to detect off-target interactions of compounds. The objective of this article is to describe the rationale and main advantages for the use of *in vitro* pharmacology in drug discovery and to illustrate how this can be applied to reduce attrition and to



Transcriptomics

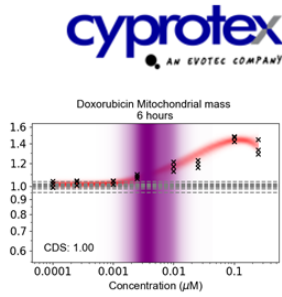
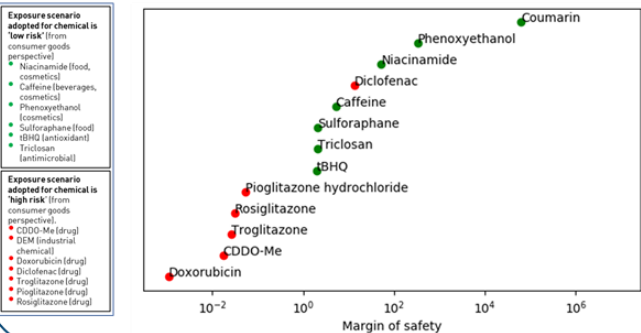
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDexpress 2



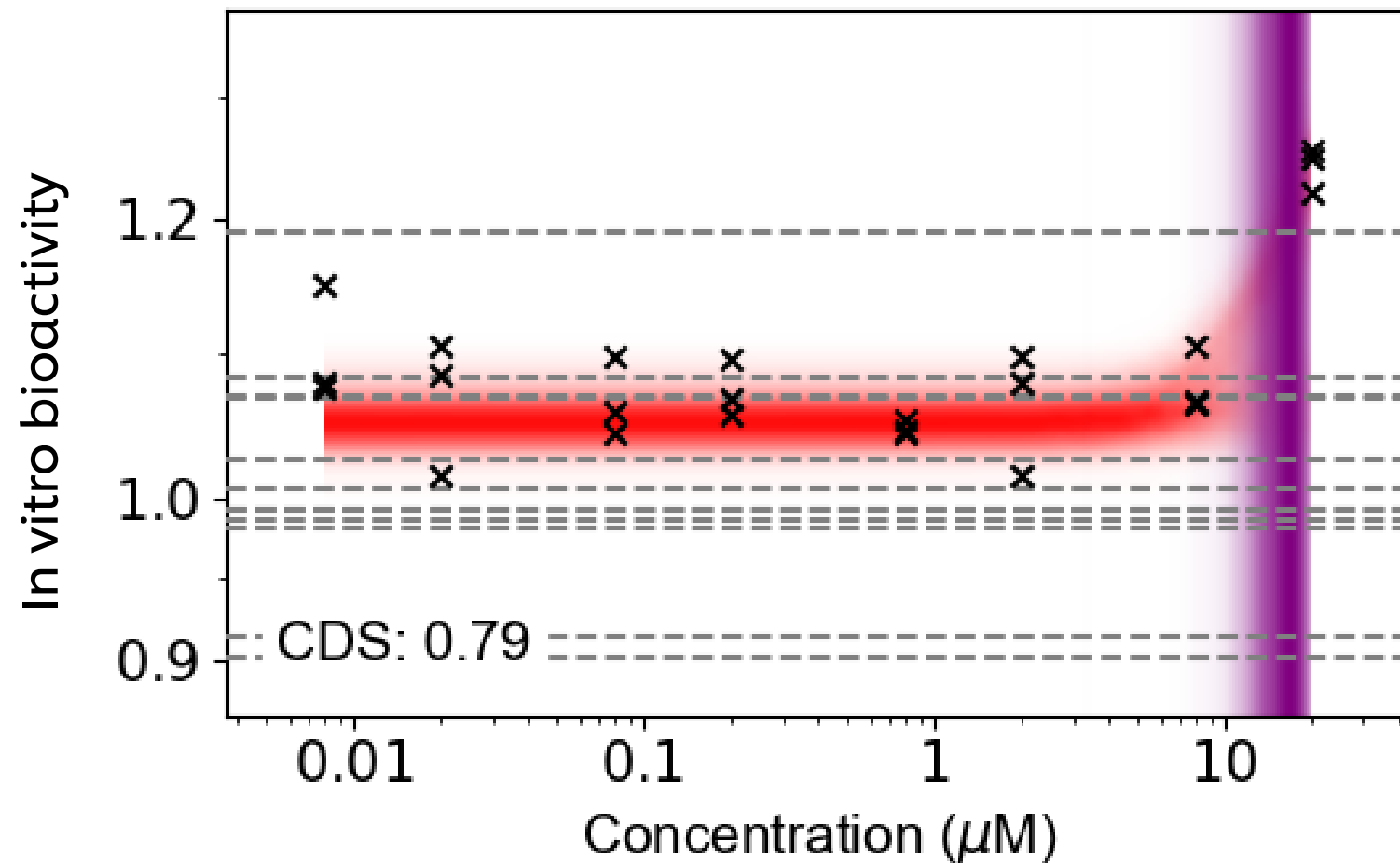
Cellular Stress Pathways

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

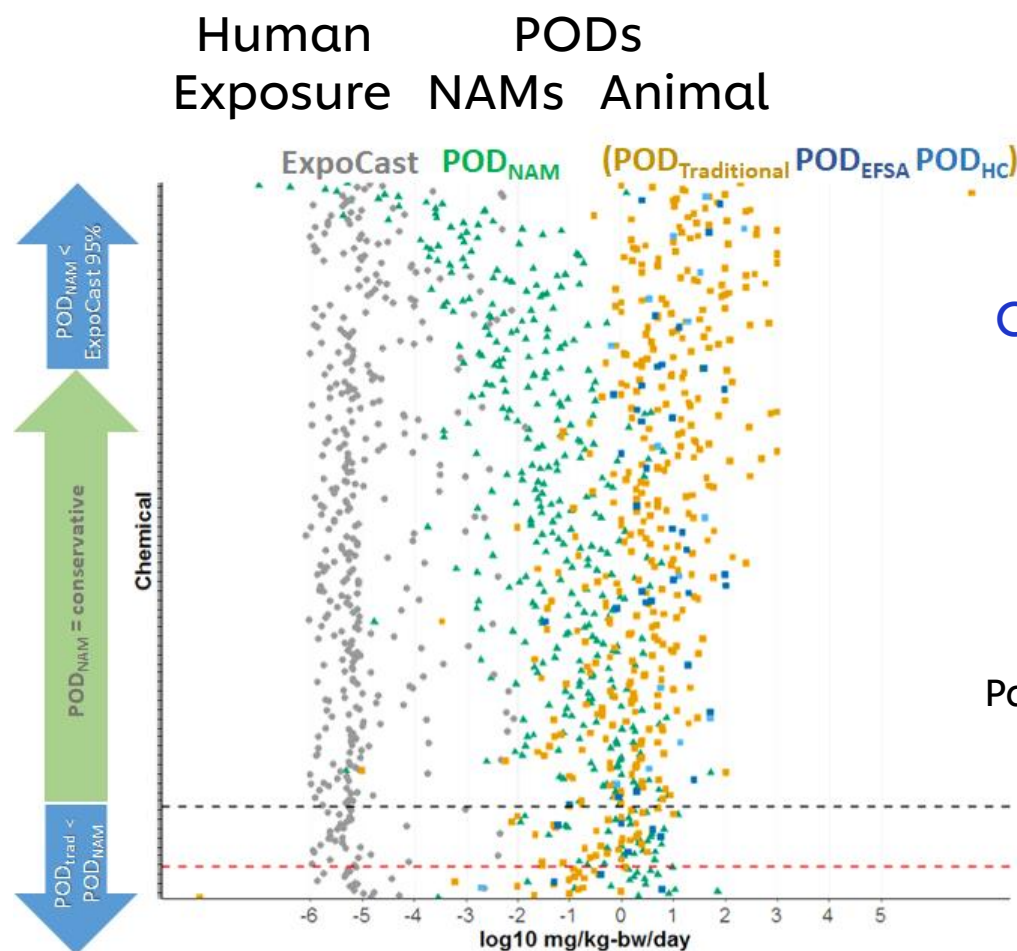


Toxicol Sci (2020), 176, 11-33

Point of Departure (POD)



Points of Departure (PODs) from NAMs can be protective



Case Studies Demonstrating Application of Bioactivity as a Protective POD

Paul-Friedman et al., 2020. *Toxicol. Sci* **173**, 202-225

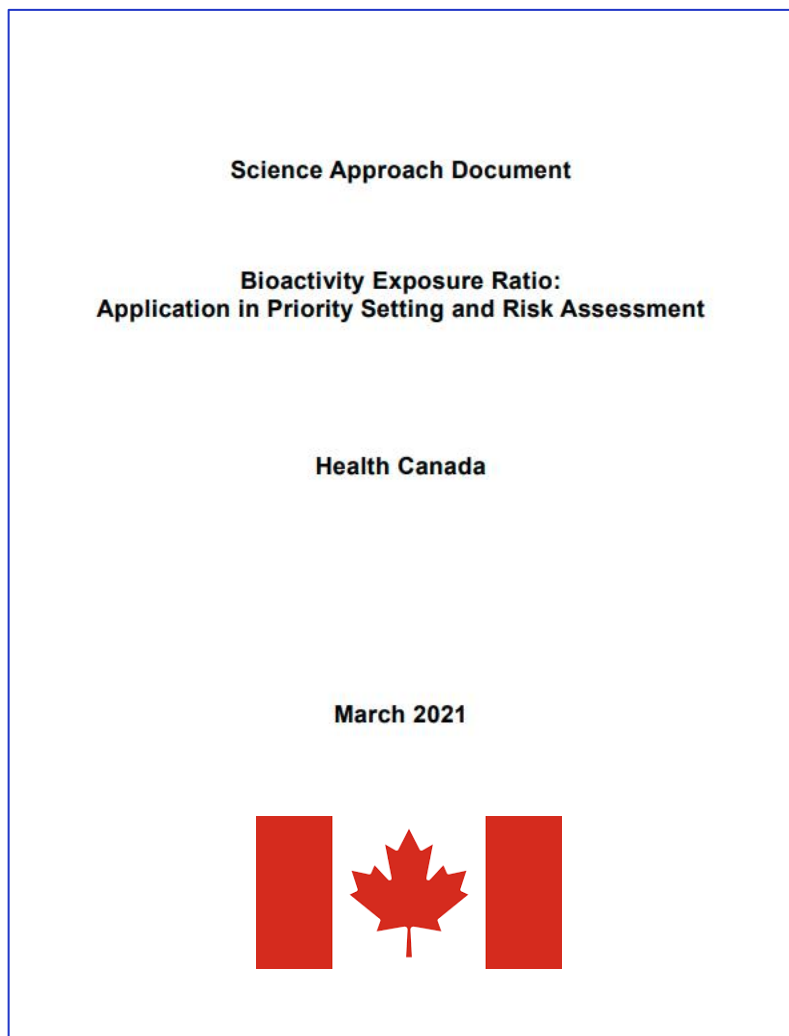
Bioactivity: Exposure Ratio (BER)

POD from *in vitro* Bioactivity Assays

Systemic exposure in humans (from PBK)

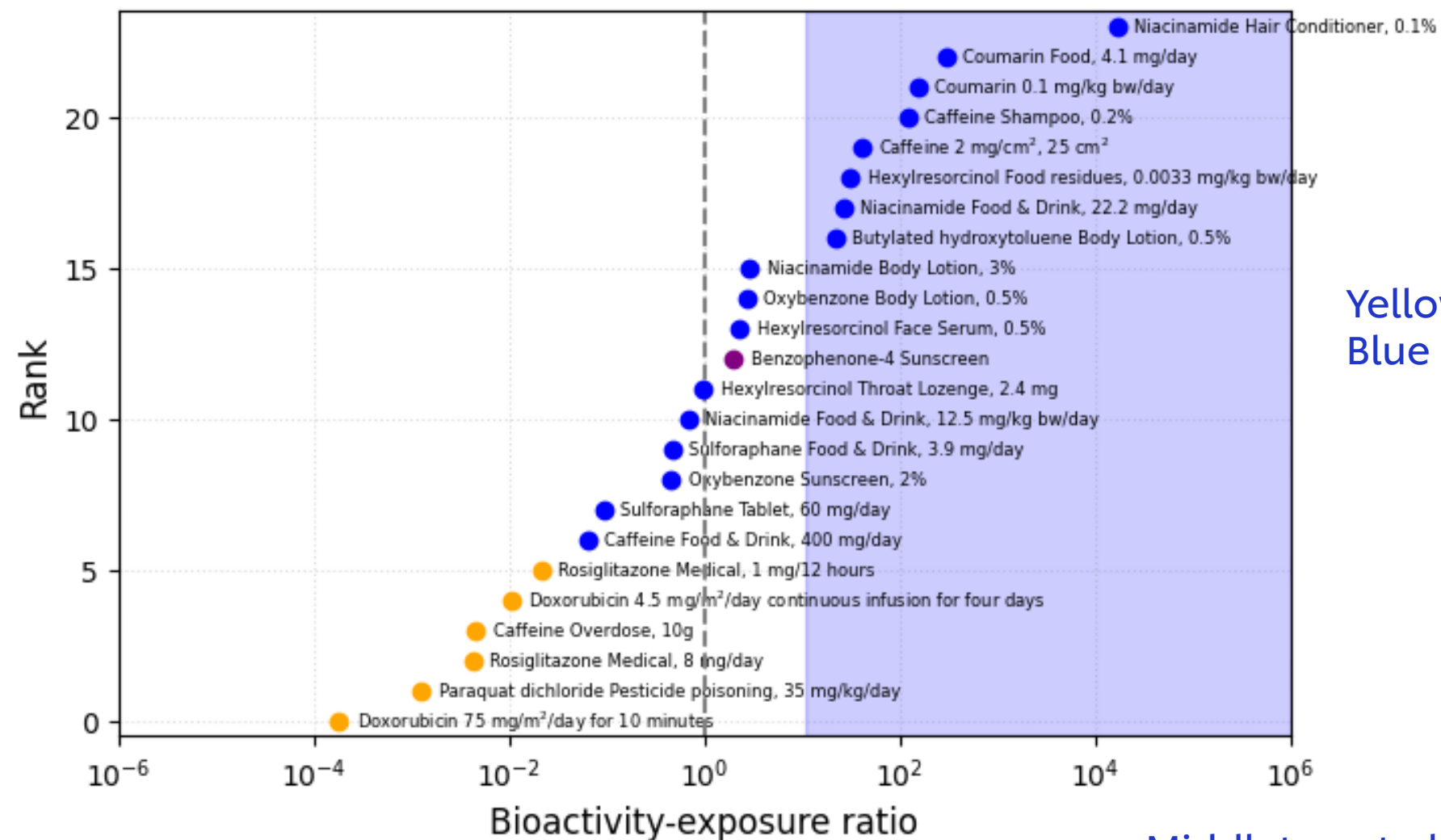
'Bioactivity exposure ratios (BERs). BERs are analogous to the traditional margin of exposure used in risk assessment in that chemicals with a lower BER possess a higher potential for risk'

Kuo *et al* (2022)



[Science approach document - Bioactivity exposure ratio: Application in priority setting and risk assessment - Canada.ca](#)

Benchmarking to determine a low-risk BER

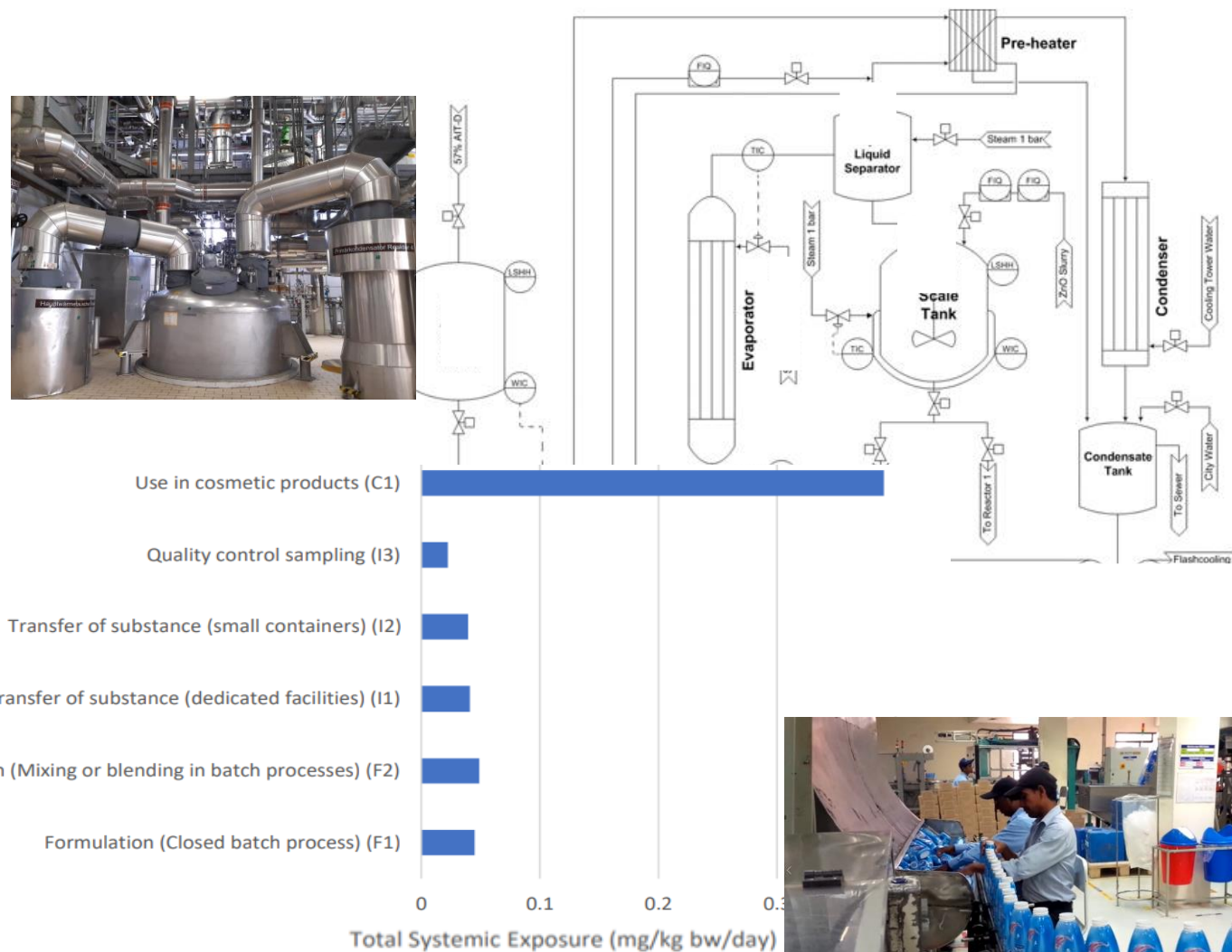


Yellow dots: high risk benchmarks
Blue dots: low risk benchmarks

Beyond consumer safety: Chemicals Regulations

NGRA for worker safety

- Understanding worker exposure
- Different routes of exposure
- Levels of exposure
- Engineering controls
- Use of personal protective equipment
- NGRA
- BER approach for worker exposure



Conclusions

- The Next Generation Risk Assessment (NGRA) toolbox is increasingly being used as part of decisions on consumer safety that do not involve animal testing
- NGRA and the use of NAMs (New Approach Methodologies) is being mentioned in some regulatory guidelines
- Working on examples of decision-making using NGRA is one of the best ways to build familiarity and confidence with the tools e.g. Baltazar *et al* (2020), *Toxicol Sci*, **176**, 236-252
- There is still work to do e.g. working on a framework for establishing scientific confidence in new approach methodologies (van der Zalm *et al*, *Archives of Toxicology*, **96**, 2865-2879)



EPA United States Environmental Protection Agency

Environmental Topics | Laws & Regulations | Report a Violation | About EPA

News Releases from Headquarters > Research and Development (ORD)

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.

EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs."

19 Aug 2021



Advancing Public Health and Animal Welfare



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