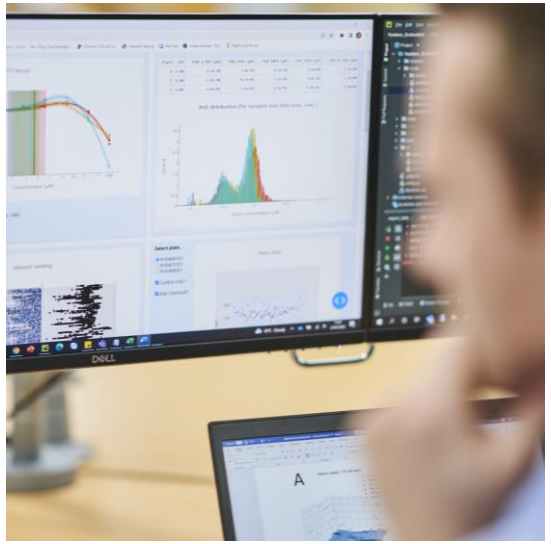
# Current Progress with NAMs in Next Generation Risk Assessment (NGRA) and opportunities in chemical registration



Carl Westmoreland

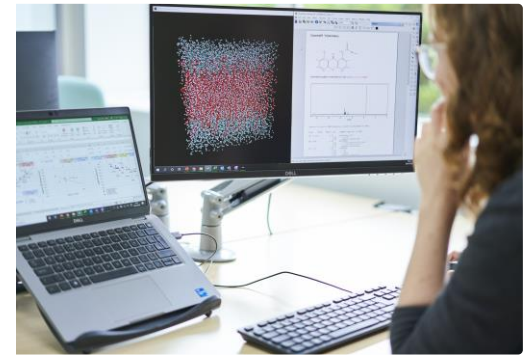
Unilever

# 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**.



https://seac.unilever.com/our-science/safety-without-animal-testing/

# All Unilever products must be safe for humans and the environment



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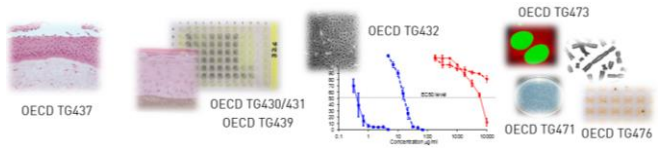
# Assuring safety without animal testing: Maximising use of existing information and non-animal approaches

## 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)

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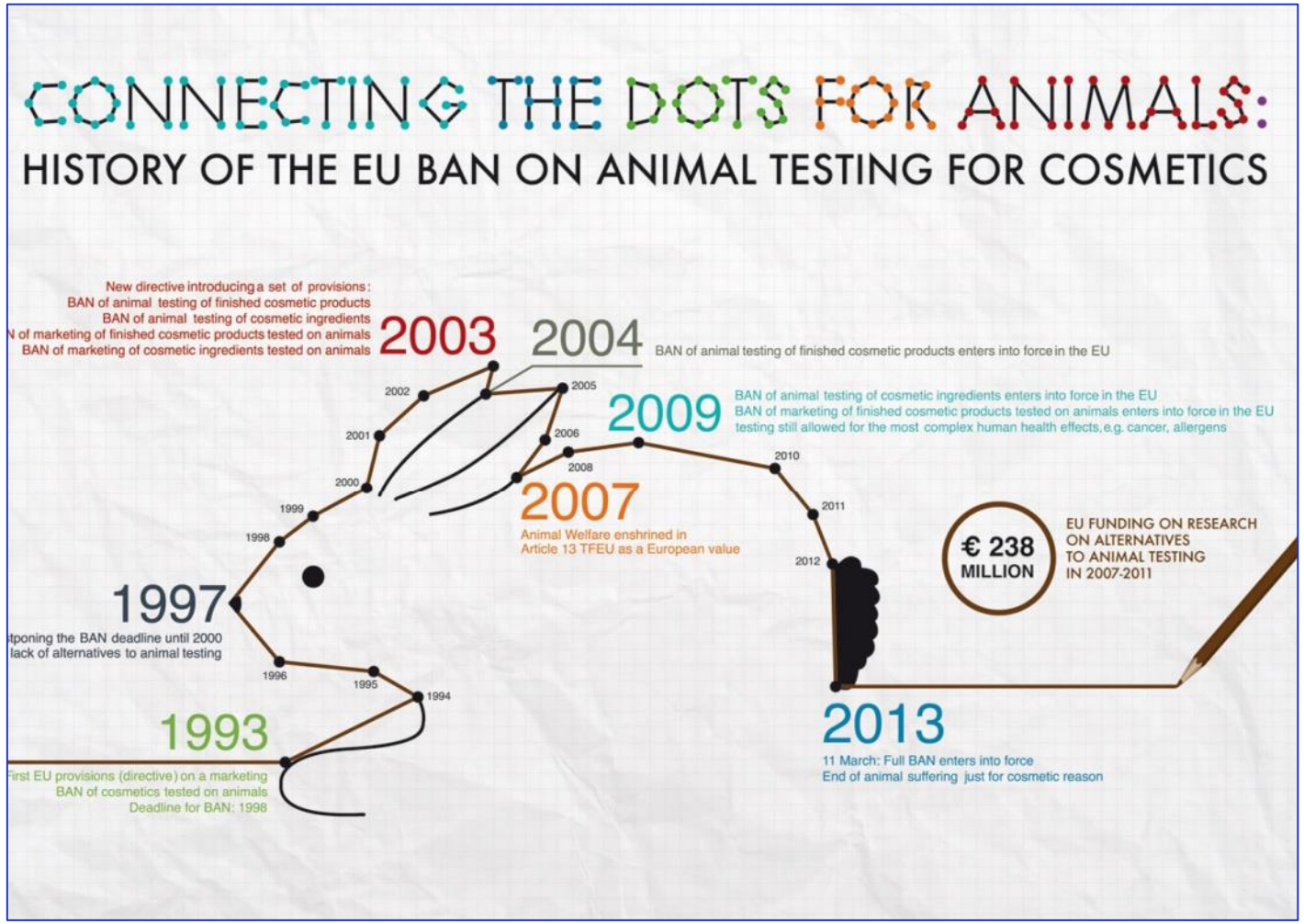
# The history of bans on animal testing for cosmetic products and ingredients in the EU

>10 years of assuring safety without animal testing




Source: https://ec.europa.eu/growth/sectors/cosmetics/ban-animal-testing_en

# What is next generation risk assessment (NGRA)?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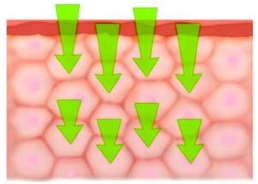
# What is next generation risk assessment (NGRA)?

*"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"*

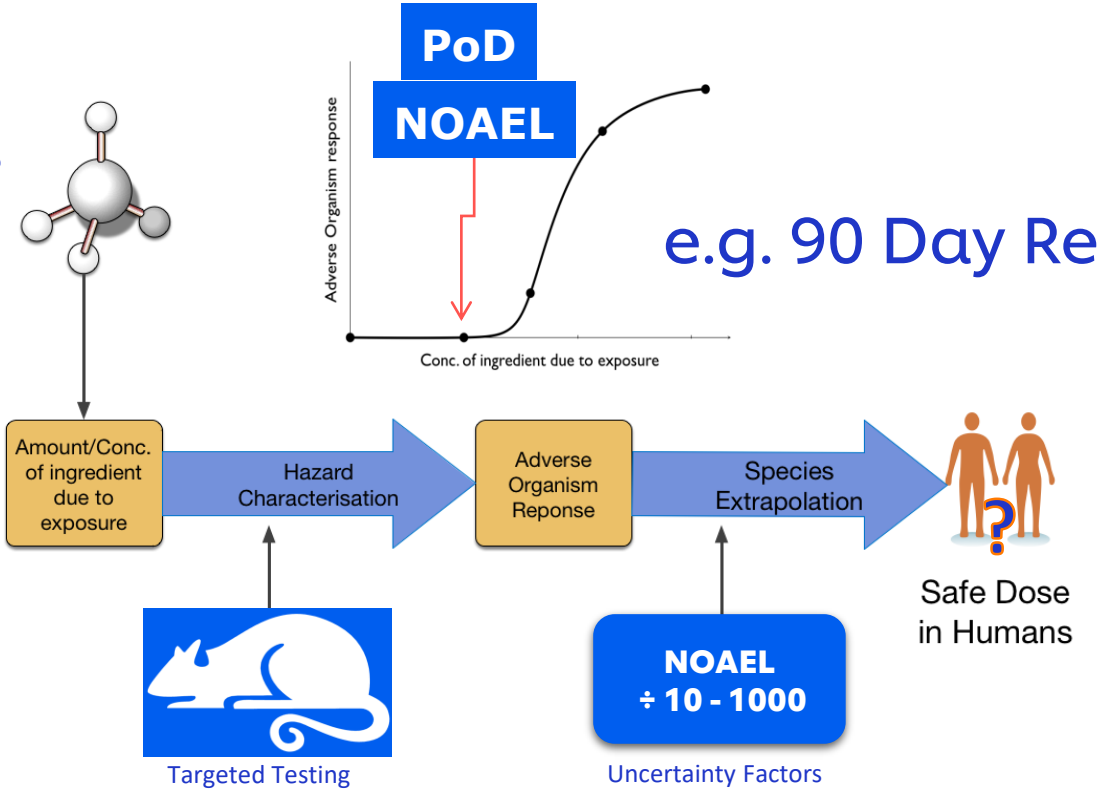
Dent *et al* ., (2018) *Comp Tox* 7:20-26

NAM = New Approach Methodology

# Why is NGRA important? The Systemic Challenge



*Is it safe?*




e.g. 90 Day Repeat Dose Study

A new non-animal paradigm is needed...

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

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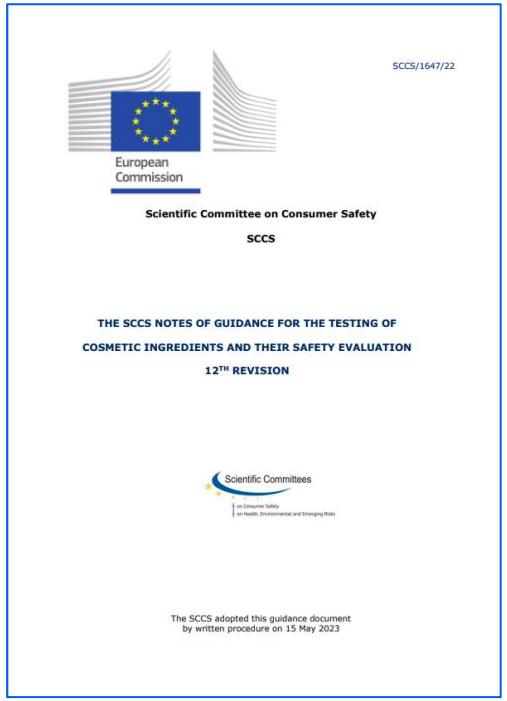
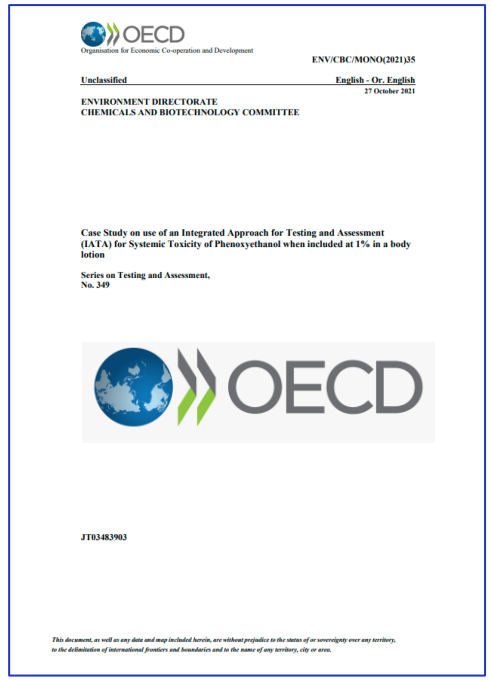
# Tiered, exposure-led NGRA means we can make robust safety decisions

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


International Cooperation on Cosmetics Regulation (2018)




European Commission: Scientific Committee on Consumer Safety (2021, 2023)




OECD (2021)

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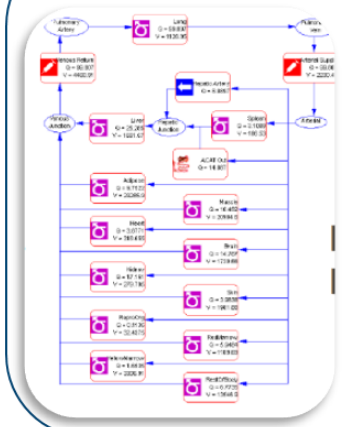
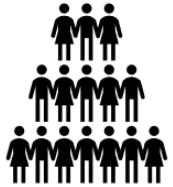
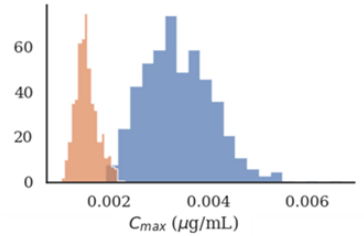
# Key tools in our NGRA approaches for Systemic Toxicity: Exposure and Bioactivity (First Tier Tools)

## PBK Modelling

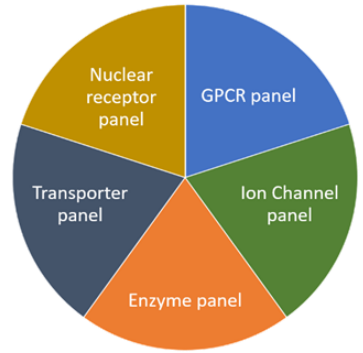







Toxicology in Vitro (2020), **63**, 104746

## In vitro pharmacological profiling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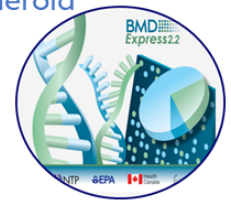
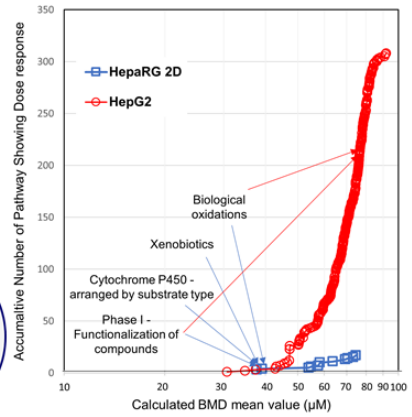
## Transcriptomics

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

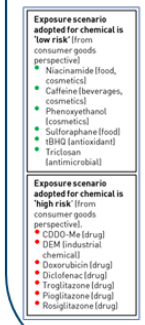
BMDexpress 2

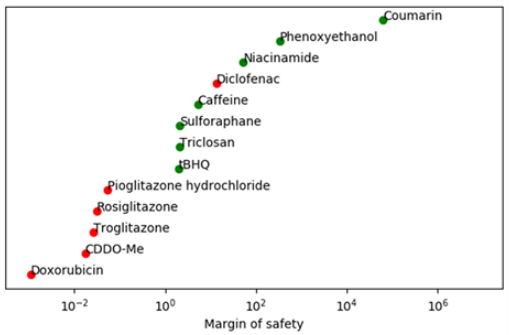


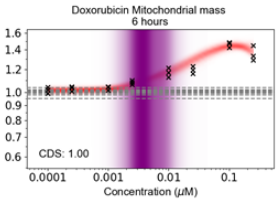

## Cellular Stress Pathways

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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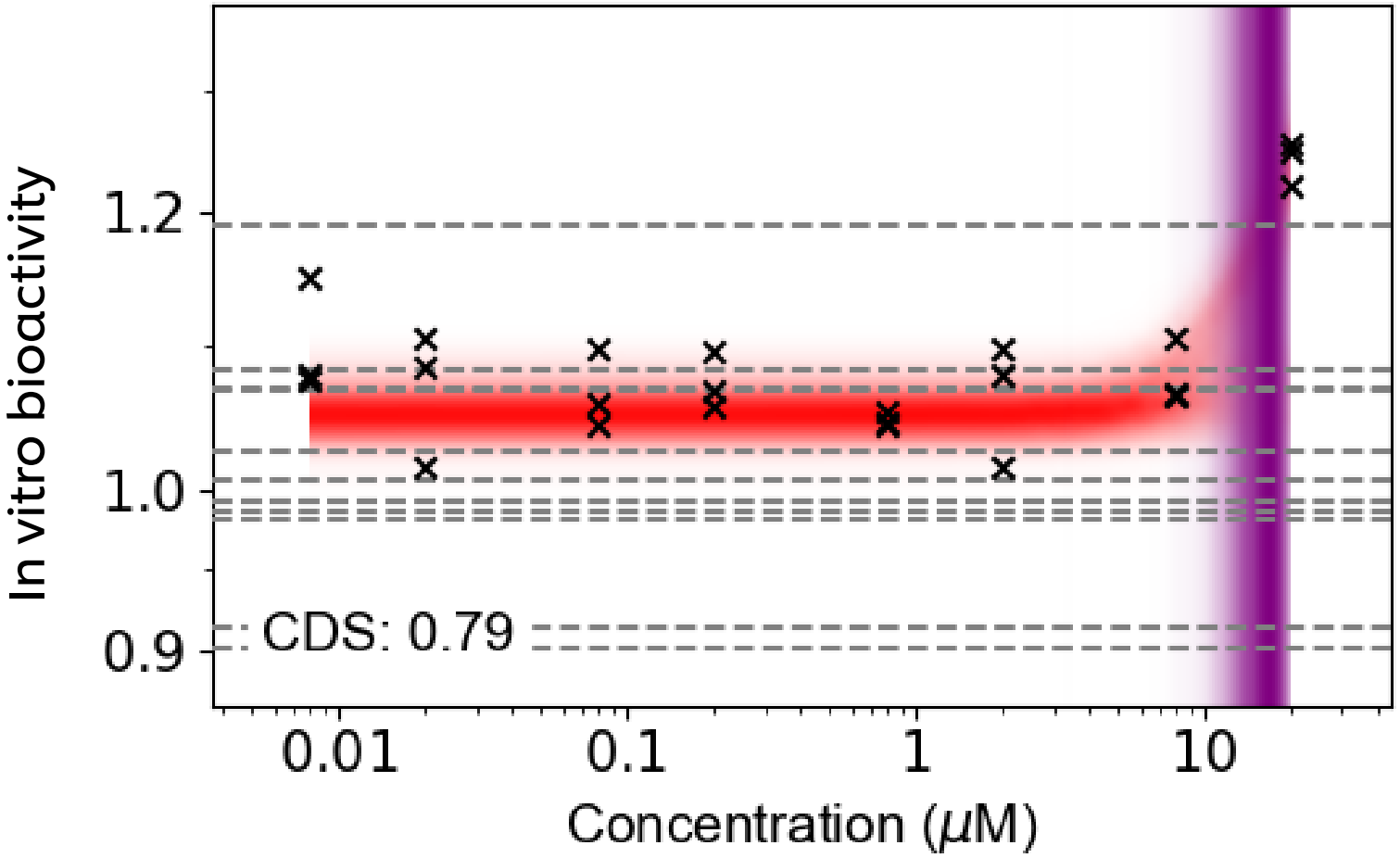
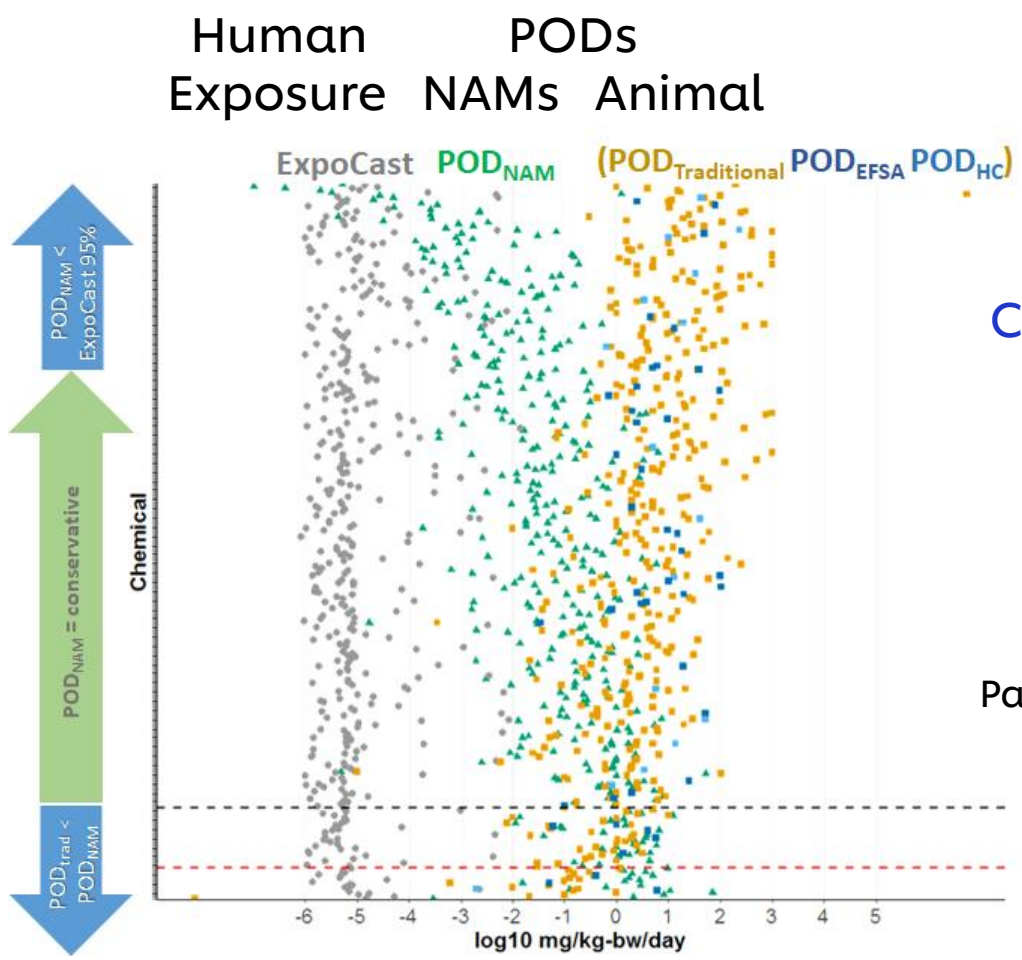
# Point of Departure (POD)



# 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

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ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

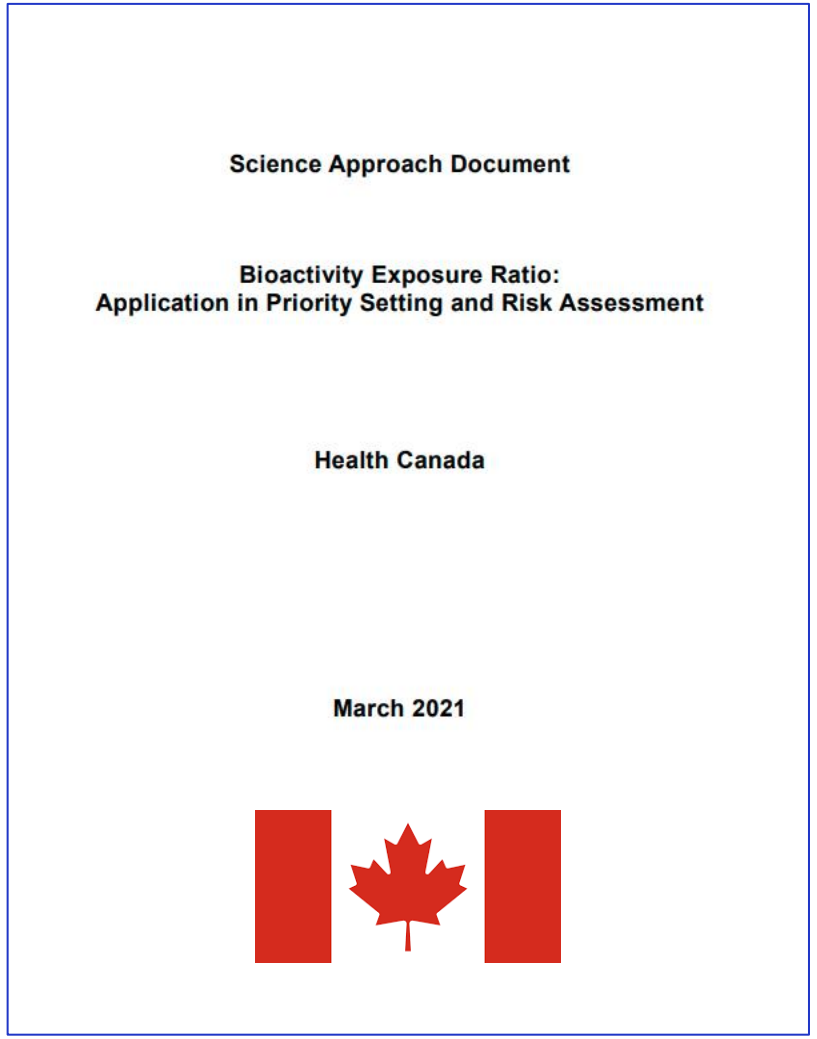
# Bioactivity: Exposure Ratio (BER)

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

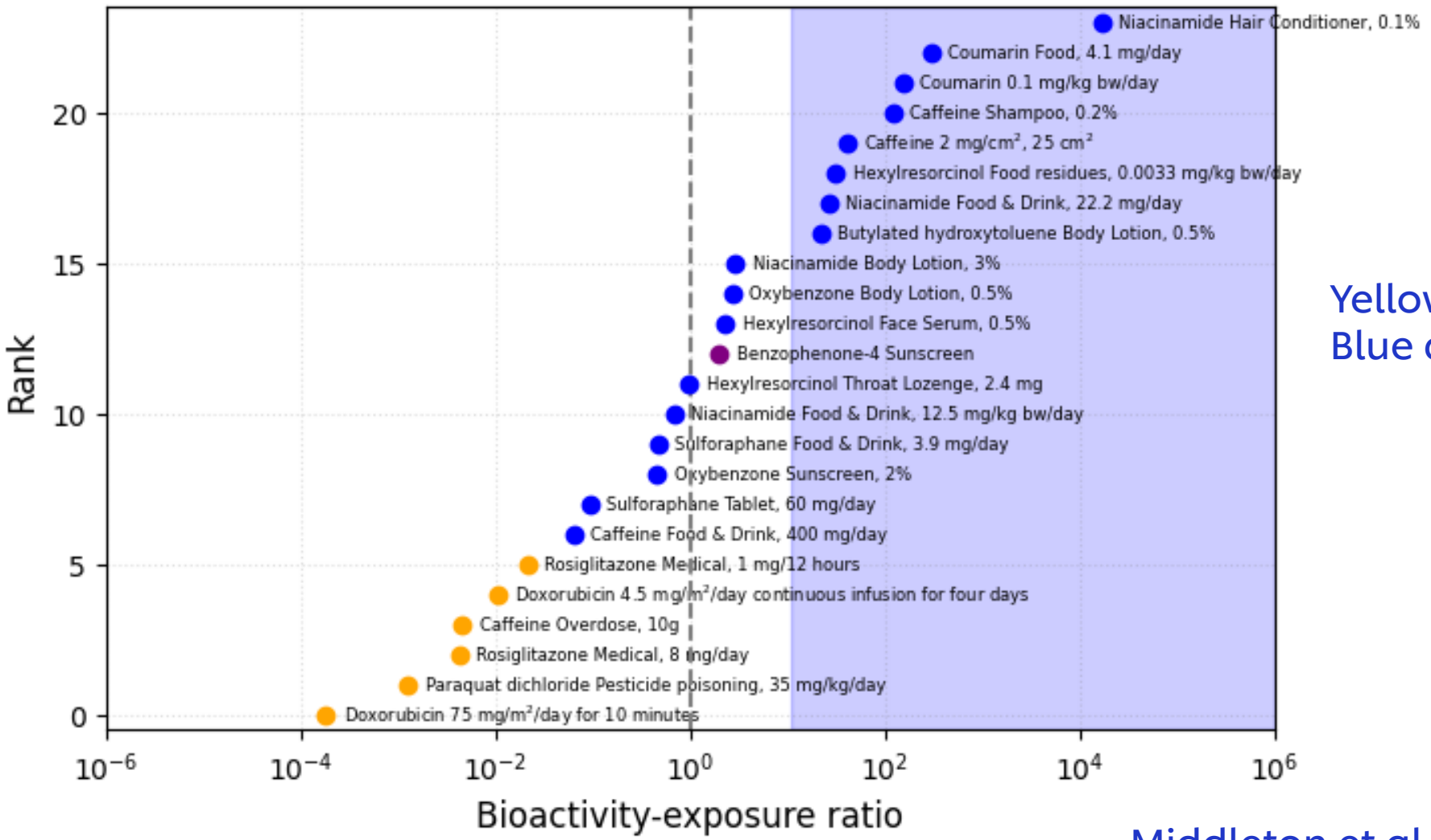
Bioactivity Exposure Ratio:
Application in Priority Setting and Risk Assessment

Health Canada

March 2021

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

# Benchmarking to determine a low-risk BER

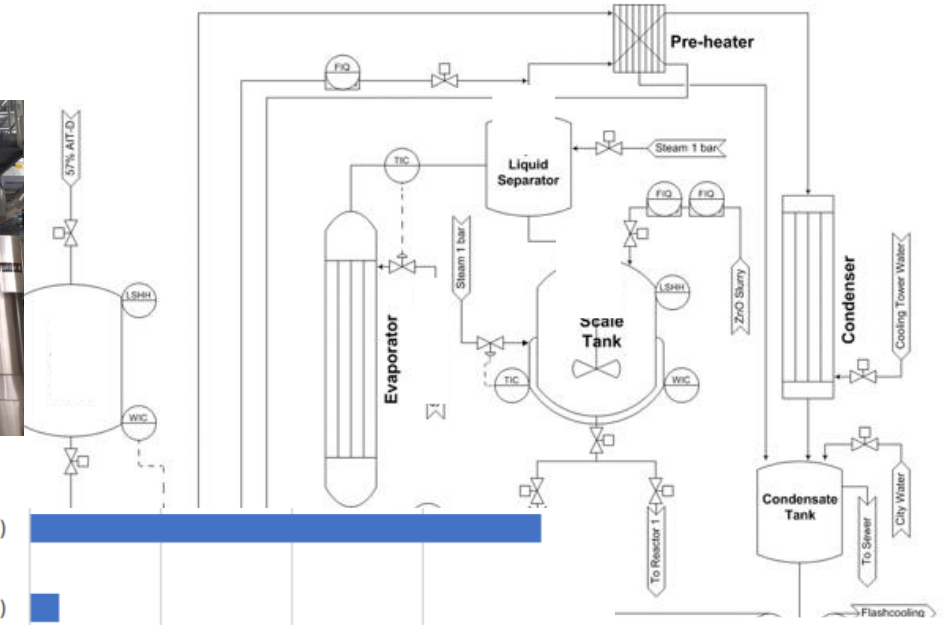


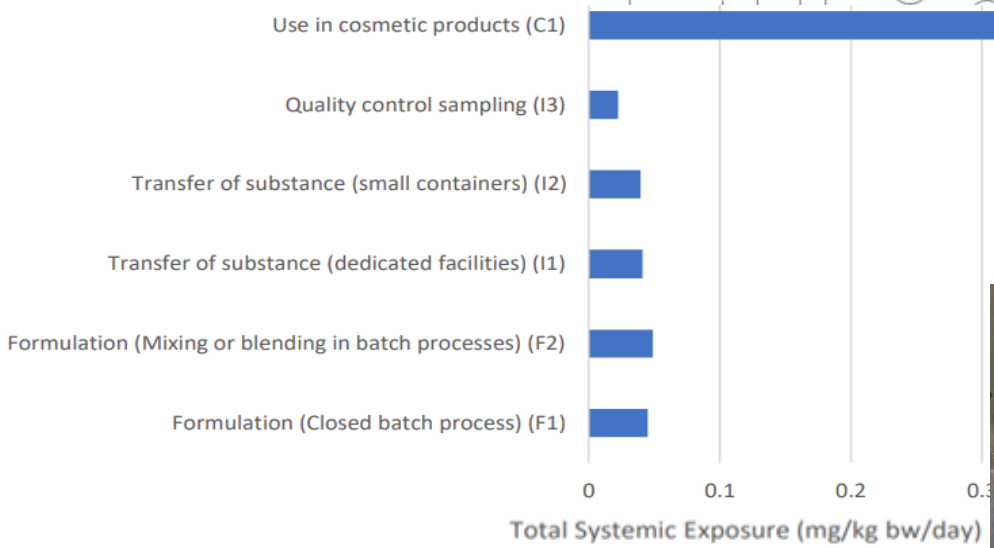

Yellow dots: high risk benchmarks
Blue dots: low risk benchmarks

Middleton et al., (2022) Toxicol Sci, 189, 124-147

# 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

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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.

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

RISK HUNT3R

epaa The European Partnership for Alternative Approaches to Animal Testing

NICEATM ICCVAM
Advancing Public Health and Animal Welfare

Unilever

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