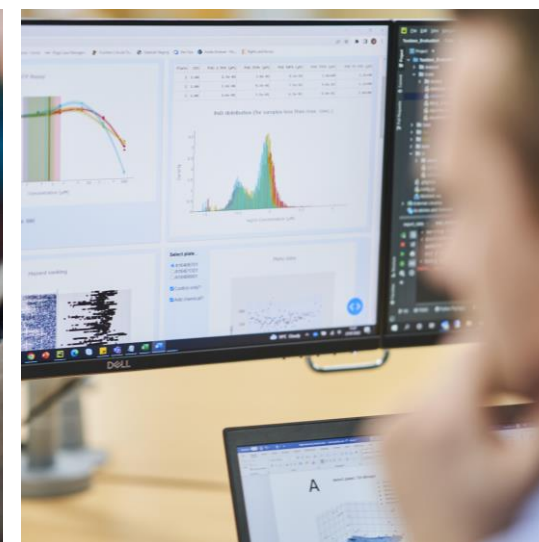
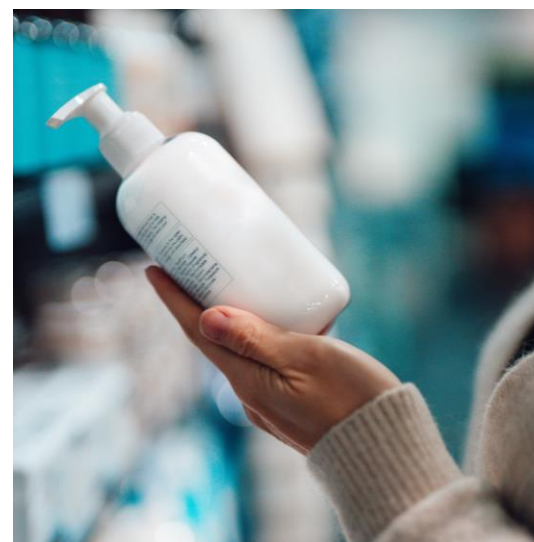


How can we facilitate the transition from animal test to full implementation of human relevant methods?

Dr Predrag Kukic
Unilever Safety and Environmental Assurance Centre

ONTOX Hackathon
21st – 23rd April 2024



Overview

1. broader societal & regulatory context for using innovative safety science approaches to replace animal tests
 - translating modern science into regulatory application
2. Identifying hurdles to full implementation of NAMs
 - identifying real and perceived scientific, technical, legislative and economic issues, as well as cultural and societal obstacles
3. How to overcome hurdles to accelerated adoption?
 - short-, mid-, and long-term goals to full acceptance of NAMs?



Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

- 1. Citizen concerns about the potential impacts of chemicals on their health & environment are high**

85% / 90% EU citizens are worried about the impact of chemicals present in everyday products on their health / the environment

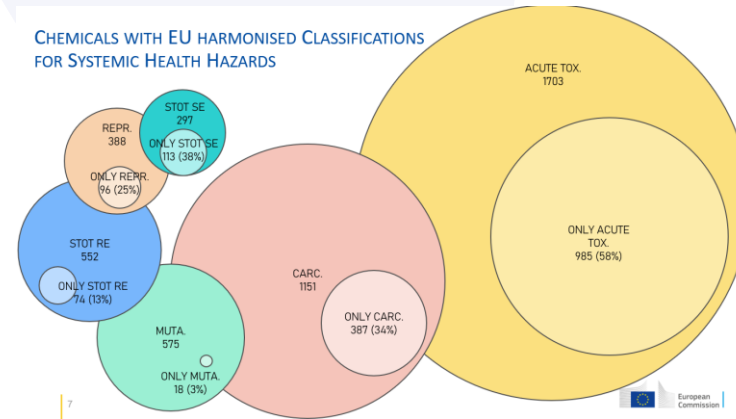
Special Eurobarometer 501



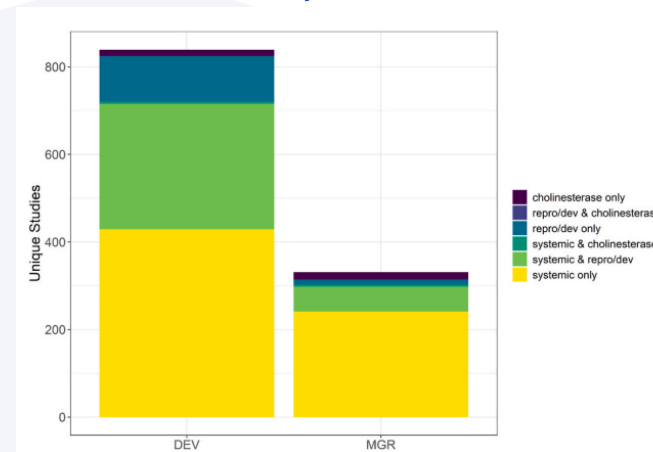
Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

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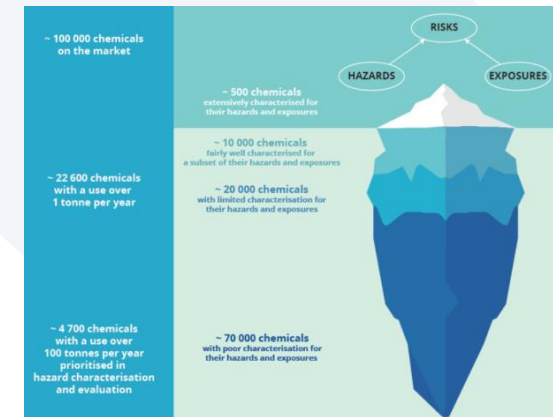
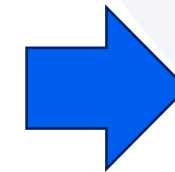
85% / 90% EU citizens are worried about the impact of chemicals present in everyday products on their health / the environment
Special Eurobarometer 501



Elisabet Berggren, EC workshop on the roadmap



Brown et al. Regul Toxicol Pharmacol, 2024



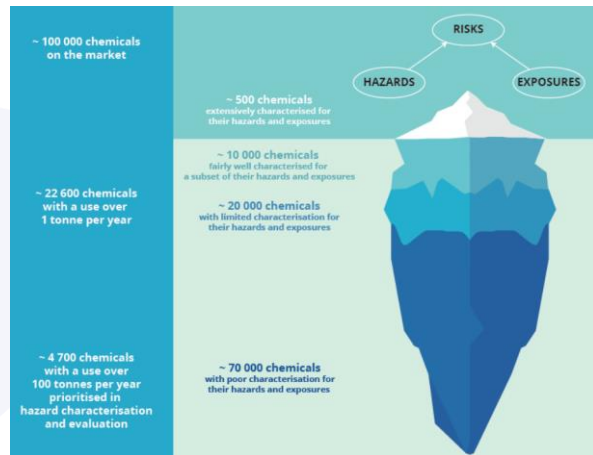
Elisabet Berggren, EC workshop on the roadmap





Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

1. Citizen concerns about the potential impacts of chemicals on their health & environment are high

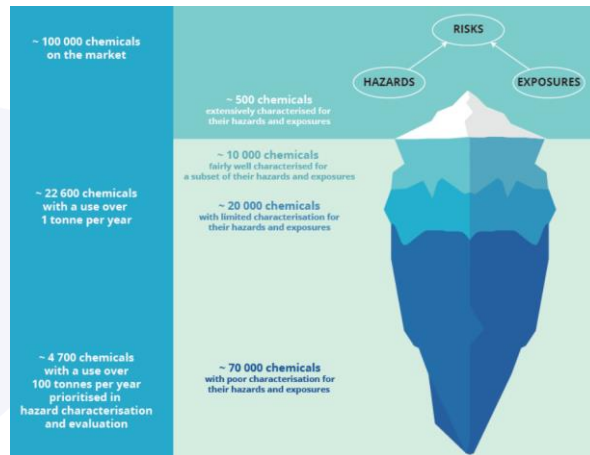


- ✓ Use high-throughput NAMs to **rebuild citizen trust that chemical regulatory frameworks are protective**



Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

1. **Citizen concerns about the potential impacts of chemicals on their health & environment are high**



✓ Use high-throughput NAMs to **rebuild citizen trust that chemical regulatory frameworks are protective**

2. **Move to more sustainable sources of chemicals (e.g. bio-based) is transforming chemical innovation & use**

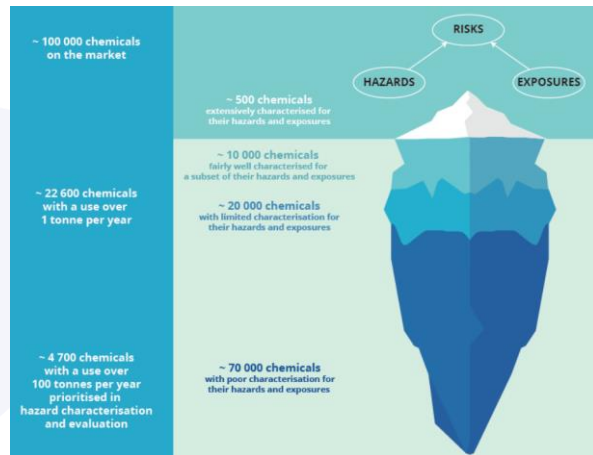


✓ Use NAMs to **ensure new chemicals are Safe & Sustainable by Design**



Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

1. **Citizen concerns about the potential impacts of chemicals on their health & environment are high**



✓ Use high-throughput NAMs to **rebuild citizen trust that chemical regulatory frameworks are protective**

2. **Move to more sustainable sources of chemicals (e.g. bio-based) is transforming chemical innovation & use**



✓ Use NAMs to **ensure new chemicals are Safe & Sustainable by Design**



3. **Regulatory Animal Testing of Chemicals is increasingly seen as unjustifiable / unethical by the majority of society**

Aug 2021 – Aug 2022:
1.4M+ signatures



✓ Use NAMs to **fully replace the need for chemical regulatory animal testing**

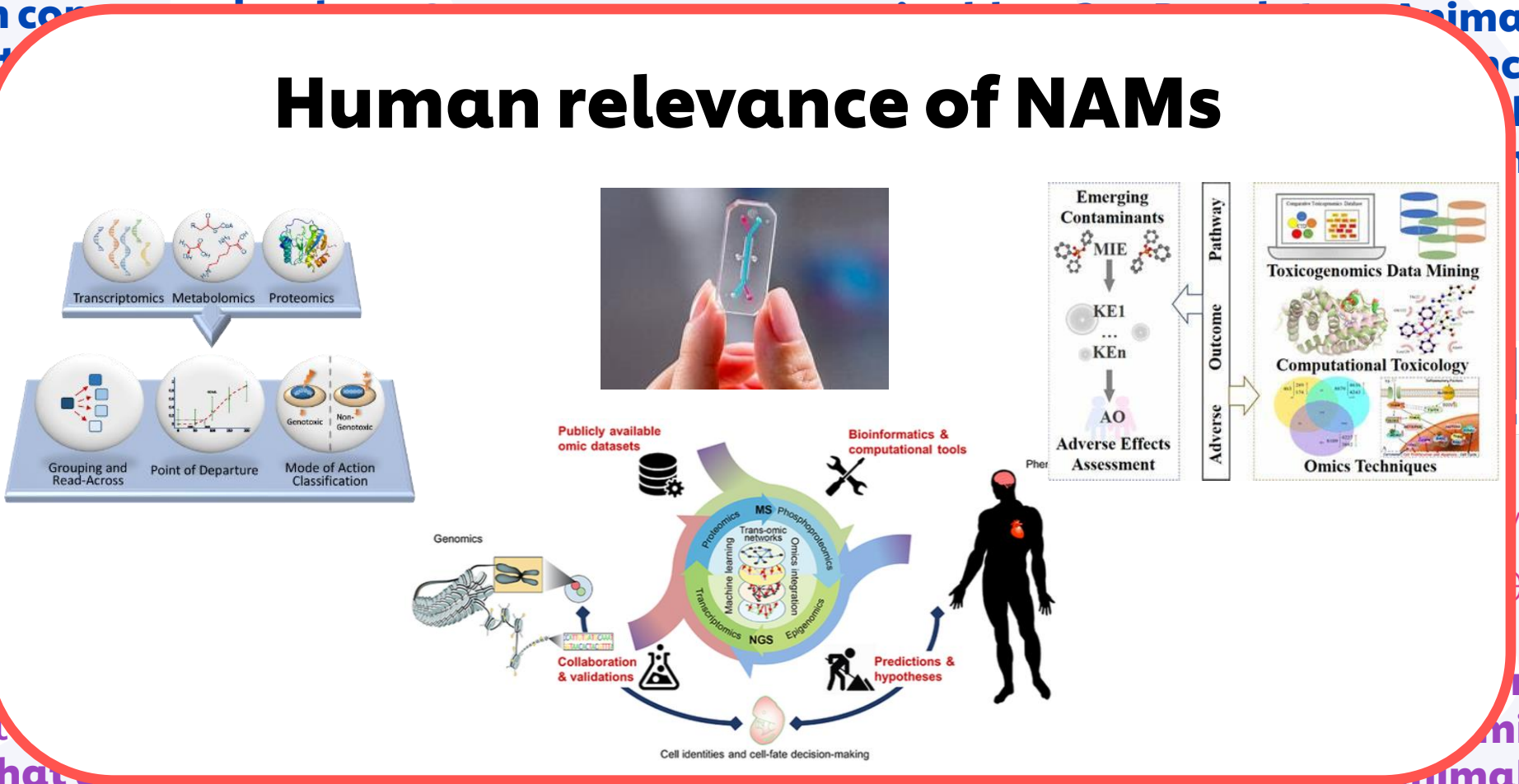


Broader societal & regulatory context for using innovative safety science approaches to replace animal tests

1. Citizen concern about the potential of chemicals & environmental health

Animal Testing increasingly unacceptable / majority of

~ 100 000 chemicals on the market
~ 22 600 chemicals with a use over 1 tonne per year
~ 4 700 chemicals with a use over 100 tonnes per year prioritised in hazard characterisation and evaluation



European Union
CITIZENS' INITIATIVE

Free
etics

replace
clinical
regulatory animal testing

Use human NAMs to build trust that chemical regulatory frameworks are protective



Advances in Safety Science



**Traditional Toxicology =
Empirical science focused on
observations from animal
studies**



**Increased focus on the use of exposure
science and understanding of human
biology (NAMs, PBK, DAs, IATAs,
protection of human health, AOPs...)**

Time

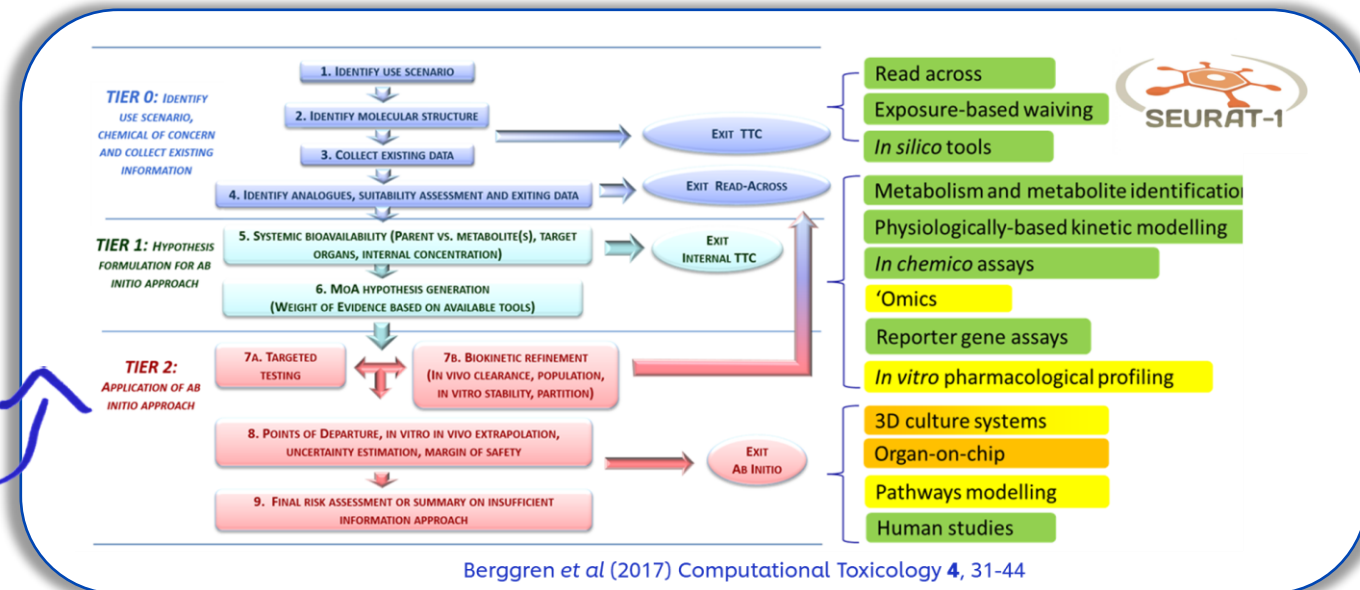
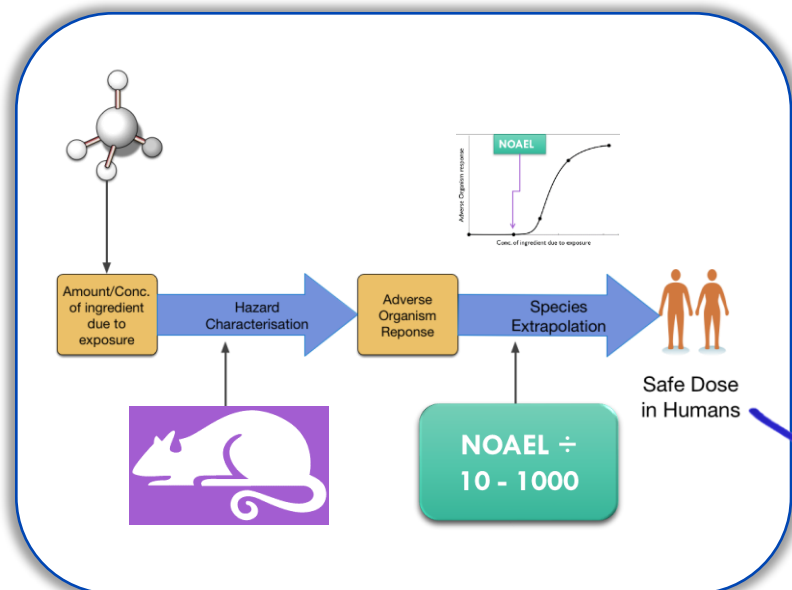
Advances in Safety Science



Traditional Toxicology = Empirical science focused on observations from animal studies



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Advances in Safety Science



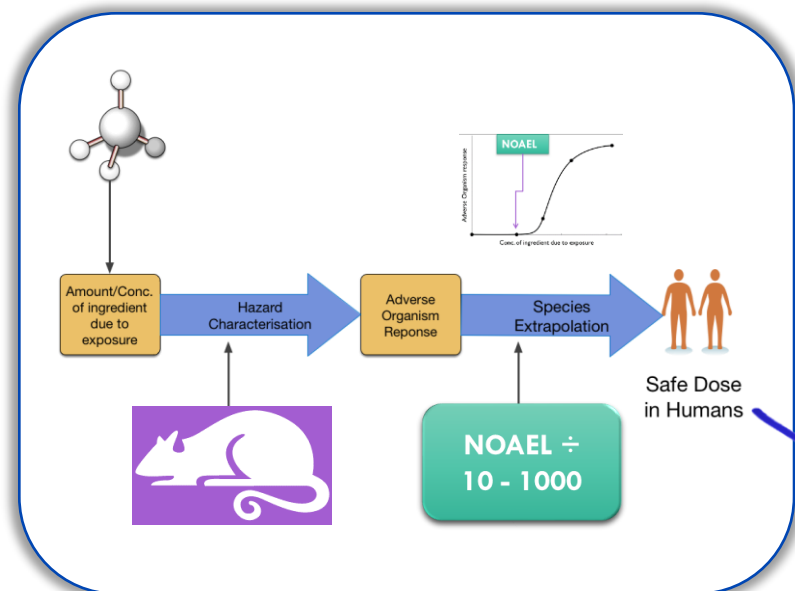
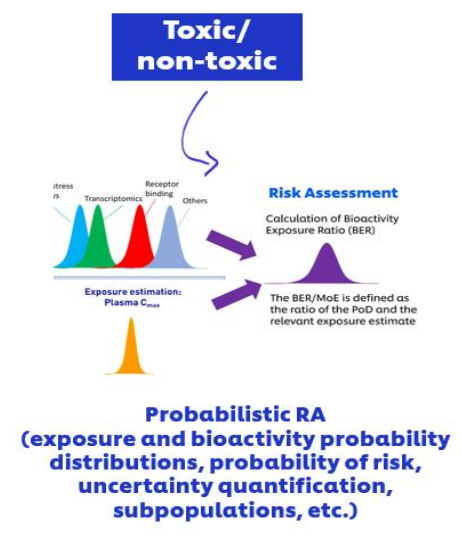
Traditional Toxicology = Empirical science focused on observations from animal studies



Increased focus on the use of exposure science and understanding of human biology (NAMs, PBK, DAs, IATAs, protection of human health, AOPs...)



ONTOX - Expert and data-driven decision making (fully multidisciplinary science)

Barriers to implementation of NAMs



Traditional Toxicology = Empirical science focused on observations from animal studies



Increased focus on the use of exposure science and understanding of human biology (NAMs, PBK, DAs, IATAs, protection of human health, AOPs...)




ONTOX - Expert and data-driven decision making (fully multidisciplinary science)

Time

Despite widely acknowledged benefits offered by NAMs, there continue to be barriers that prevent or limit application of NAMs for decision-making in chemical safety assessment:

- **Scientific/Technical barriers**
- **Societal/Cultural barriers**
- **Regulatory/Legislative barriers**
- **Economic barriers**

New approach methodologies (NAMs): identifying and overcoming hurdles to accelerated adoption 

Fiona Sewell ✉, Camilla Alexander-White, Susy Brescia, Richard A Currie, Ruth Roberts, Clive Roper, Catherine Vickers, Carl Westmoreland, Ian Kimber

Toxicology Research, Volume 13, Issue 2, April 2024, tfae044,
<https://doi.org/10.1093/toxres/tfae044>

Published: 25 March 2024 **Article history** ▼

Scientific/Technical barriers – establishing performance standards

- **Significant progress in the adoption of NAMs for assessing specific local, defined toxicity endpoints**
- **Toxicities driven by chemical reactivity or physicochemical properties:**
 1. **skin corrosion/irritation**
 2. **serious eye damage/eye irritation**
 3. **skin sensitisation and skin absorption.**
- **Data from the animal tests (and human data where available) allowed individual NAMs to be validated for hazard identification and potential potency categorisation.**




> Toxicol In Vitro. Feb-Apr 1997;11(1-2):141-79. doi: 10.1016/s0887-2333(96)00069-0.

A summary report of the COLIPA international validation study on alternatives to the draize rabbit eye irritation test



Scientific/Technical barriers – establishing performance standards

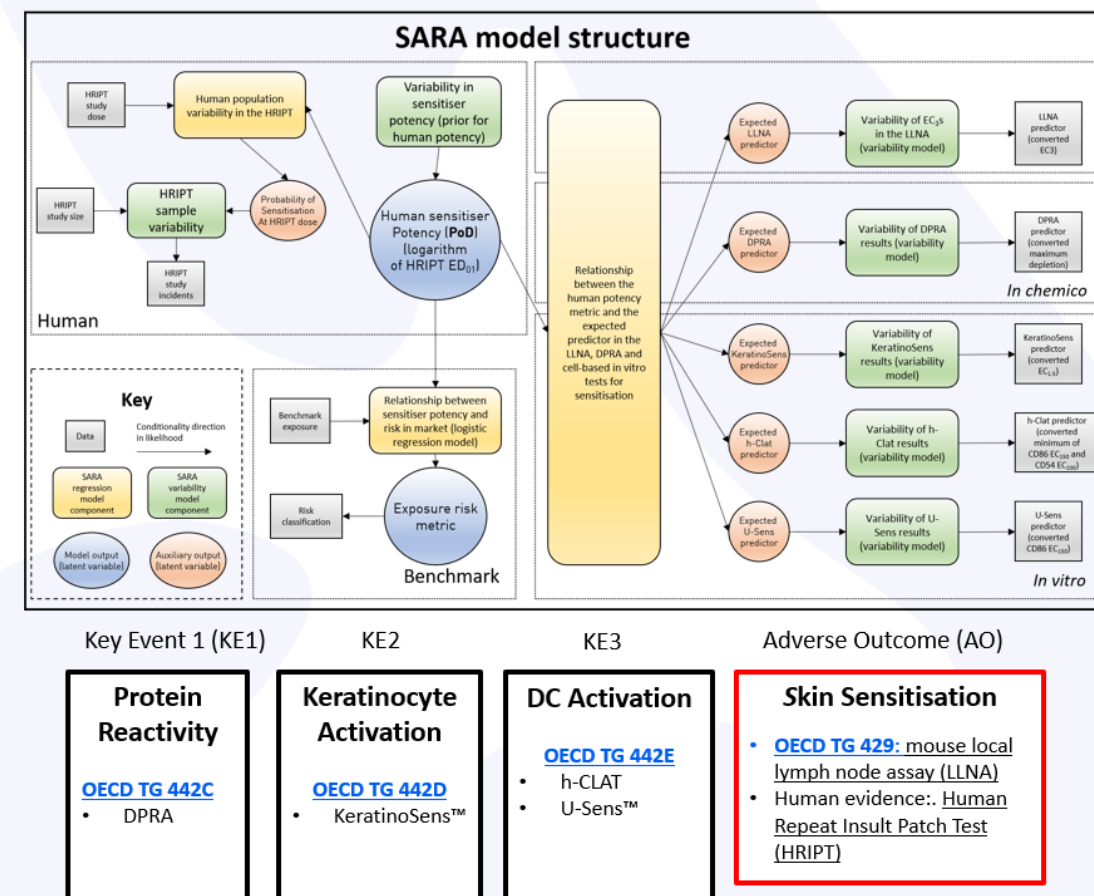
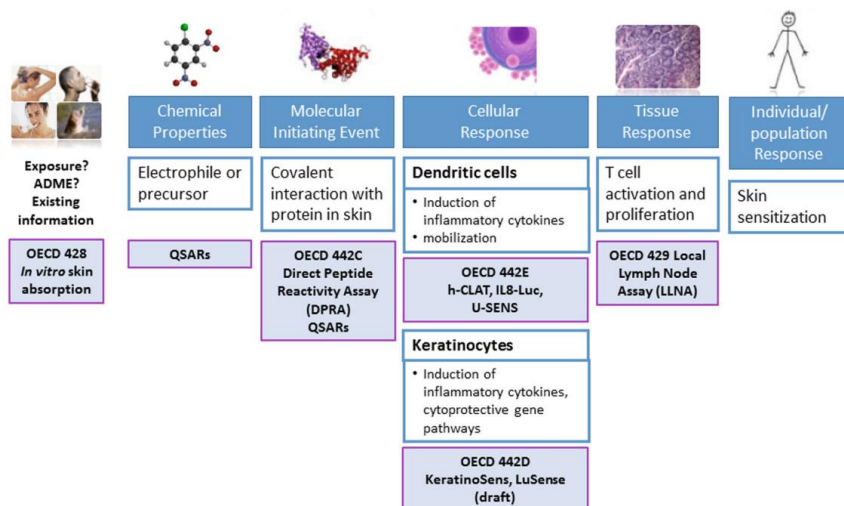
Combination of 3 human-based *in vitro* NAMs for skin sensitisation had a similar performance but outperformed the LLNA in terms of specificity.



Guideline No. 497: Defined Approaches on Skin Sensitisation

A Defined Approach (DA) consists of a selection of information sources (e.g. in silico predictions, in chemico, in vitro data) used in a specific combination, and resulting data are interpreted using a fixed data interpretation procedure (DIP) (e.g. a mathematical, rule-based model). DAs use methods in combination and are intended to overcome some limitations of the individual, stand-alone methods. The first three DAs included in this Guideline use combinations of OECD validated ✓ More

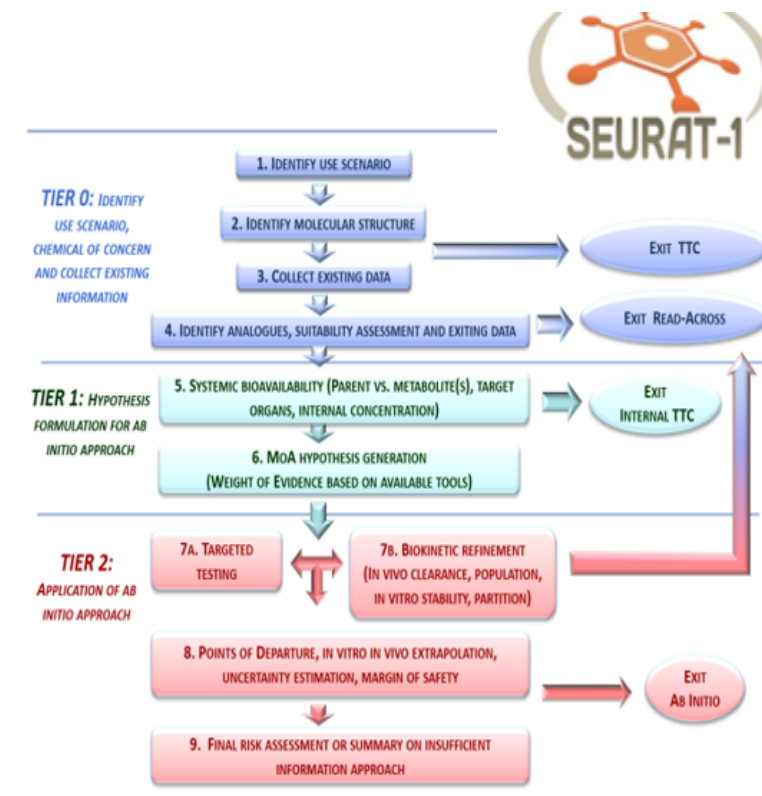
Published on June 22, 2021 Also available in: French



Reynolds et al. Computational Toxicology, 2019

Scientific/Technical barriers – establishing performance standards

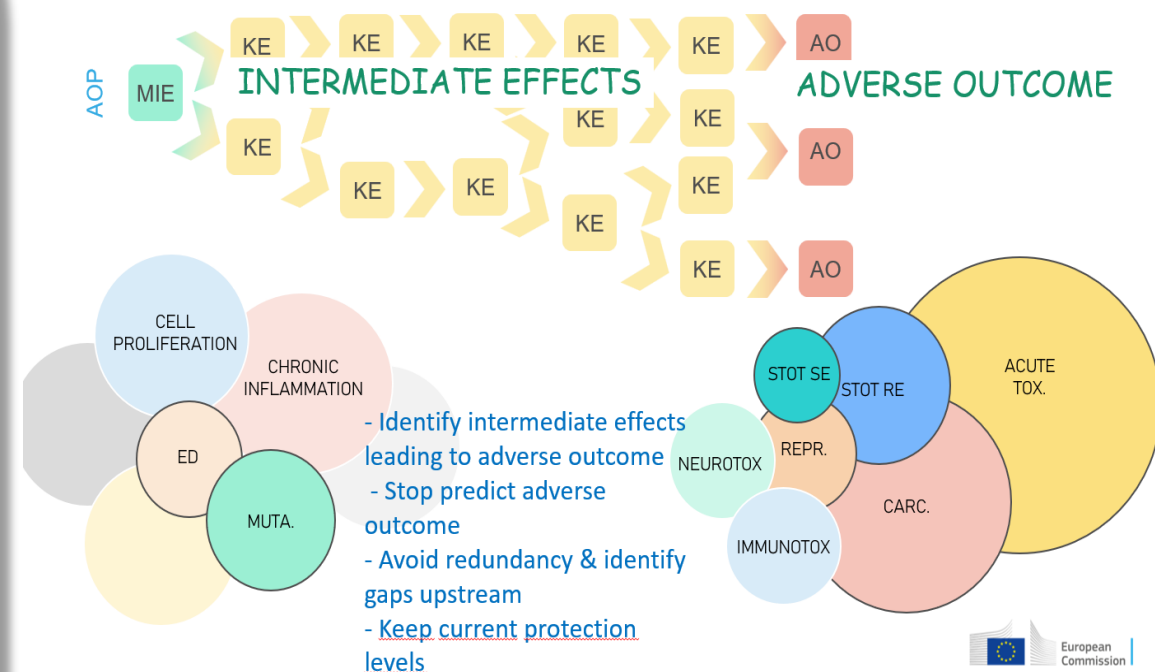
- Effects resulting from **systemic exposure** (carcinogenicity, developmental and reproductive toxicity) or chronic/repeat dose effects subject to **multiple mechanisms are more complex.**
- **Slow progress so far in the adoption of NAMs.**
- **The aim is to provide information on a chemical using a combination of NAMs.**
- **Achieve a more relevant exposure-based safety assessment for human (or relevant environmental species).**



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

Scientific/Technical barriers – establishing performance standards

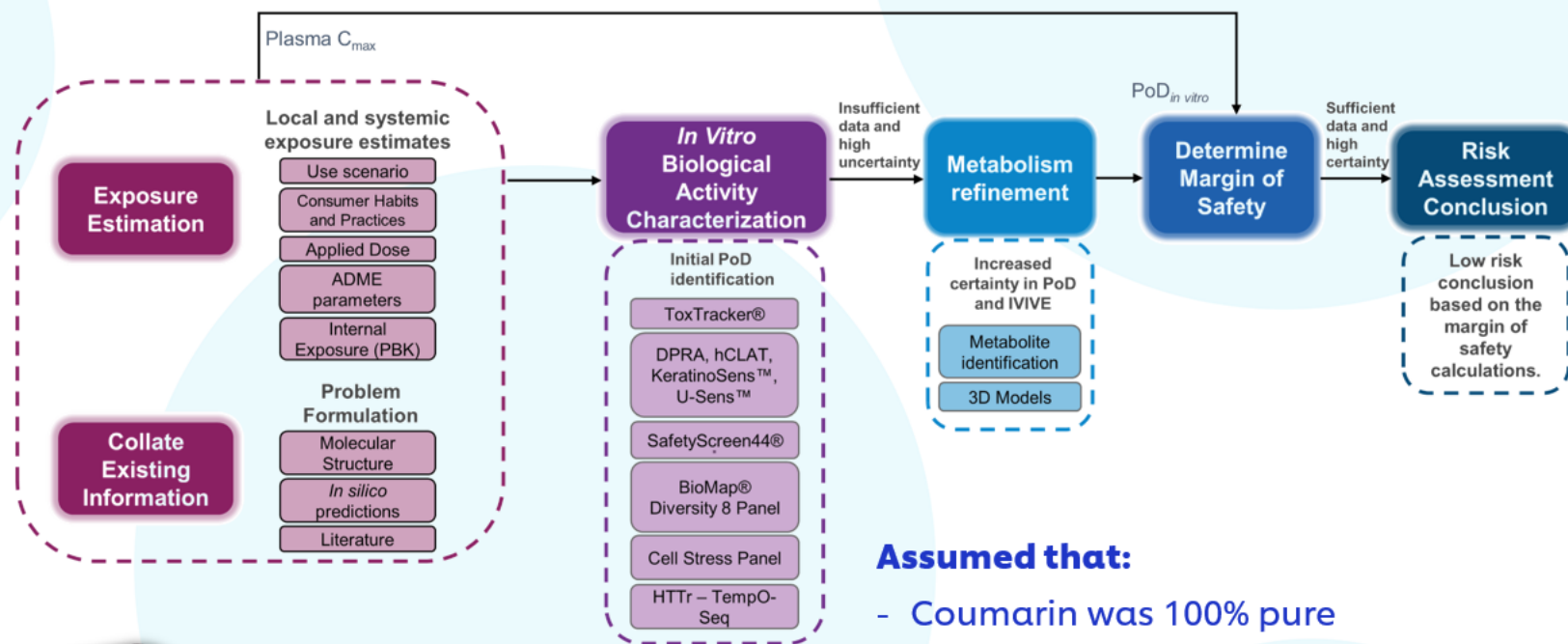
- **This approach is conceptually different from the tradition of assessing toxicity in whole animals as a basis for human safety.**
- **The aim is not to recapitulate the animal test without the animal.**
- **Have clarity on the current levels of health protection offered by animal models including data variability – current 'gold standard'.**
- **Define reference dataset to evaluate performance of NAM(s).**
- **Ensure similar or higher level of protection.**



Elisabet Berggren, EC workshop on the roadmap

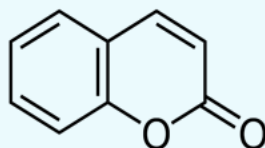
Scientific/Technical barriers – increase scientific confidence in NAMs end-to-end case studies

NGRA for Systemic Exposure & Effects: 0.1% coumarin in face cream



Assumed that:

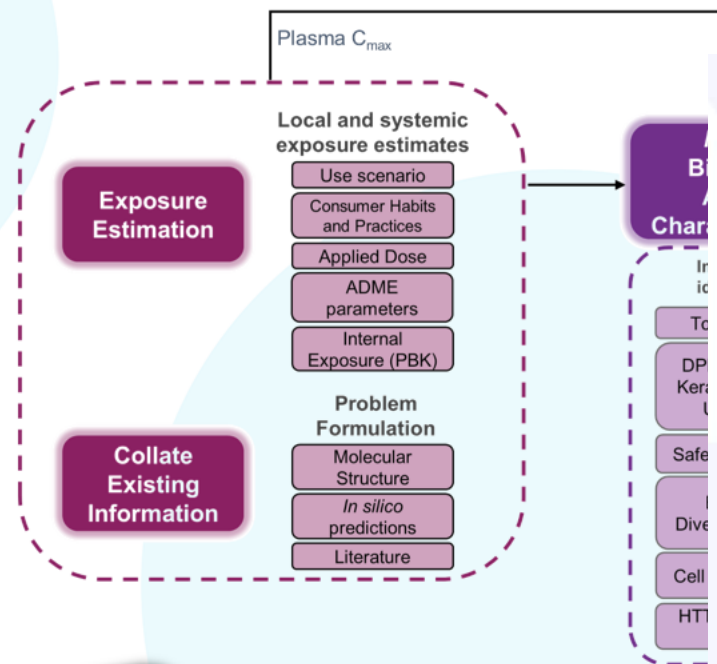
- Coumarin was 100% pure
- No *in vivo* data was available such as animal data, history of safe use (HoSU) or clinical data or use of animal data in read across



Baltazar et al., (2020) *Tox Sci* Volume 176, Issue 1, 236–252

Scientific/Technical barriers – increase scientific confidence in NAMs end-to-end case studies

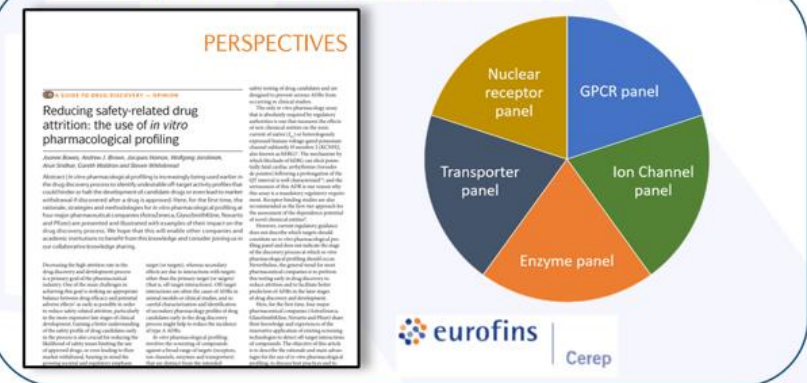
NGRA for Systemic Exposure & Effects: 0.1% coumarin in face cream



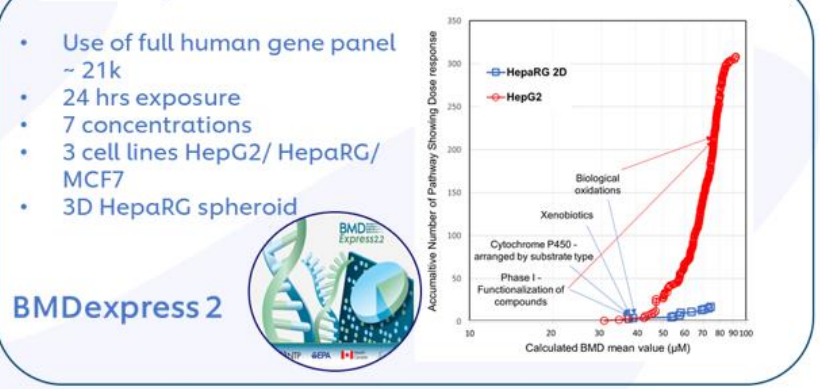
PBK Modelling



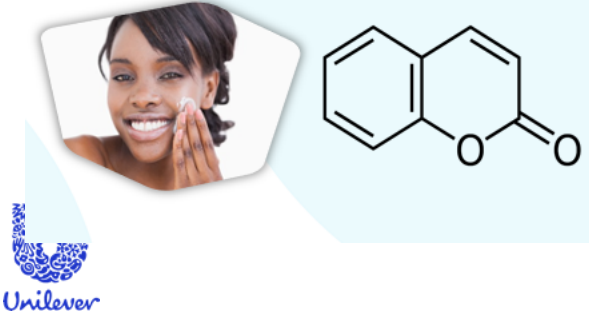
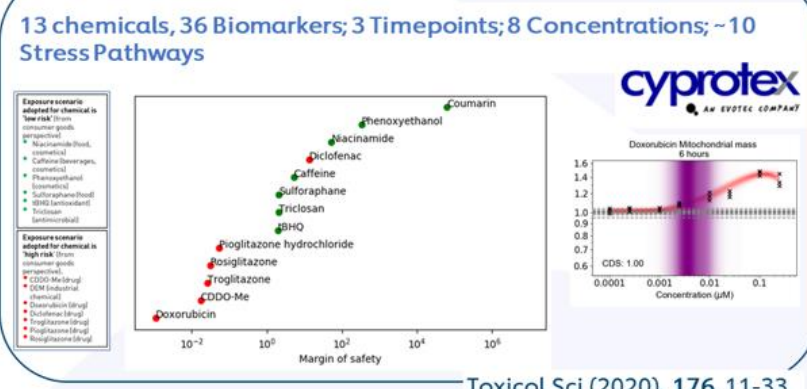
In vitro pharmacological profiling



Transcriptomics

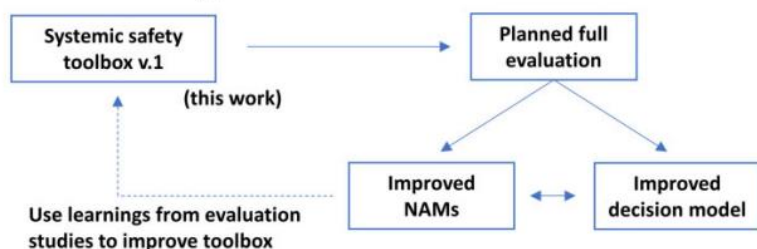


Cellular Stress Pathways



Scientific/Technical barriers – increase scientific confidence in NAMs end-to-end case studies

A An iterative evaluation approach



B

Exposure estimation

Current version

- Population average C_{max}
- Metric based on plasma concentration
- Uncertainty in PBK C_{max} model error, captured using CMED model
- Adult population

Potential improvements

- Extension to other dose metrics (AUC, CSS)
- Use of metrics based on other compartments (e.g. liver, kidney)
- Population variability in C_{max} /AUC/CSS
- PBK modelling of other age groups

POD estimation

Current version

- Based on 3 bioactivity platforms (HTTR, CSP and IPP)
- HTTr and CSP use immortalized cell lines.
- PODs summarised as point estimates

Potential improvements

- Increase biological coverage (inc. metabolic competence) of cell line models
- Use of iPSC or primary cells from different donors to capture interindividual variability.
- Estimate POD inter-laboratory and intra-laboratory variability between independent replicates

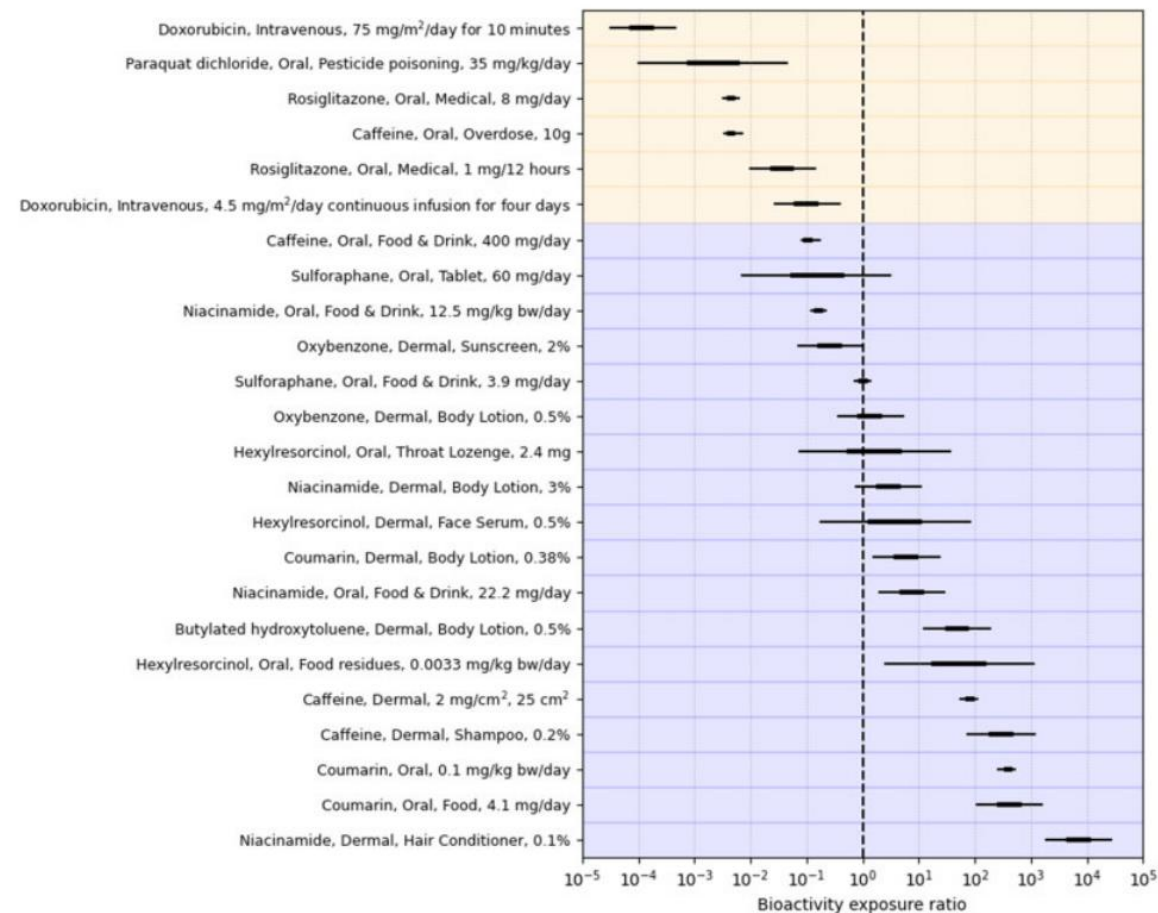
BER estimation and decision model

Current version

- BER distribution reflects the potential error in the PBK C_{max} estimate
- Decision model based on 24 benchmark exposure scenarios (this work)

Potential improvements

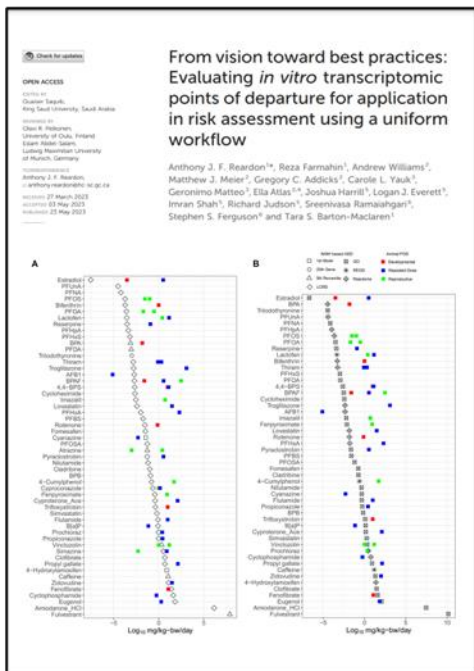
- Extend BER to consider other forms of variability and uncertainty (e.g. population variability, interlaboratory variability)
- Increase number and diversity of benchmark exposure scenarios (i.e. planned full evaluation).



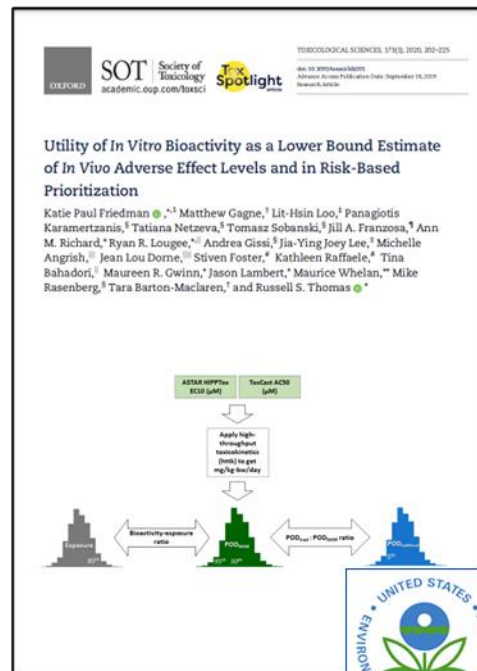
Middleton et al. 2022

Scientific/Technical barriers – increase scientific confidence in NAMs end-to-end case studies

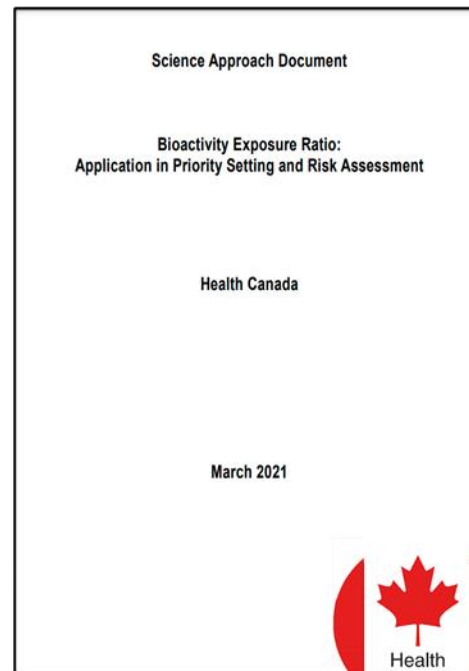
≈40 compounds



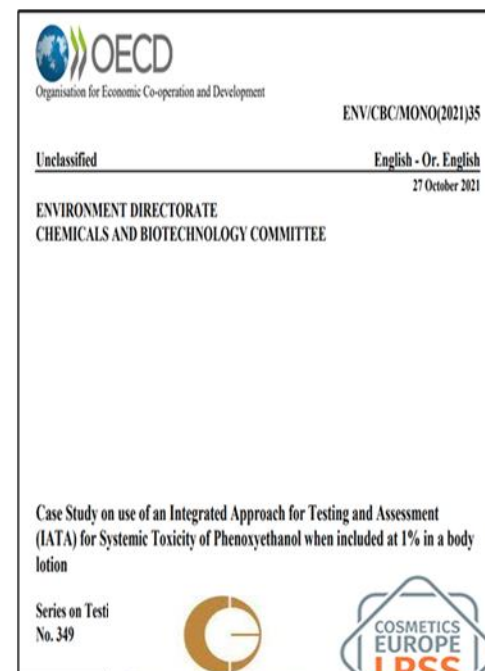
448 compounds



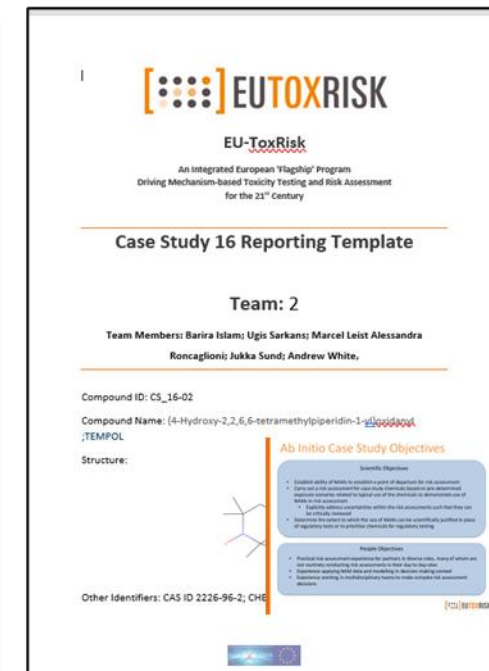
46 compounds



30 compounds



>22 compounds



“The primary conclusion of our work is that for **89% of the chemicals in this case study**, the HTS approach to derivation of a **POD_{NAM,95}** for screening and prioritization purposes produced **a value less than or equal to the POD_{traditional}** from *in vivo* toxicology studies.”

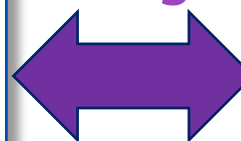
Cultural/Societal barriers – a mindset shift

Regulators

There is a long history of experimental animal use - change from the status quo can prove uncomfortable:

- **Inertia, familiarity, and comfort with established methods** – also driven by understandable concerns to avoid error and ensure safety.
- **Concerns around loss of data continuity**
- **Ambiguities around the acceptance of NAMs and lack of interpretation standards (e.g. DNT)**
- **Little experience with NAM data that haven't been submitted in dossiers**

Lack of iterative dialogue



Industry and CROs

- **Uncertainty about how new approaches can be used and applied in the regulatory context**
- **Perceptions around what will be expected and accepted by regulatory authorities**
- **NAM approaches usually not submitted even though they might be available (e.g. recent submission of the NAM dossier along the traditional dossier for BP-4 to SCCS)**
- **Hard to make business case for investment in NAM development when acceptance by regulators is uncertain**

Regulatory/Legislative barriers

- The law demands **classification** based on identification of hazards based on animal studies. High doses are driven with the aim of identifying hazard in the animal, irrespective of the exposure
- Even though legislation allows for flexibility (e.g. REACH Annex XI, animals as 'last resort'), there remain **ambiguities on the interpretation of the law (legal defensibility)**
- Differences between the horizontal and vertical legislations (e.g. cosmetics)
- Lack of available resource, including knowledge and experience in handling and interpreting new datasets

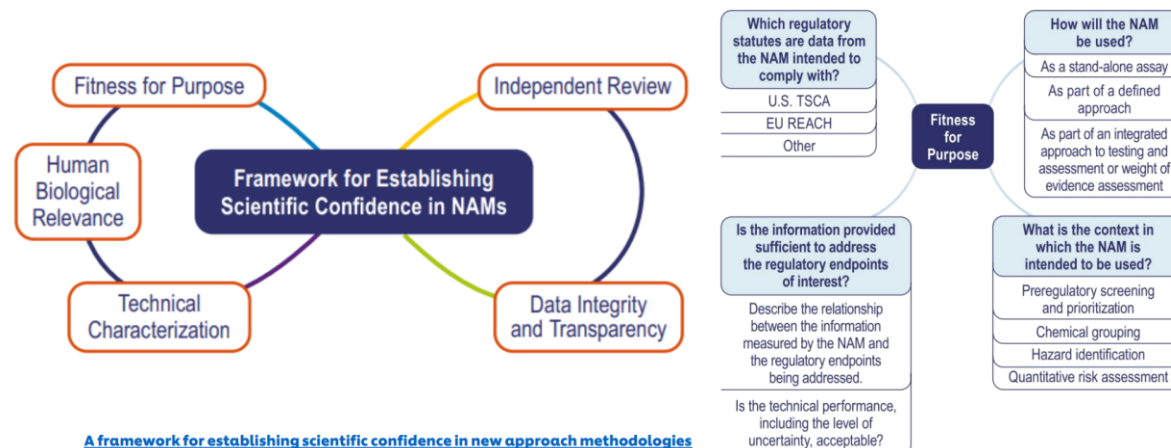
EU's chemicals legislation



Bercaru Offelia, ECHA workshop 2023

Validation/Regulatory Acceptance of NAMs

- Understanding the needs for formal validation at an international level
- Current validation process is slow and based on traditional animal tests
- Need for a framework/guidance for fit for purpose validation at an international level, e.g. update of OECD GD 34
- Standardised reporting templates to facilitate regulatory use (exposure, QSAR, omics, IATA, etc.)
- Classification that is not based on animal studies but on modern science (e.g. EPAA)



← Increasing Potency

	Category 1 Hazard	Category 2 Hazard	Category 3 Hazard	Category 4 Hazard
Category A Exposure				
Category B Exposure				
Category C Exposure				
Category D Exposure				
Category E Exposure				

↑ Increasing Exposure

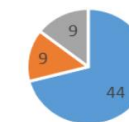
A framework for establishing scientific confidence in new approach methodologies

van der Zalm et al. Archives of Toxicology (2022) 96:2865–2879

Economic barriers – top/down planning

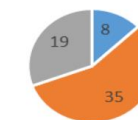
- **Perceived business risk and uncertainty associated with building NAM capability and capacity**
- **Increased public funding for method validation (OECD workshop Dec 2023)**
- **Who should support method validation? Funding of validation should not be left to the method developer only (in the range of 200K – 500K Euros, depending on the complexity of the assay)**
- **A viable business case for CROs is needed to switch away from animal studies to NAM-based approaches**
- **Need for significant investment in training and resources from all stakeholders (regulators, industry, CROs)**

Validation is a common good and should be sponsored by all the stakeholders?



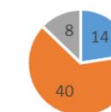
■ Agree ■ Disagree ■ No opinion

The validation should be funded by the test method developer?



■ Agree ■ Disagree ■ No opinion

Laboratories participating in a validation study should not have a commercial interest in the method?



■ Agree ■ Disagree ■ No opinion

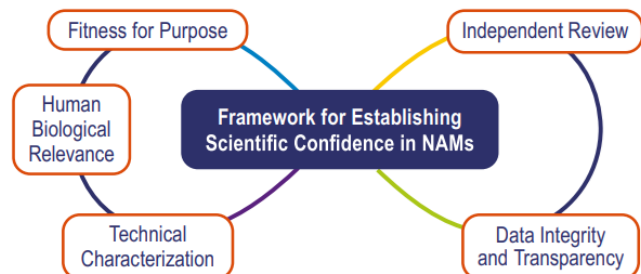
Source: OECD stakeholders' survey

How can we further accelerate the transition – initial thoughts

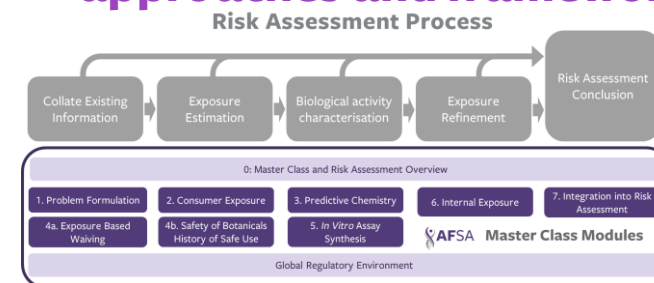
1. Build confidence in NAM-based frameworks by validating whether or not they're 'fit for regulatory use'

2. Co-create NAM best practice through open industry: regulator scientific dialogue using NGRA case studies

3. Update toxicological training to include NAM-based approaches and frameworks



A framework for establishing scientific confidence in new approach methodologies



4. Collaborate globally to pool resources & share learnings





ICCS

INTERNATIONAL
COLLABORATION ON
COSMETICS SAFETY

A Global Not-for-Profit Organization

Mission: to facilitate acceptance of animal-free safety assessments through Research, Education, and Regulatory Engagement

- 27** Cosmetic Product and Ingredient Manufacturers

 - Amorepacific
 - BASF
 - Beiersdorf
 - Chanel
 - Colgate
 - Coty
 - Croda
 - Estée Lauder
 - Edgewell
 - Evonik
 - Haleon
 - Henkel
 - IFF
 - Inolex
 - Innospec
 - Kao
 - Kenvue (J&J)
 - L'Oréal
 - LVMH
 - Oriflame
 - P&G
 - Reckitt
 - Shiseido
 - Takasago
 - Solvay
 - Unilever
 - Wella

10 Cosmetic & Chemical Trade and Research Associations

 - CAC, Cosmetics Alliance Canada
 - CE, Cosmetics Europe
 - CTPA, Cosmetic, Toiletry & Perfumery Assoc. (UK)
 - EFCCI, European Federation for Cosmetic Ingredients
 - FCA, Fragrance Creators Association
 - IFRA, International Fragrance Association
 - JCIA, Japan Cosmetic Industry Association
 - CASIC, Latin American Cosmetic, Personal Care and Home Care Industries Association
 - PCPC, Personal Care Products Council (US)
 - RIFM, Research Institute for Fragrance Materials

5 NGOS

 - CFI, Cruelty Free International
 - HSI, Humane Society International
 - IIVS, Institute for In Vitro Sciences
 - PCRM, Physicians Committee for Responsible Medicine
 - PSCI, Peta Science Consortium International

Conclusions

1. A global transition is underway as use of animal-free safety science increases & moves beyond innovators/early adopters; however, the progress has been slow
2. Translating NAMs into regulatory frameworks is facing scientific/technical, social/cultural, legislative/regulatory & economic barriers
3. Can we examine how these barriers can be overcome to drive wider exploitation and acceptance of the modern safety science? Can we define short-, mid-, long-term plans?

