Next generation risk assessment (NGRA) for consumer products

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Outline

- What is NGRA?
- How is it being applied today?
- Where next?

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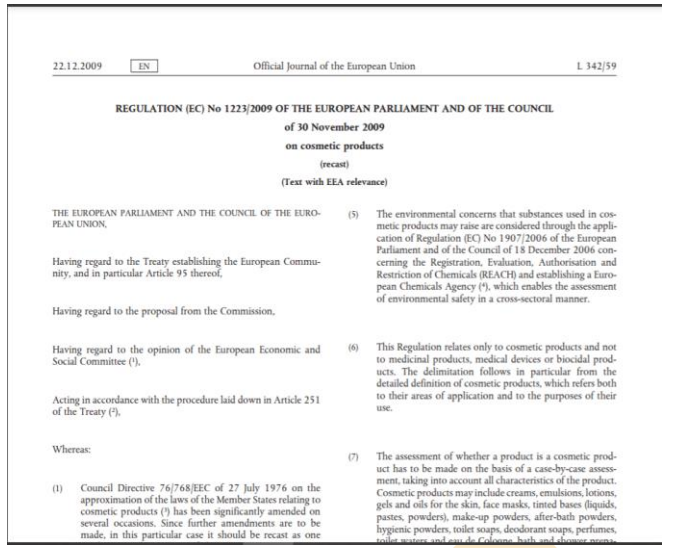
The need for non-animal approaches

Societal Attitudes/Consumer Preference

Human Relevance



22.12.2009 EN Official Journal of the European Union L 342/59

REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 30 November 2009
on cosmetic products
(recast)
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Economic and Social Committee (1),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (2),

Whereas:

(1) Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (3) has been significantly amended on several occasions. Since further amendments are to be made, in this particular case it should be recast as one

(5) The environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency (4), which enables the assessment of environmental safety in a cross-sectoral manner.

(6) This Regulation relates only to cosmetic products and not to medicinal products, medical devices or biocidal products. The delimitation follows in particular from the detailed definition of cosmetic products, which refers both to their areas of application and to the purposes of their use.

(7) The assessment of whether a product is a cosmetic product has to be made on the basis of a case-by-case assessment, taking into account all characteristics of the product. Cosmetic products may include creams, emulsions, lotions, gels and oils for the skin, face masks, tinted bases (liquids, pastes, powders), make-up powders, after-bath powders, hygienic powders, toilet soaps, deodorant soaps, perfumes, toilet waters and eau de Cologne, bath and shower prepa-

Regulatory Change

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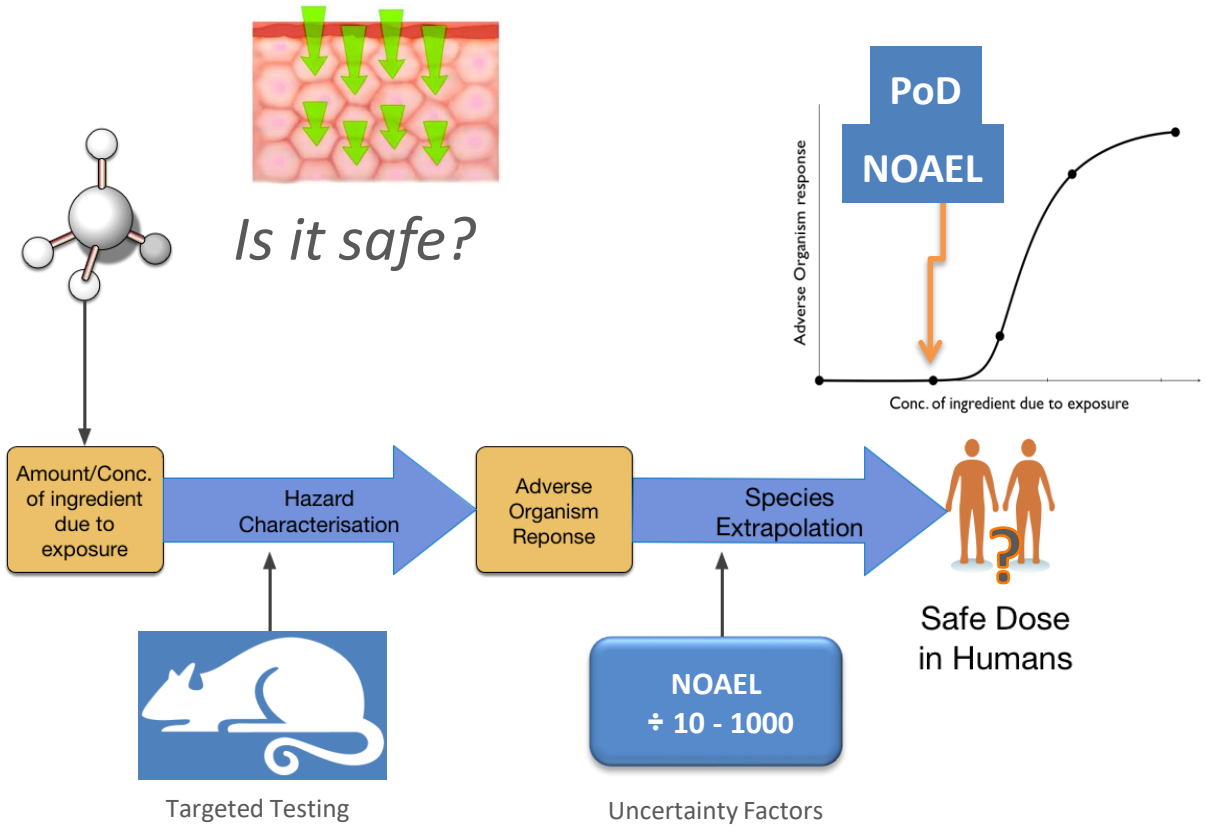
Why do we need NGRA?



Existing approaches

Threshold of Toxicological Concern

(Yang et al 2017)

https://doi.org/10.1016/j.fct.2017.08.043

Read across

History of Safe Use

(Neely et al 2011)

https://doi.org/10.4103/0971-6580.85882

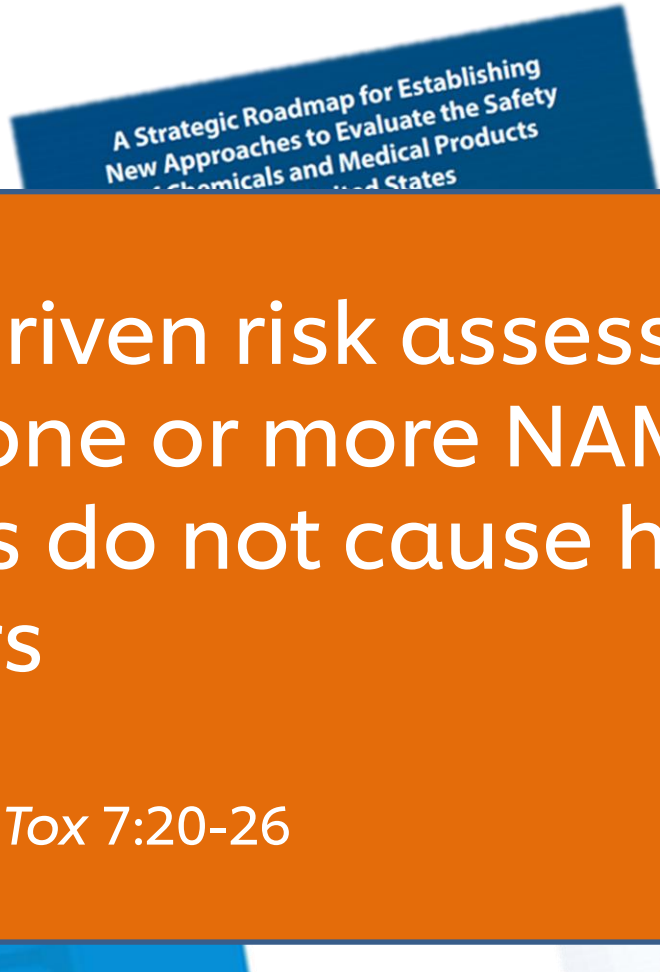
~~e.g. 90 Day Repeat Dose Study~~

A new non-animal paradigm is needed…

…replacement of animal test data is not the answer

→NGRA

What is 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

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Principles of NGRA from ICCR (International Cooperation on Cosmetics Regulation)

4 Main overriding principles:

The overall goal is a human safety risk assessment
The assessment is exposure led
The assessment is hypothesis driven
The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

Following an appropriate appraisal of existing information
Using a tiered and iterative approach
Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

Sources of uncertainty should be characterized and documented
The logic of the approach should be transparent and documented

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

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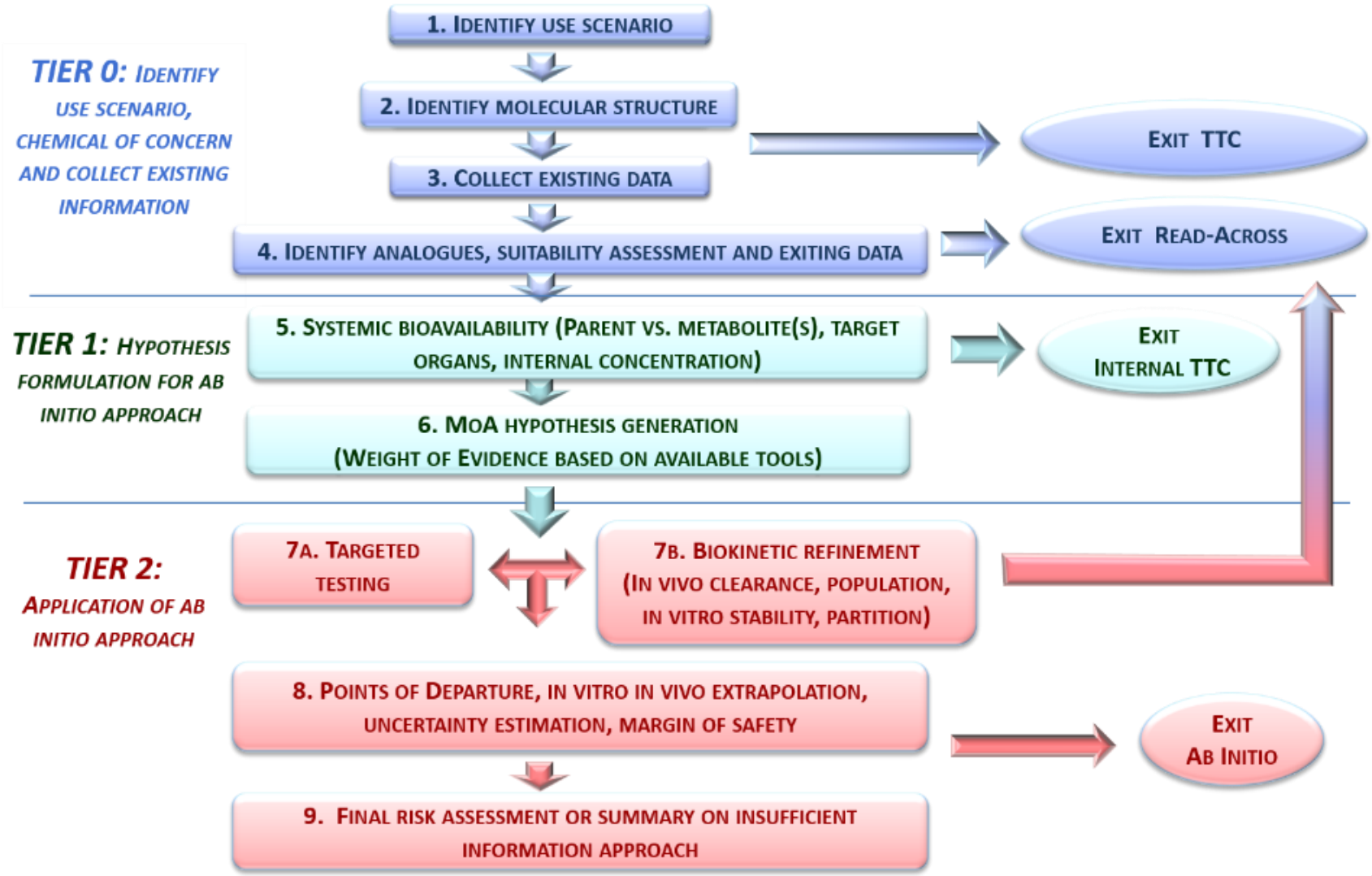
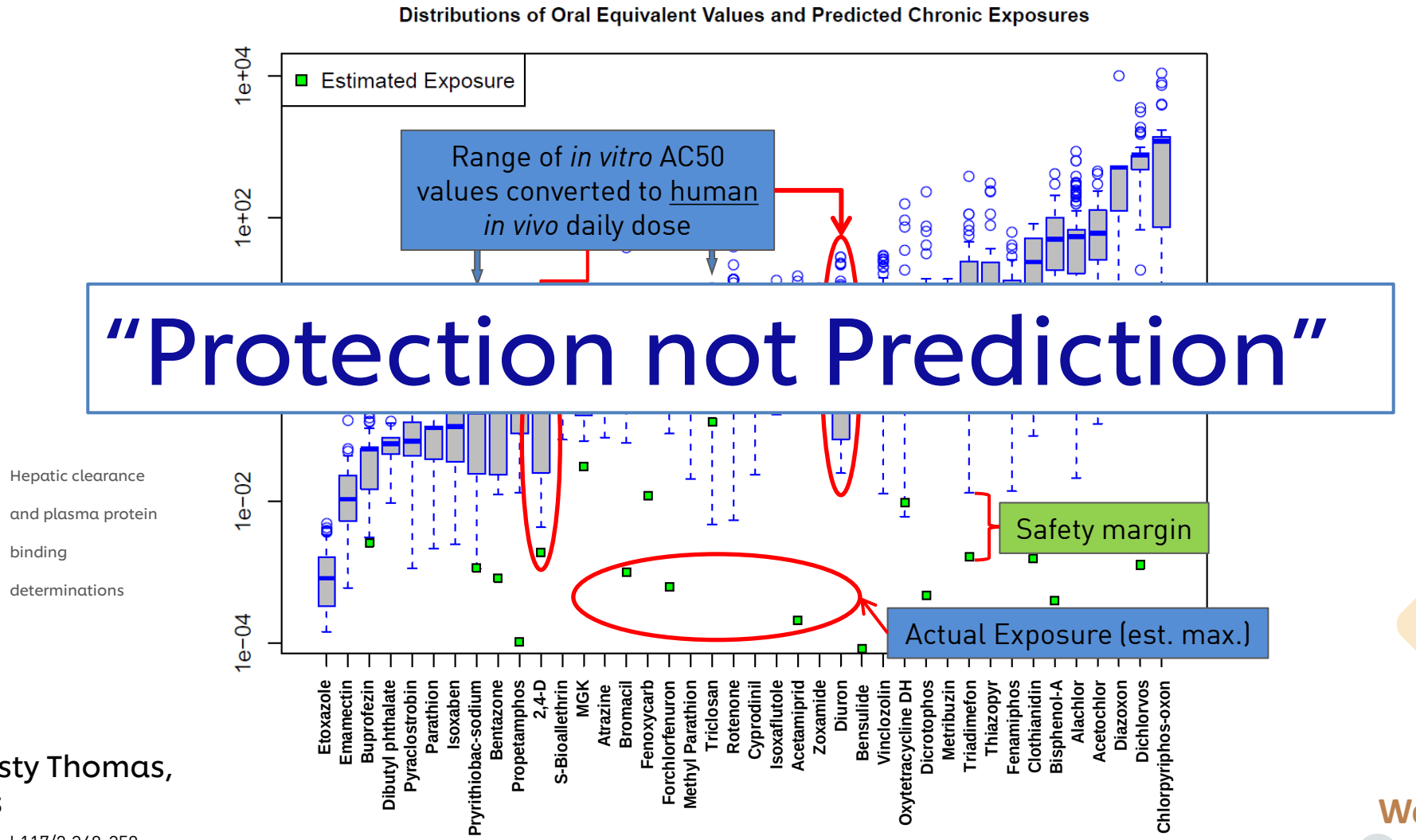
Integrating different lines of evidence for safety decision making



Berggren et al 2017 (https://doi.org/10.1016/j.comtox.2017.10.001)

Low-tier NGRA



Slide from Dr Rusty Thomas, EPA, with thanks

Rotroff, *et al.* Tox.Sci 2010 Vol 117/2 348-358

https://doi.org/10.1093/toxsci/kfq220

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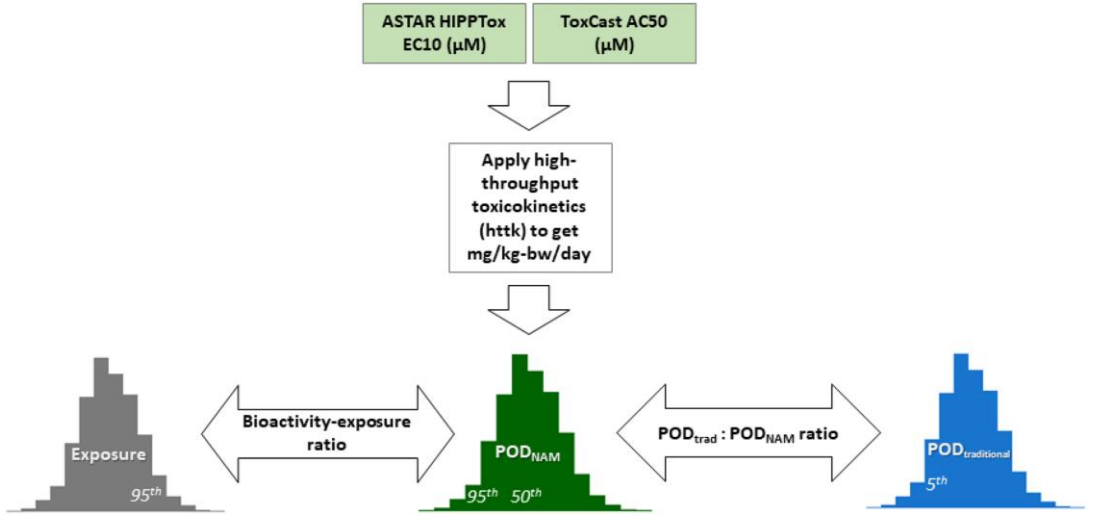
How protective are the NAMs?
Example from the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

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

Katie Paul Friedman ,*,[1] Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,[*] Ryan R. Lougee,[*,||] Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,[|||] Jean Lou Dorne,[||||] Stiven Foster,[#] Kathleen Raffaele,[#] Tina Bahadori,[||] Maureen R. Gwinn,[*] Jason Lambert,[*] Maurice Whelan,[**] Mike Rasenberg,[§] Tara Barton-Maclaren,[†] and Russell S. Thomas *



Of the 448 substances, 89% had a $POD_{NAM,95}$ that was less than the traditional POD ($POD_{traditional}$) value.

Bioactivity:exposure ratios (BERs), useful for identification of priority substances, demonstrated that high-throughput exposure predictions were greater than the PODNAM,95 for 11 substances.

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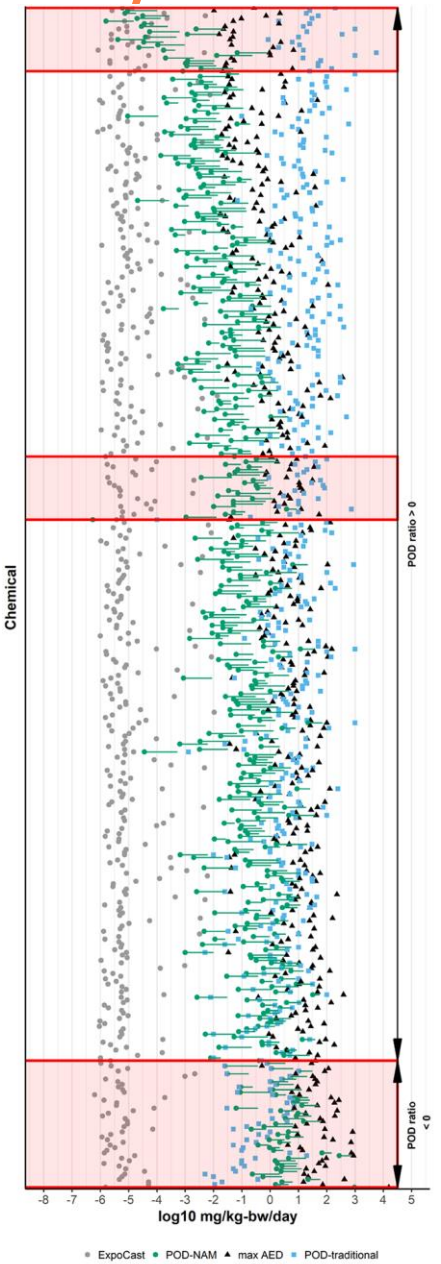
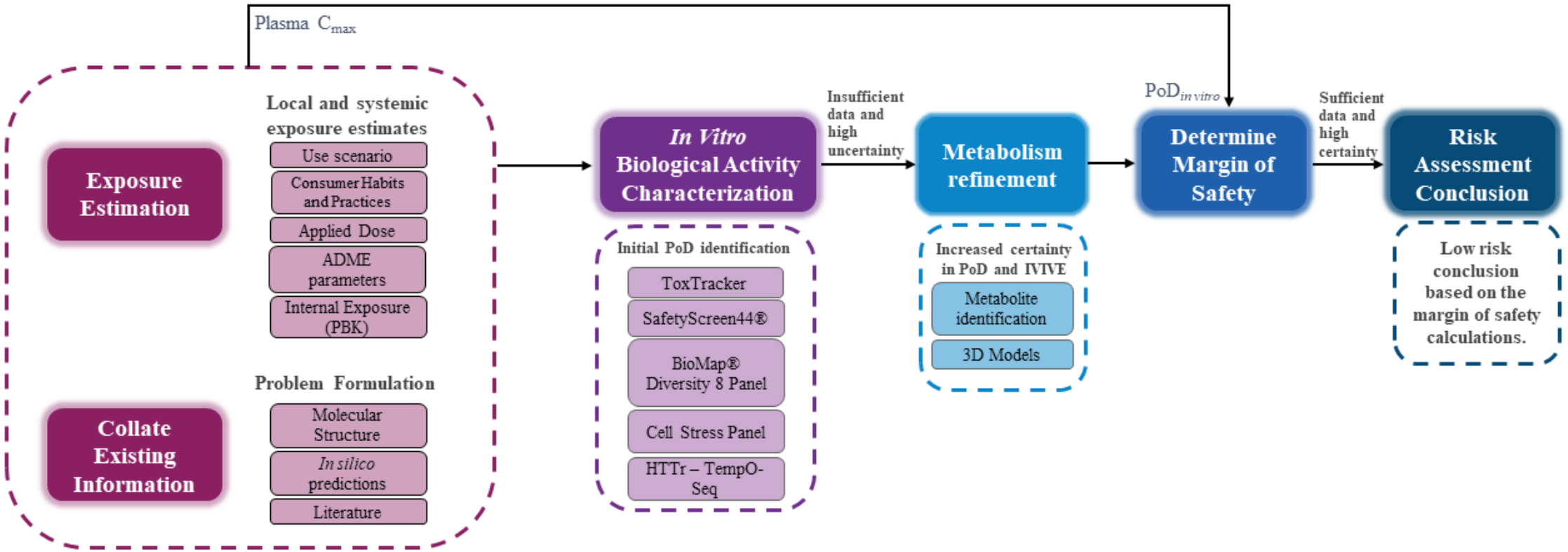
https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/science-approach-document-bioactivity-exposure-ratio-application-priority-setting-risk-assessment.html



Application of NGRA principles and framework to exposure-led risk assessment: Coumarin example



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Baltazar *et al.*, (2020) *Toxicological Sciences* 176(1): 236-252
https://doi.org/10.1093/toxsci/kfaa048

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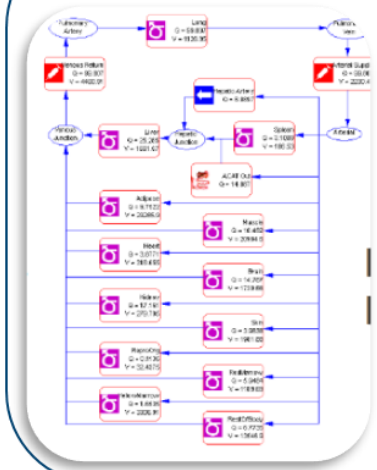
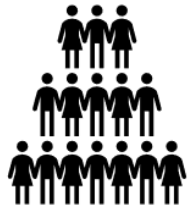
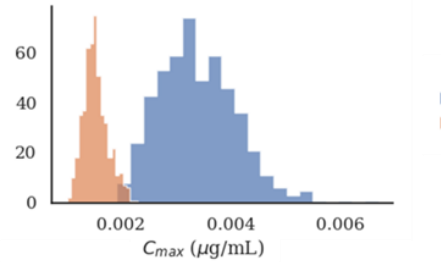
Some key elements in the NGRA toolbox

PBK Modelling







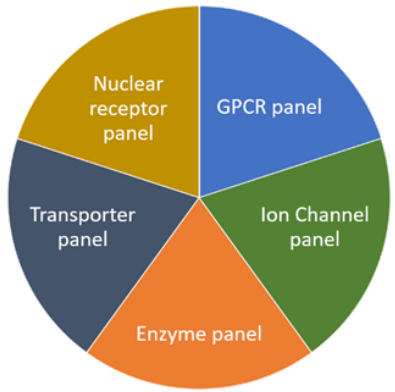
Toxicology in Vitro (2020), **63**, 104746

In vitro pharmacological profiling


PERSPECTIVES

A GUIDE TO DRUG DISCOVERY — OPINION

Reducing safety-related drug attrition: the use of *in vitro* pharmacological profiling

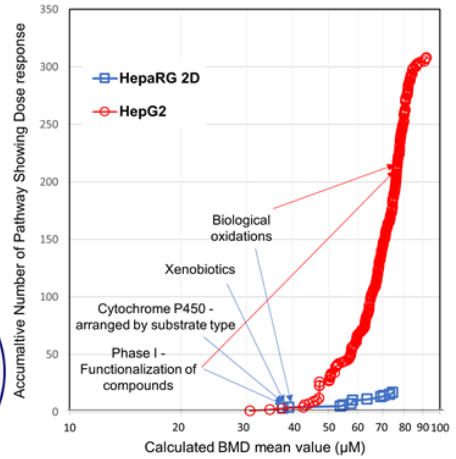


eurofins | Cerep

Transcriptomics

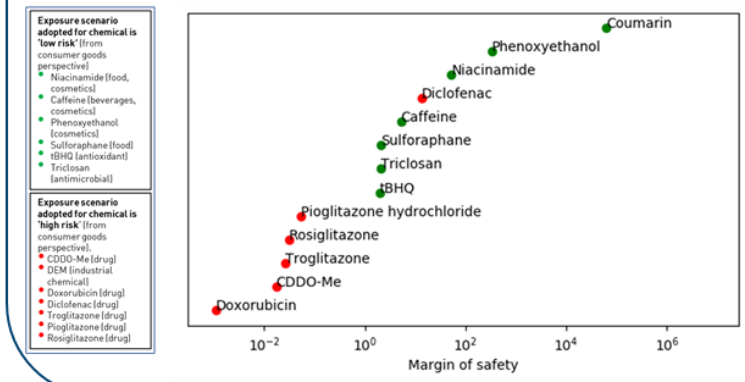
- Use of full human gene panel ~ 21k
- 24 hrs exposure
- 7 concentrations
- 3 cell lines HepG2/ HepaRG/ MCF7
- 3D HepaRG spheroid

BMDexpress 2

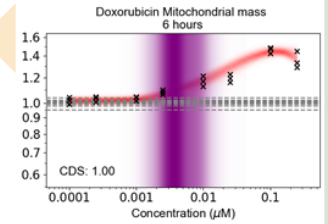


Cellular Stress Pathways

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



cyprotex AN EVOTEC COMPANY



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Toxicol Sci (2020), **176**, 11-33

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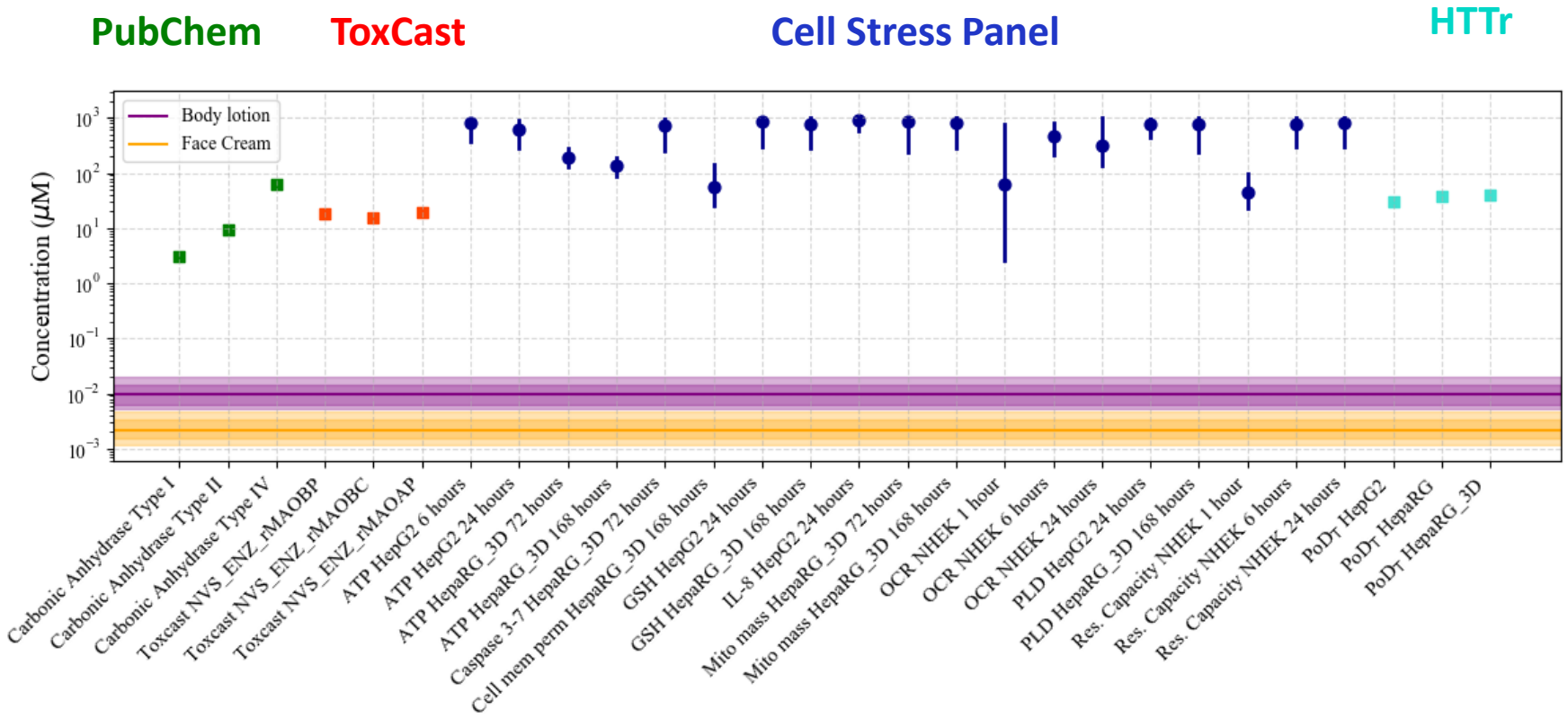
Margin of Safety considering PODs and Exposure

PoDs and plasma C_{max} (µM) are expressed as total concentration

C_{max} expressed as a distribution:

- Line = median (50th percentile)
- Inner band = 25th-75th percentile
- Outer band = 2.5th-97.5th percentile (95th credible interval)



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Where next? Points to visit during our workshop.

- Clarity on the level of protection offered by this approach
  - Bioactivity *vs.* Adversity
- What does our ‘base set’ look like?
- Role of metabolism – how to handle pragmatically
- Adequacy of cell lines, timepoints, study designs – what to do when the ‘protective not predictive’ NGRA fails and higher-tier tools are needed