Next Generation Risk Assessment:
Emerging Best Practice & Opportunities for Regulatory Use

Dr Gavin Maxwell, gavin.maxwell@unilever.com

17th June 2026, SOT RASS Risk Assessment Syllabus Webinar

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Emerging Best Practice & Opportunities for Regulatory Use

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1. **Next Generation Risk Assessment**
   a) NGRA Paradigm Shift
   b) Emerging Best Practice
2. **Opportunities for Regulatory Use**
   a) Cosmetics
   b) Chemicals
   c) Medicines
3. **Have we reached a tipping point?**
   a) Tipping point concept
   b) Where are we?
4. **Accelerating the paradigm shift**

Next Generation Risk Assessment (NGRA) Paradigm Shift

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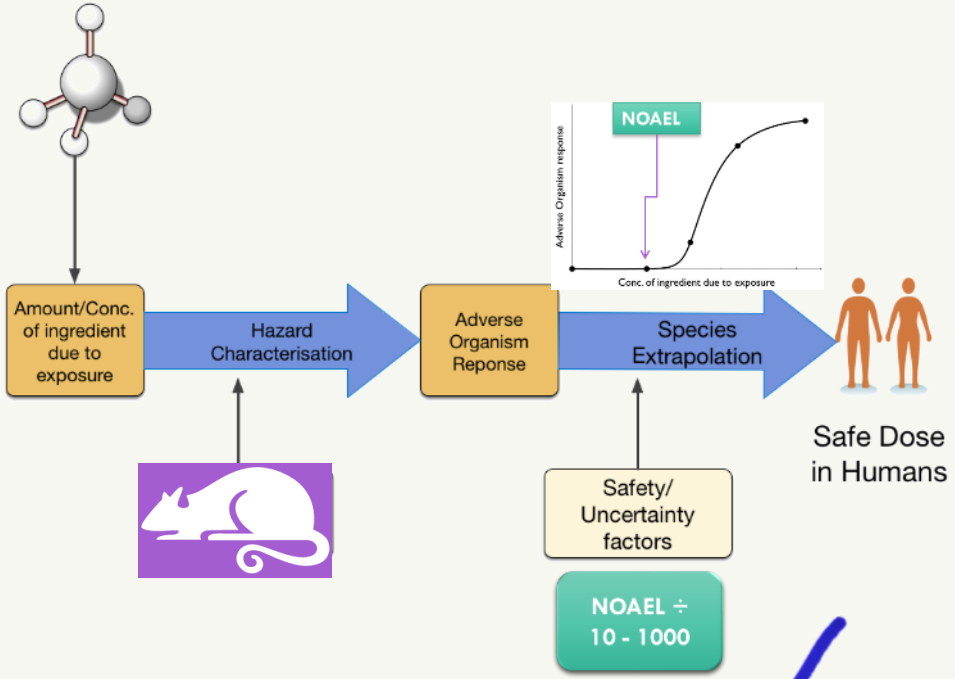
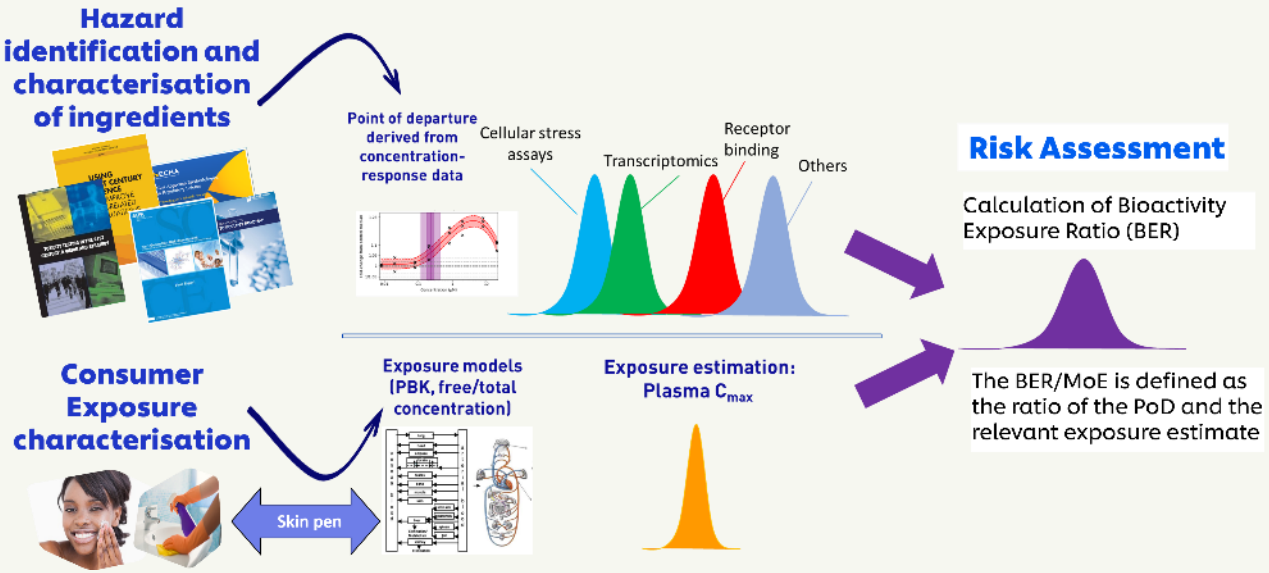
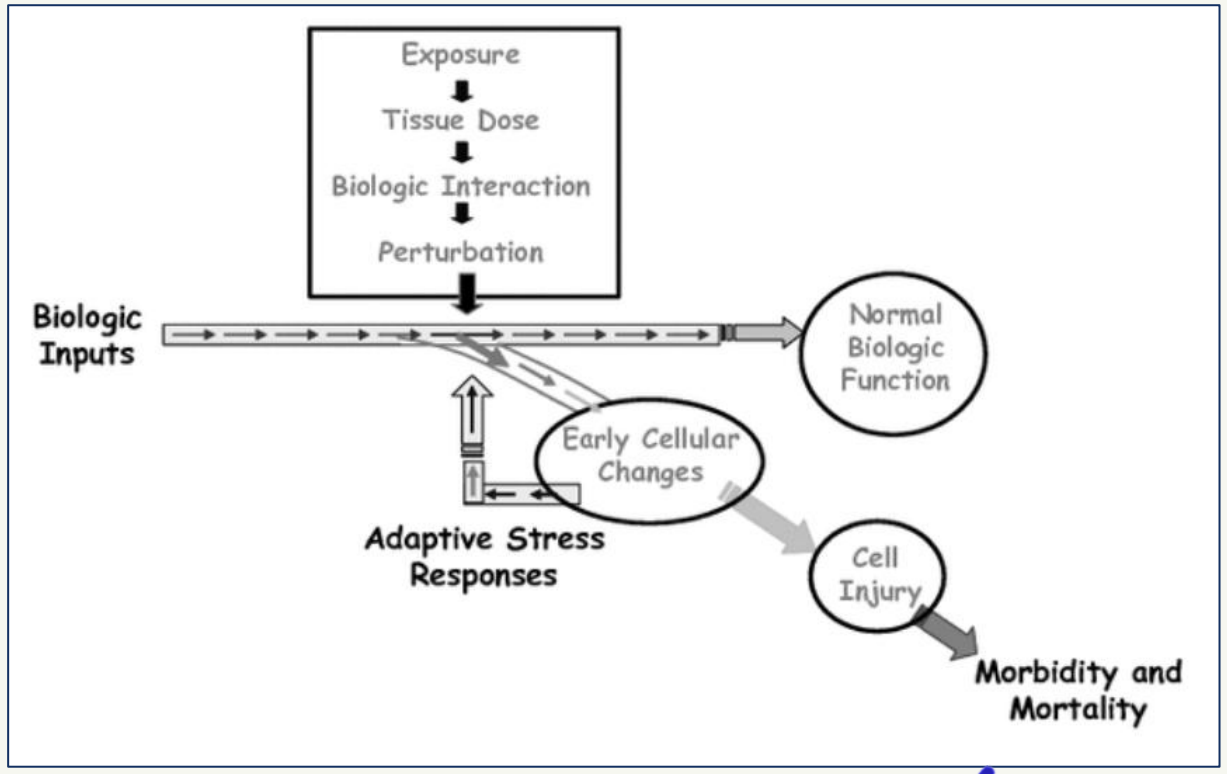
'Traditional' Risk Assessment

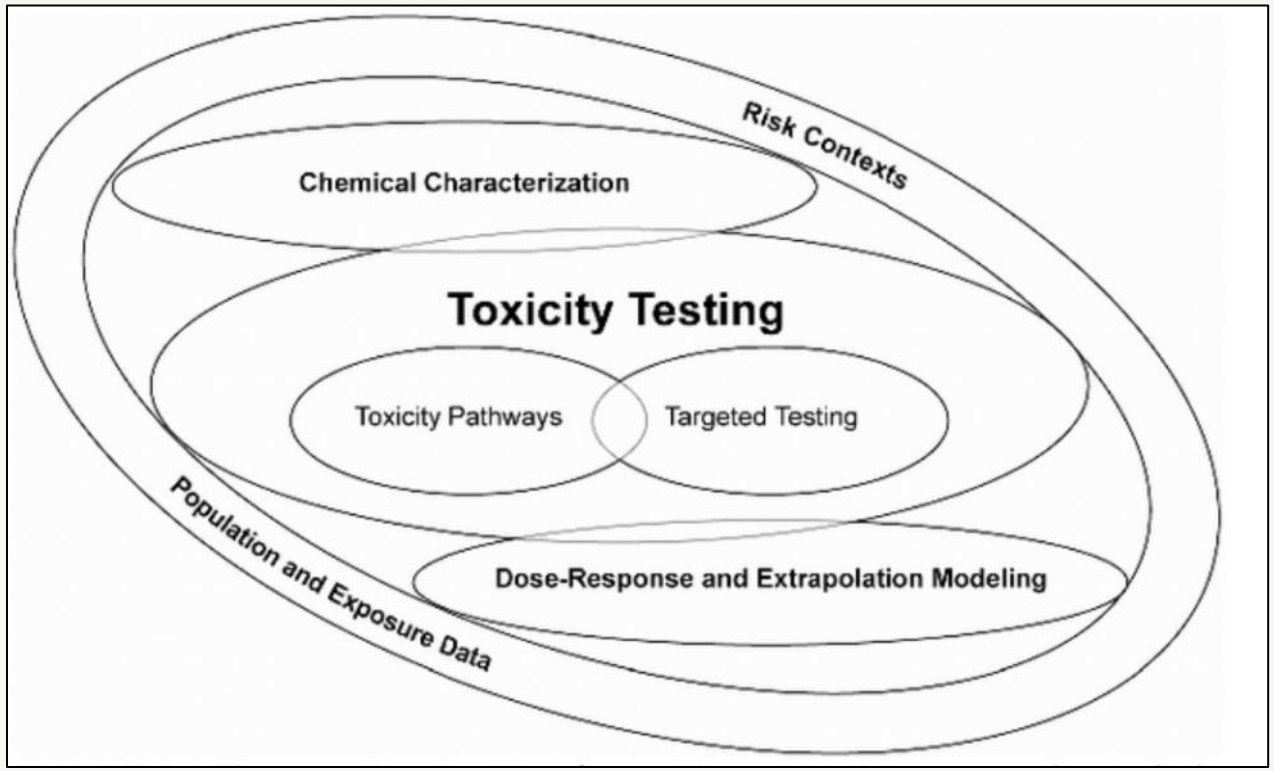


'Next Generation' Risk Assessment

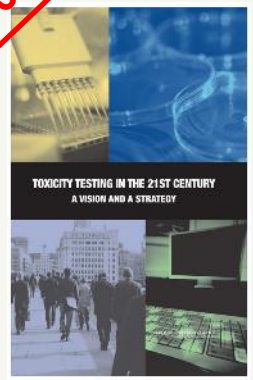


Next Generation Risk Assessment (NGRA) concepts





2007



[Toxicity Testing in the 21st Century: A Vision and a Strategy | The National Academies Press]

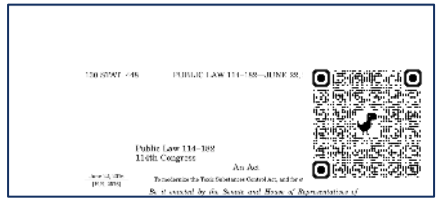
Milestones in US TT21c vision implementation

2008-2012

Tox 21 collaboration (EPA, NCATs, NIEHS/NTP, FDA) to develop more human-relevant approaches for evaluating chemical toxicity

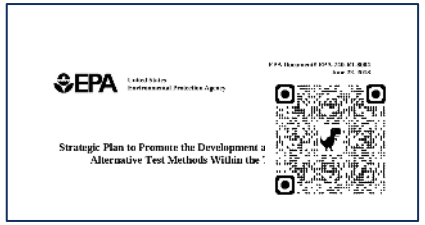
2016

Frank R. Lautenberg Chemical Safety Act amendments to TSCA directs EPA to reduce and replace animal testing and promote alternative methods



2018-present

Toxic Substances Control Act (TSCA) strategic plan & NAM list operationalize the Lautenberg Act's alternative testing mandate



2019-present

EPA NAMs Work Plan to phase regulatory use of NAMs and, in so doing, eliminate mammalian testing by 2035. Reinstated in 2026.

Applying the NGRA concepts to safety assessment: aim is protection, not prediction

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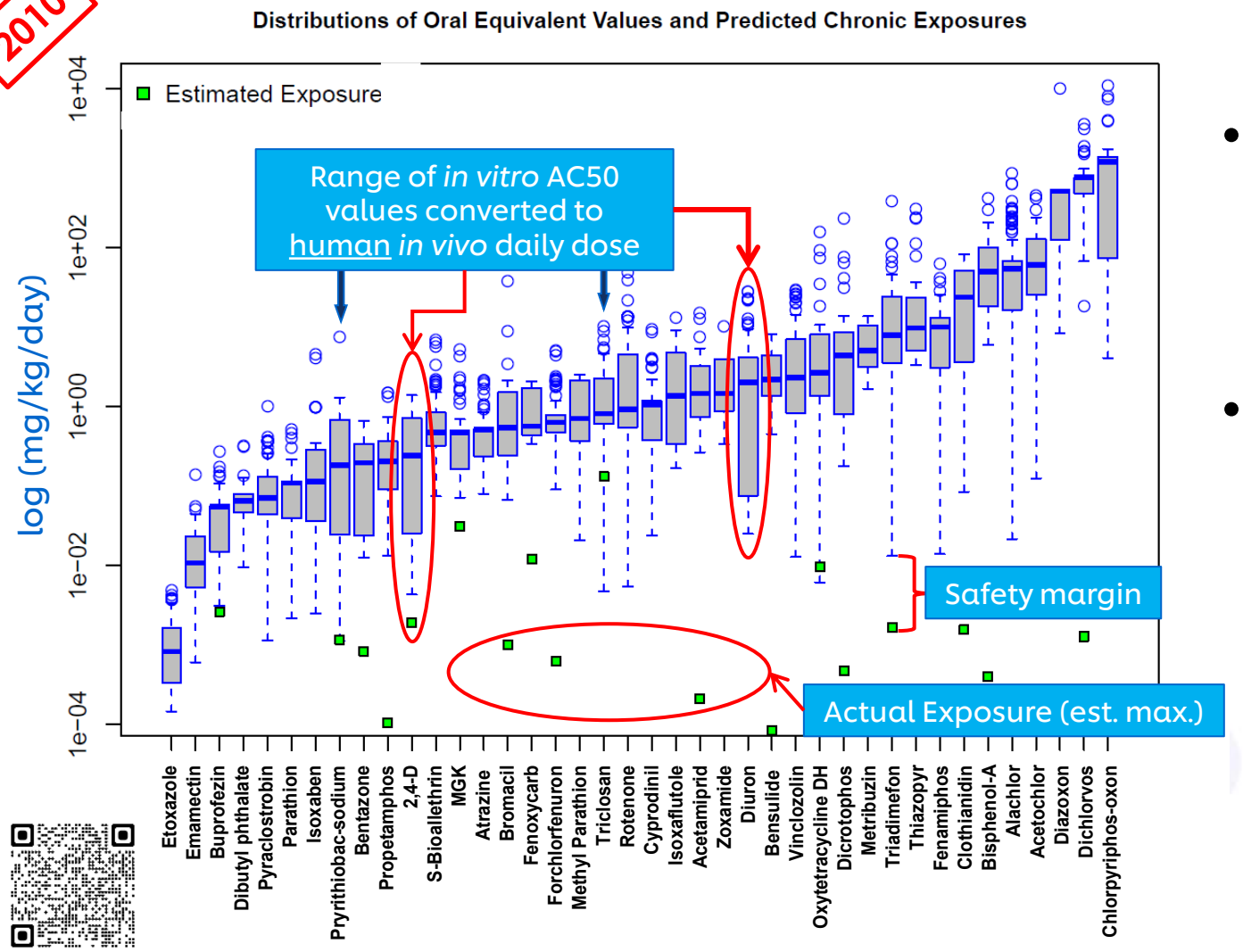
2010



- If no bioactivity is observed at relevant exposures, there can be no adverse effects.
- No need to predict the results of high dose toxicology studies in animals.

Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

US EPA Next Generation Blueprint Tiered Testing Framework

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2019

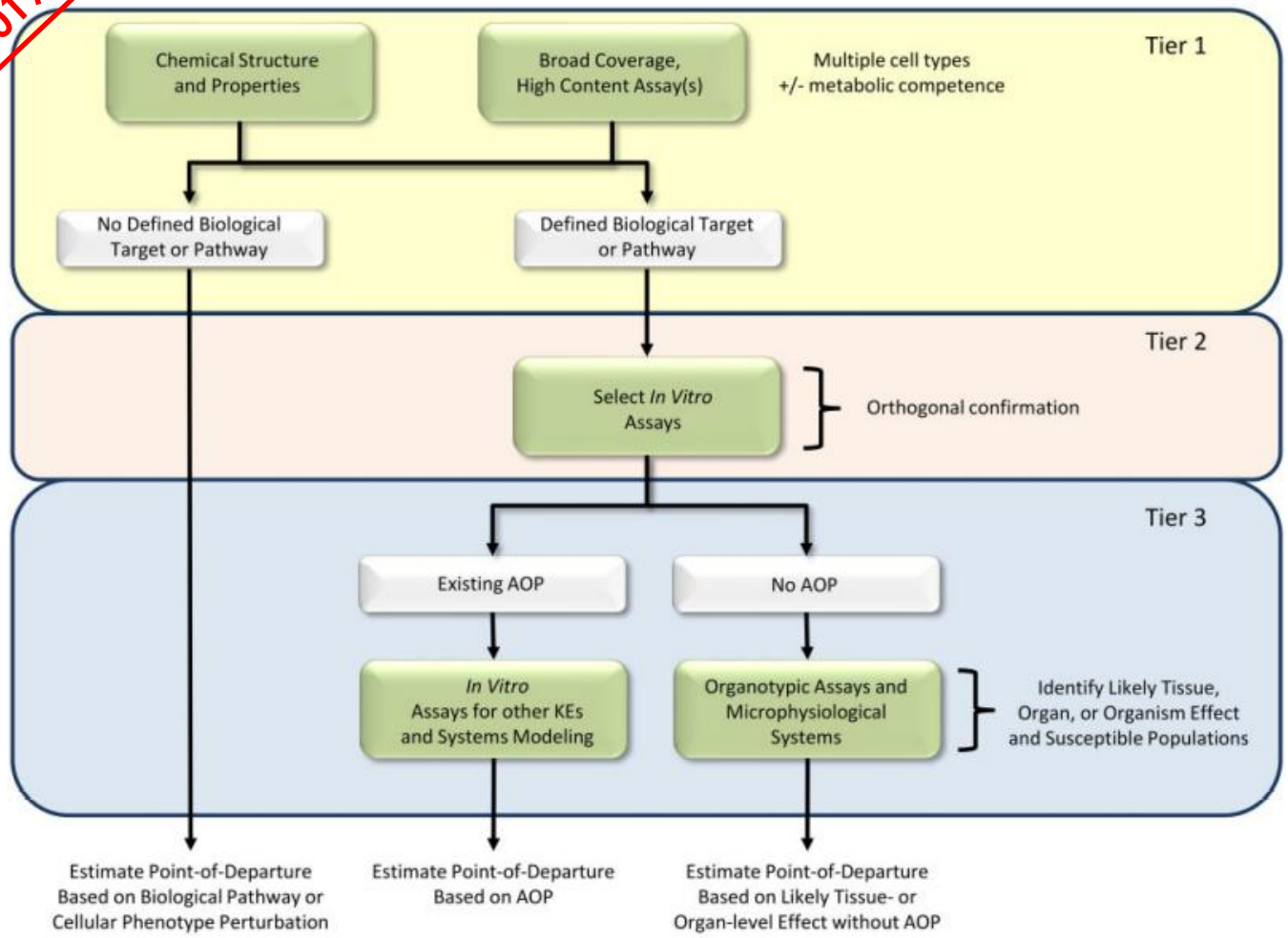

Figure 2. Tiered testing framework for hazard characterization. Tier 1 uses both chemical structure and broad coverage, high content assays across multiple cell types for comprehensively evaluating the potential effects of chemicals and grouping them based on similarity in potential hazards. For chemicals from Tier 1 without a defined biological target / pathway, a quantitative point-of-departure for hazard is estimated based on the absence of biological pathway or cellular phenotype perturbation. Chemicals from Tier 1 with a predicted biological target or pathway are evaluated Tier 2 using targeted follow-up assays. In Tier 3, the likely tissue, organ, or organism-level effects are considered based on either existing adverse outcome pathways (AOP) or more complex culture systems. Quantitative points-of-departure for hazard are estimated based on the AOP or responses in the complex culture system.

https://pubmed.ncbi.nlm.nih.gov/30835285/

EPA United States Environmental Protection Agency

OXFORD SOT Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 169(2), 2019, 317–332
doi: 10.1093/toxsci/kfz058
Advance Access Publication Date: March 5, 2019
Forum

FORUM

The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency

Russell S. Thomas,*,[1] Tina Bahadori,† Timothy J. Buckley,‡ John Cowden,* Chad Deisenroth,* Kathie L. Dionisio,‡ Jeffrey B. Frithsen,§ Christopher M. Grulke,* Maureen R. Gwinn,* Joshua A. Harrill,* Mark Higuchi,¶ Keith A. Houck,* Michael F. Hughes,¶ E. Sidney Hunter, III,¶ Kristin K. Isaacs,‡ Richard S. Judson,* Thomas B. Knudsen,* Jason C. Lambert,‖ Monica Linnenbrink,* Todd M. Martin,‖‖ Seth R. Newton,‡ Stephanie Padilla,¶ Grace Patlewicz,* Katie Paul-Friedman,* Katherine A. Phillips,‡ Ann M. Richard,* Reeder Sams,* Timothy J. Shafer,¶ R. Woodrow Setzer,* Imran Shah,* Jane E. Simmons,¶ Steven O. Simmons,* Amar Singh,* Jon R. Sobus,‡ Mark Strynar,‡ Adam Swank,‡ Rogelio Tornero-Valez,‡ Elin M. Ulrich,‡ Daniel L. Villeneuve,‖‖ John F. Wambaugh,* Barbara A. Wetmore,‡ and Antony J. Williams*

*National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, †National Center for Environmental Assessment, U.S. Environmental Protection Agnecy, Washington, D.C. 20004, ‡National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, §Chemical Safety for Sustainability National Research Program, U.S. Environmental Protection Agency, Washington, D.C. 20004, ¶National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, ‖National

Accelerating the Pace of Chemical Risk Assessment (APCRA) case studies demonstrate the feasibility of NGRA approaches

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APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

Led by: Health Canada Santé Canada ECHA EUROPEAN CHEMICALS AGENCY

https://apcra.net/case-studies/

2020

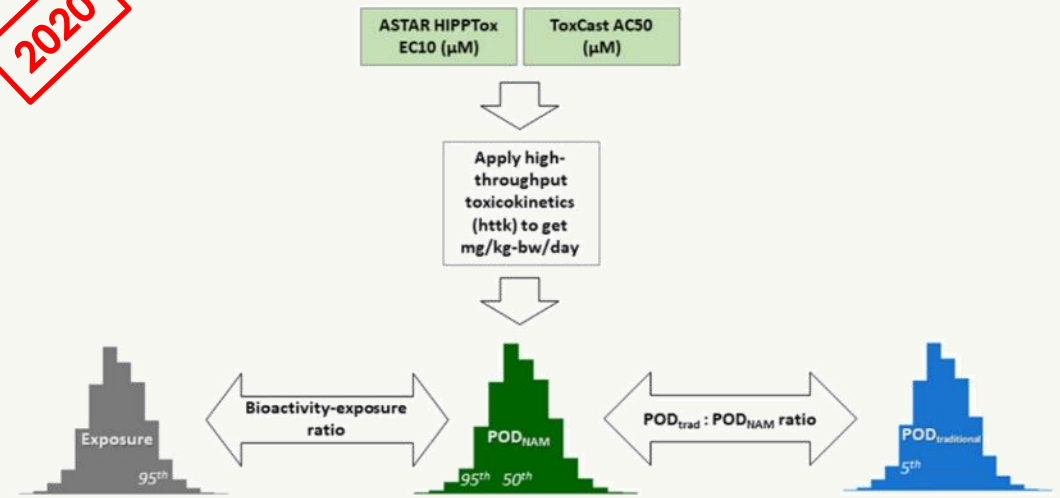
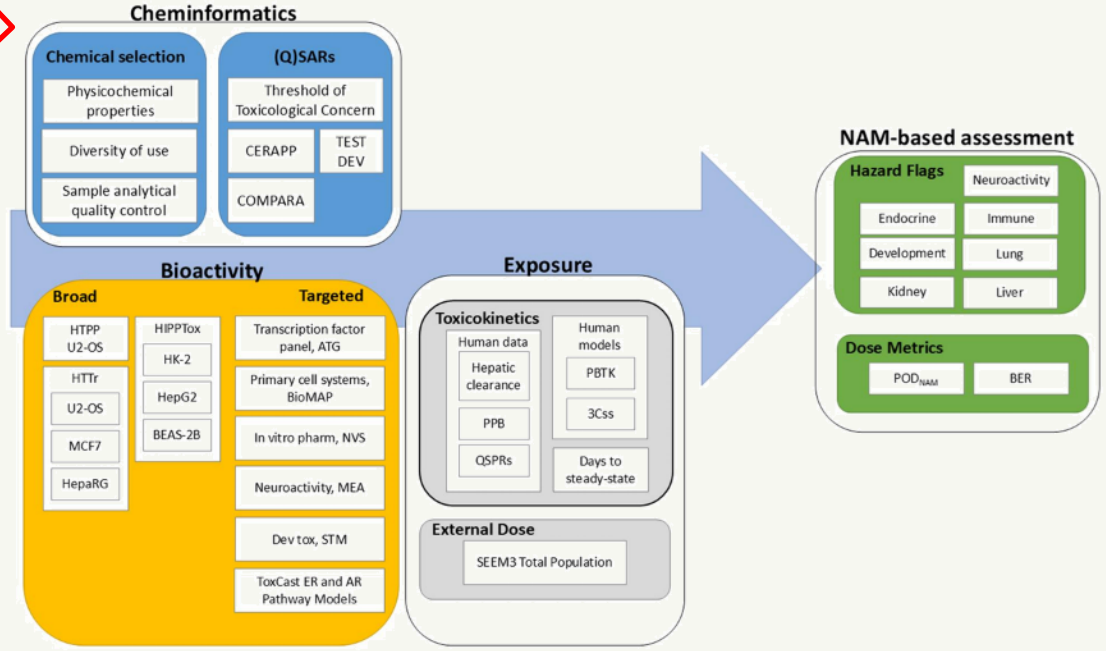


Figure 1. Overall workflow of the case study. This case study includes 448 substances with exposure predictions, *in vitro* assay data, HTTK information using the httk R package, and *in vivo* hazard information. The 50th and 95th percentile from the Monte Carlo simulation of interindividual toxicokinetic variability were used to estimate administered equivalent doses (AEDs), and the minimum of either the ToxCast or HIPPTox-based AEDs were selected as the $POD_{NAM,\ 50}$ or $POD_{NAM,\ 95}$. The POD_{NAM} estimates were compared with the fifth percentile from the distribution of the $POD_{traditional}$ values obtained from multiple sources to obtain the $\log_{10}$ POD ratio. The $\log_{10}$ bioactivity:exposure ratio (BER) was obtained by comparing the POD_{NAM} estimates to exposure predictions. All values used for computation were in $\log_{10}$-mg/kg-bw/day units.

2025



Paul-Friedmann et al. 2020 APCRA 'retrospective' case study - To elucidate whether a "region of safety" , i.e. a threshold below which no bioactivity or toxicity would be anticipated, can be identified using NAMs for a list of chemicals with existing human health evaluations.

Paul-Friedmann et al. 2025 APCRA 'prospective' case study - To demonstrate how NAM data and classical toxicological studies can be used to inform the hazard and safety profile of chemicals with limited or unclear toxicological data

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   a) Tipping point concept
   b) Where are we?
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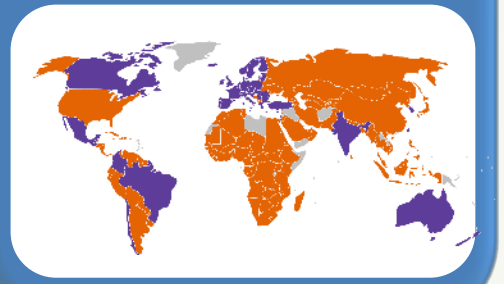
Cosmetics: milestones in regulatory use of NAMs/NGRA

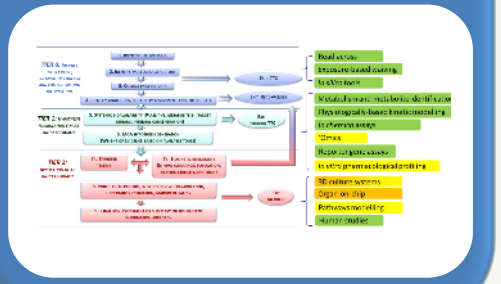
1998 - Present

Cosmetics Animal Testing bans (45 countries and 12 US states) drive investment in non-animal safety and 'replacement mindset'



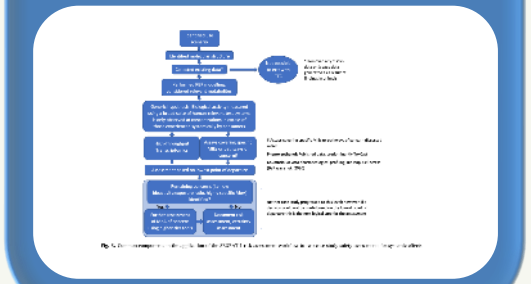
2019

SEURAT-1 Systemic Toxicity framework adaptation of tiered hazard assessment frameworks to allow exposure-driven safety assessment



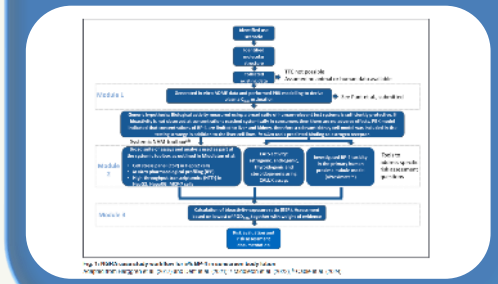
2021

International Cooperation on Cosmetic Regulation (ICCR) – definition of NGRA principles to pave the way for regulatory use



2023-25

Inclusion of SEURAT-1 framework in SCCS Notes of Guidance enables submission of first Cosmetic NGRA dossier for BP4



Cosmetic Animal Testing Bans (45 Countries & 12 US states) drive adoption of NGRA approaches & replacement mindset

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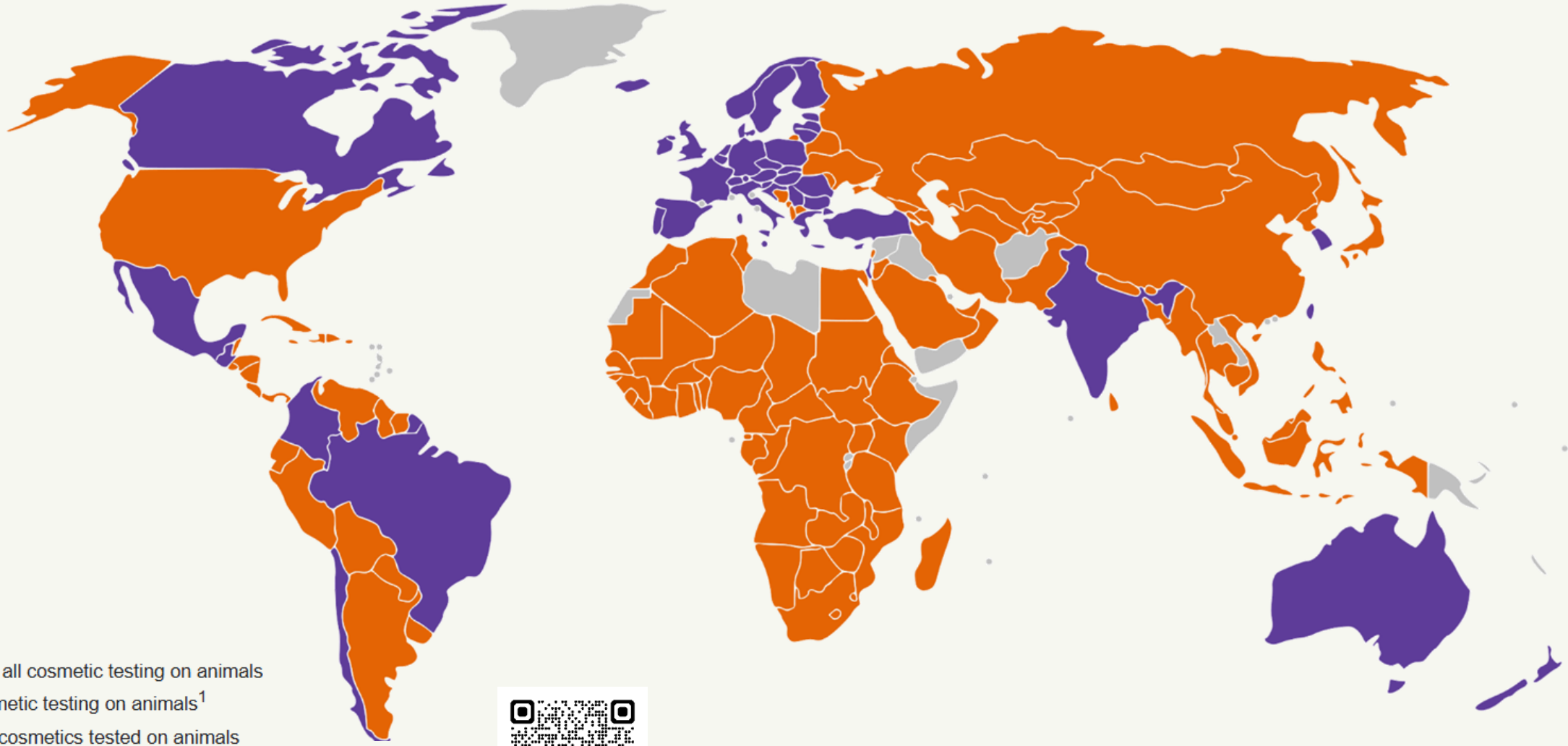

- Nationwide ban on all cosmetic testing on animals
- Partial ban on cosmetic testing on animals[1]
- Ban on the sale of cosmetics tested on animals
- No ban on any cosmetic testing on animals
- Unknown

[1] some methods of testing are excluded from the ban or the laws vary within the country

https://en.wikipedia.org/wiki/Testing_cosmetics_on_animals#cite_note-1

SEURAT-1 NGRA framework: tiered testing to support human health safety assessment

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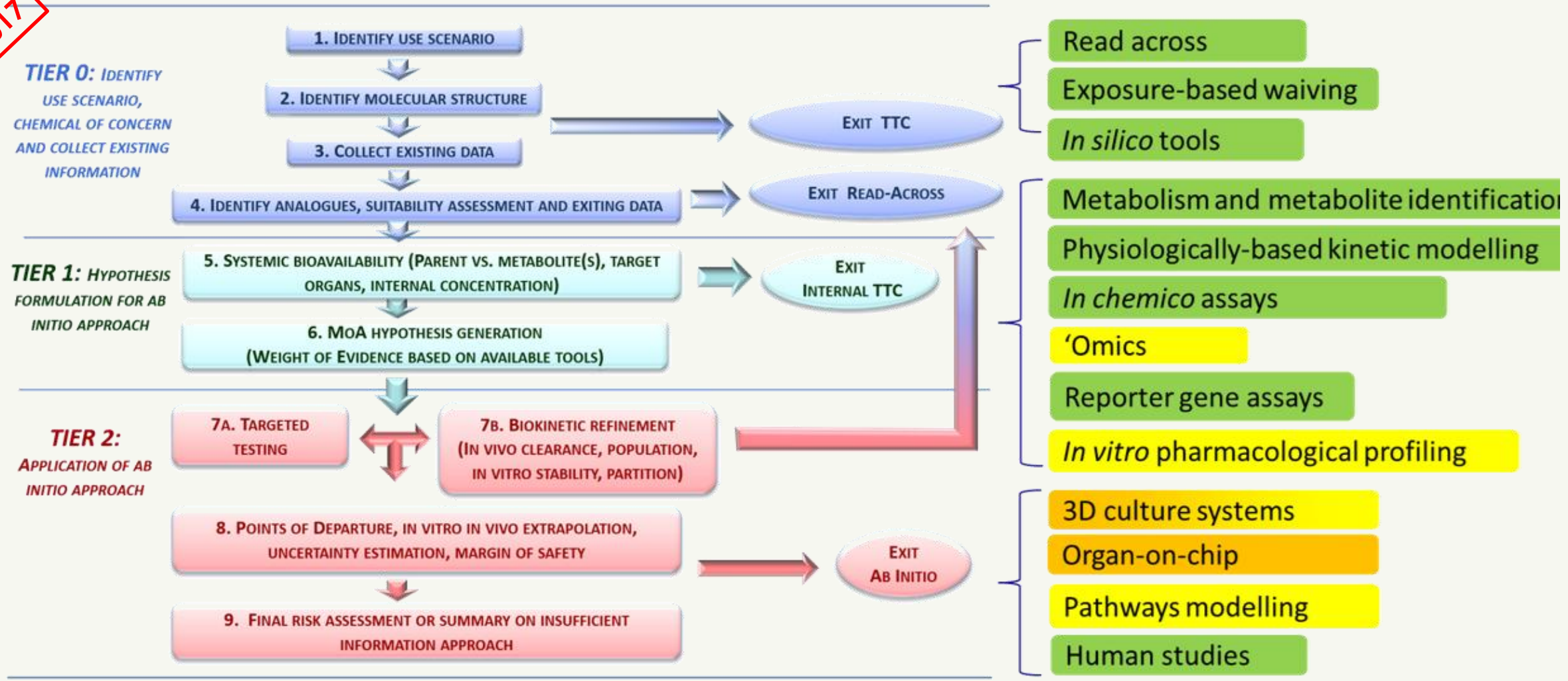
SEURAT-1

2017



https://doi.org/10.1016/j.comtox.2017.10.001

Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods

Standardising global best practice for NGRA for Cosmetics Safety:
International Cooperation on Cosmetics Regulation (ICCR) reports

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ICCR International Cooperation on Cosmetics Regulation

2021

Regulatory Toxicology and Pharmacology 125 (2021) 105026

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

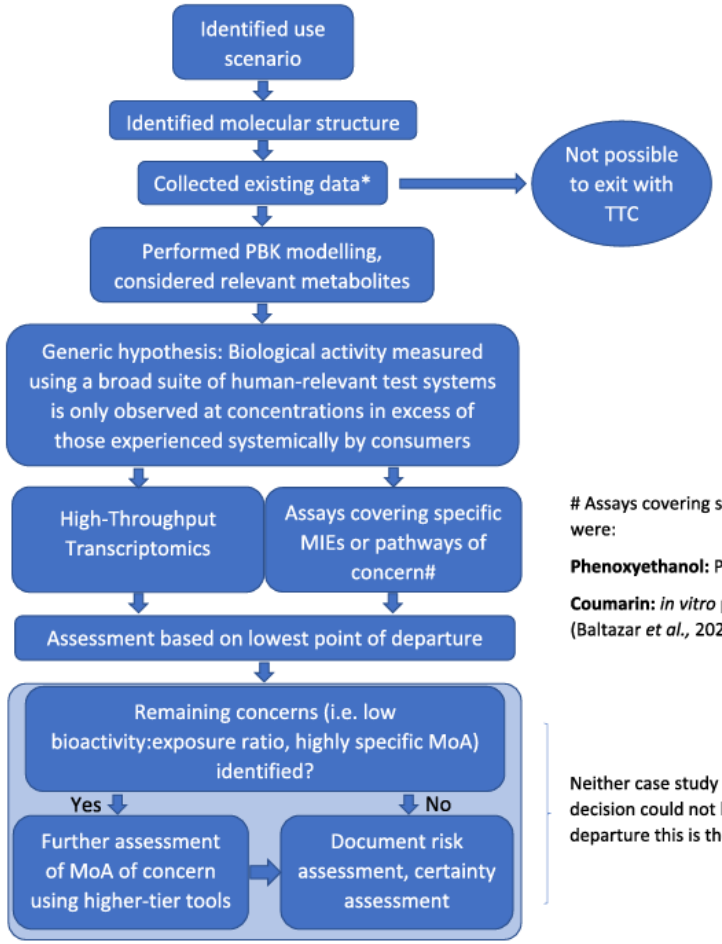
Paving the way for application of next generation risk assessment to safety decision-making for cosmetic ingredients

M.P. Dent, E. Vaillancourt, R.S. Thomas, P.L. Carmichael, G. Ouedraogo, H. Kojima, J. Barroso, J. Ansell, T.S. Barton-Maclaren, S.H. Bennekou, K. Boekelheide, J. Ezendam, J. Field, S. Fitzpatrick, M. Hatao, R. Kreiling, M. Lorencini, C. Mahony, B. Montemayor, R. Mazaro-Costa, J. Oliveira, V. Rogiers, D. Smegal, R. Taalman, Y. Tokura, R. Verma, C. Willett, C. Yang

ARTICLE INFO

ABSTRACT

https://doi.org/10.1016/j.yrtph.2021.105026



* Removed any *in vivo* data or *in vitro* data generated as a result of findings in animals

\# Assays covering specific MIEs or pathways of concern discussed were:

Phenoxyethanol: Published data, predominantly ToxCast

Coumarin: *in vitro* pharmacological profiling, BioMap, Cell Stress (Baltazar *et al.*, 2020)

Neither case study progressed to this level; however, if a decision could not be made based on the lowest point of departure this is the next logical step for the assessment

Fig. 3. Common components in the application of the SEURAT-1 risk assessment workflow to two case study safety assessments for systemic effects.

Paving the way for application of NGRA to safety decision-making for cosmetic ingredients

EU Scientific Committee for Cosmetics Safety (SCCS) created a 'safe space' to explore ab initio use of NGRA approaches for Cosmetics Safety

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Cosmetics Europe
the personal care association

2023

SCCS/1647/22
Corrigendum 2

Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION 12TH REVISION

Scientific Committees

The SCCS adopted this guidance document by written procedure on 15 May 2023

The corrigendum 1 was adopted during plenary meeting on 26 October 2023, and the corrigendum 2 by written procedure on 21 December 2023

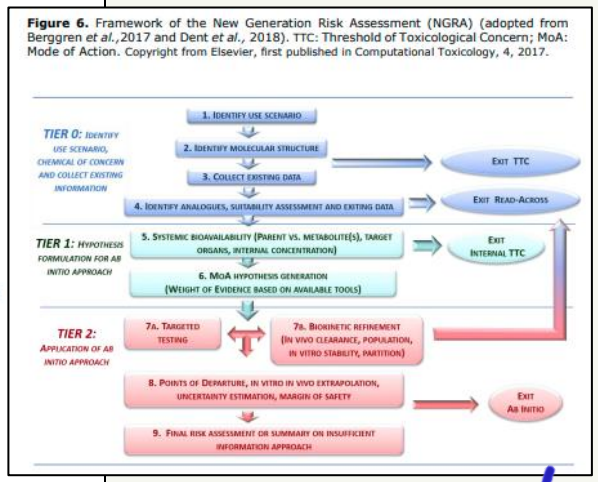

Figure 6. Framework of the New Generation Risk Assessment (NGRA) (adopted from Berggren *et al.*, 2017 and Dent *et al.*, 2018). TTC: Threshold of Toxicological Concern; MoA: Mode of Action. Copyright from Elsevier, first published in Computational Toxicology, 4, 2017.

2025

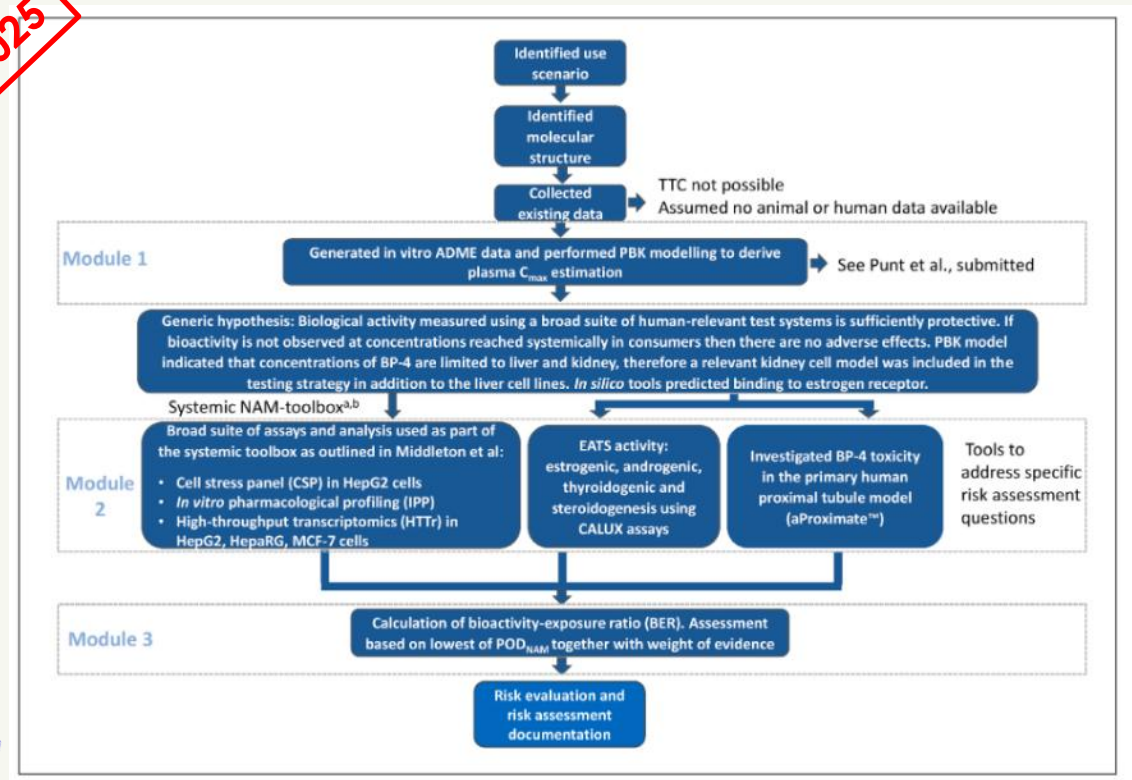

Fig. 1: NGRA case study workflow for 5% BP-4 in sunscreen body lotion
Adapted from Berggren et al. (2017) and Dent et al. (2021); [a] Middleton et al. (2022), [b] Cable et al. (2024).

SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 12th revision

SCCS 12th revision Notes of guidance

Making safety decisions for a sunscreen active ingredient using next-generation risk assessment: Benzophenone-4 case study

https://doi.org/10.14573/altex.2501201

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Skin Sensitisation: applying an NGRA mindset to validation & OECD guidance development

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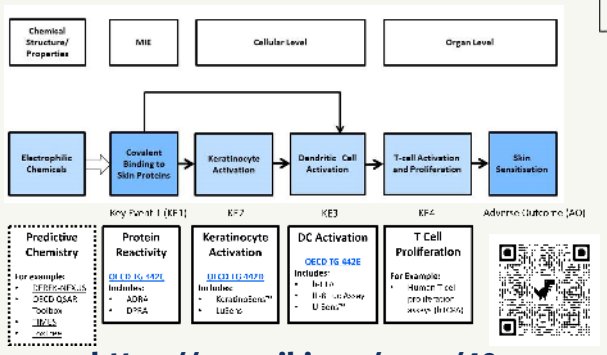
2012

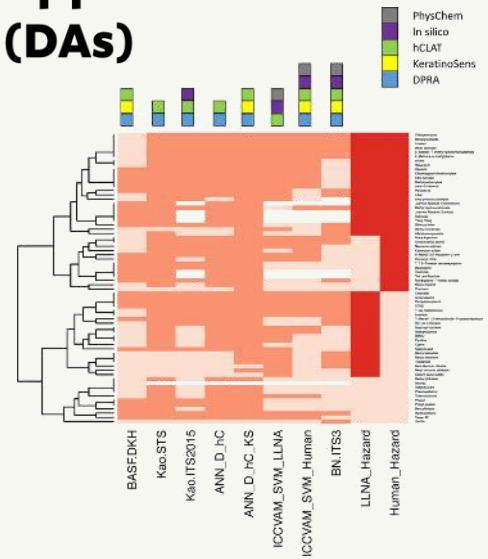
New Approach Methodologies (NAMs)



https://aopwiki.org/aops/40

2016

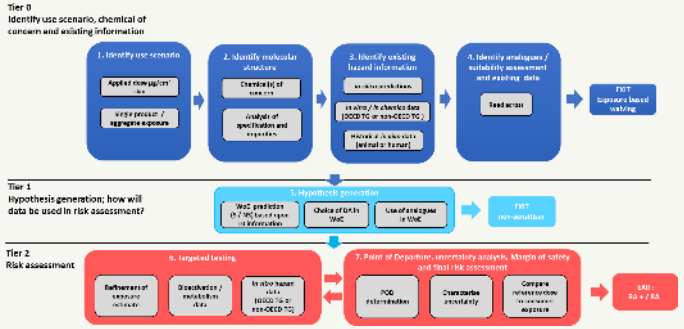
Defined Approaches (DAs)



OECD TG No. 255: Reporting of Defined Approaches to be used within Integrated Approaches to Testing and Assessment

2020

Integrated Approaches to Testing & Assessment (IATA)



https://doi.org/10.1016/j.yrtph.2020.104721

+

OECD Integrated Approaches to Testing & Assessment (IATA) & guidance are driving global standardisation of NGRA for chemical safety

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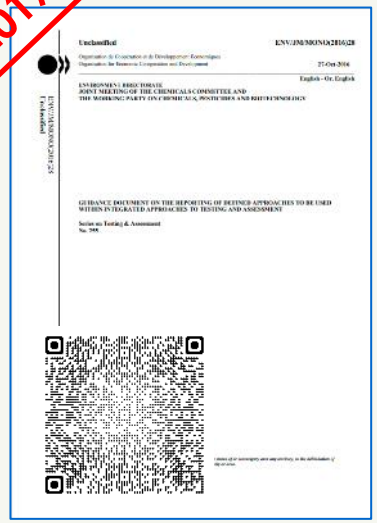
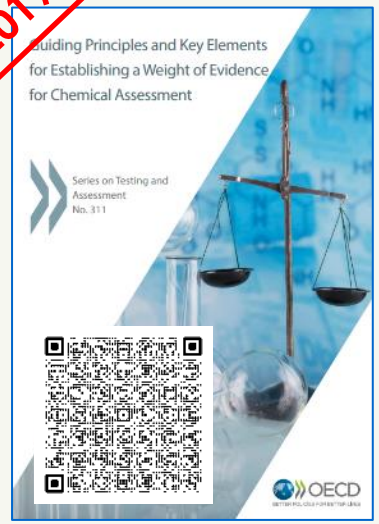
IATA combine multiple sources of information to conclude on the toxicity of chemicals and are developed to address a specific regulatory scenario or decision context.

2017



Guidance document on reporting of **Defined Approaches** for use in IATA

2019

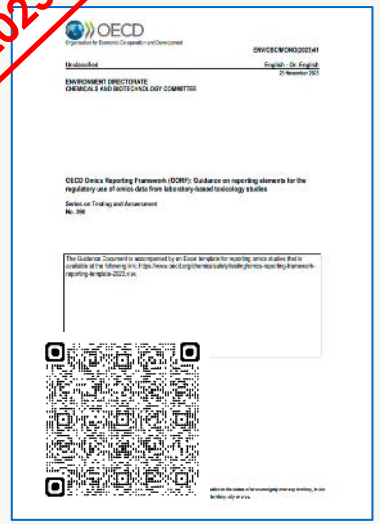


Guiding principles for establishing a **Weight of Evidence** for Chemical Assessment

2021

Guidance document on reporting of **Physiologically Based Kinetic (PBK) models**

2023



Omics Reporting Framework (OORF): Guidance on reporting elements for **omics data**

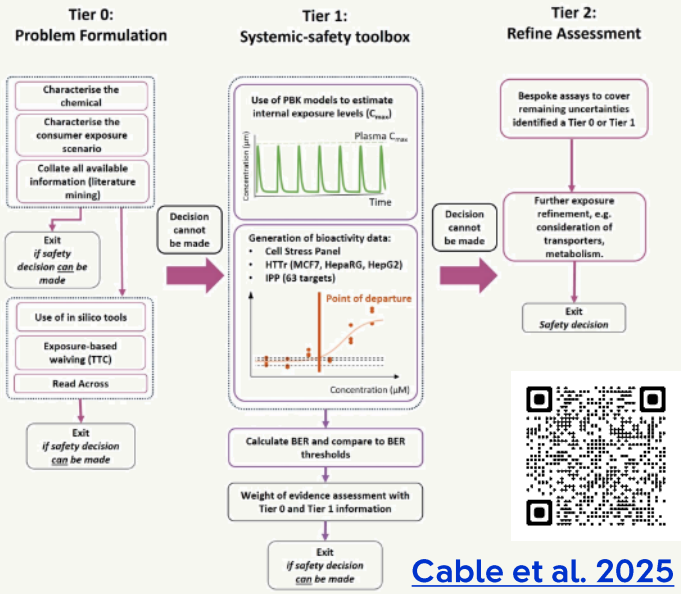
2023

(Q)SAR Assessment Framework: Guidance for **(Quantitative) Structure Activity Relationship models** and predictions

https://www.oecd.org/en/topics/sub-issues/assessment-of-chemicals/integrated-approaches-to-testing-and-assessment.html

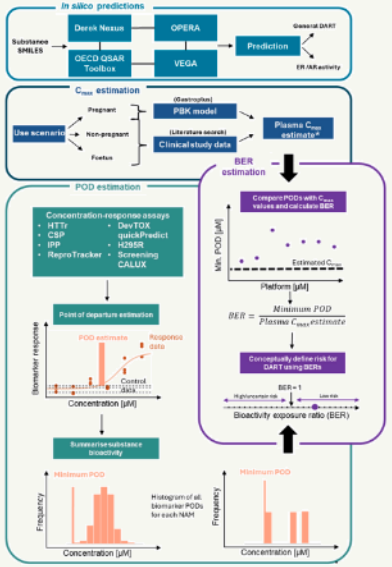
Unilever NGRA frameworks for chemical safety assessment

Systemic



Cable et al. 2025

Developmental & Reproductive



Muller et al. 2025

Occupational Safety

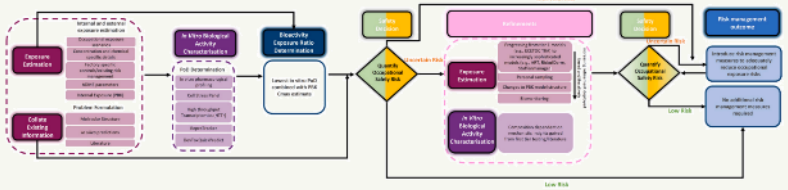
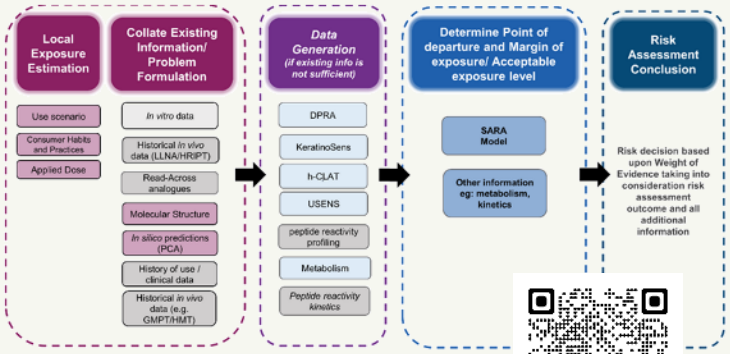


Fig. 1. Occupational Next Generation Risk Assessment (NGRA) Workflow.

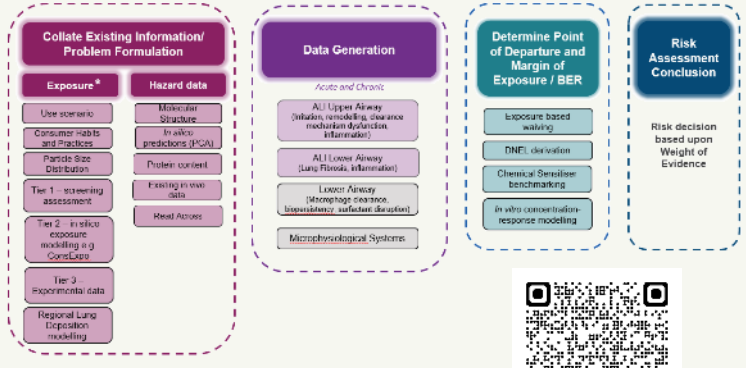
Wood et al 2024

Skin Sensitisation



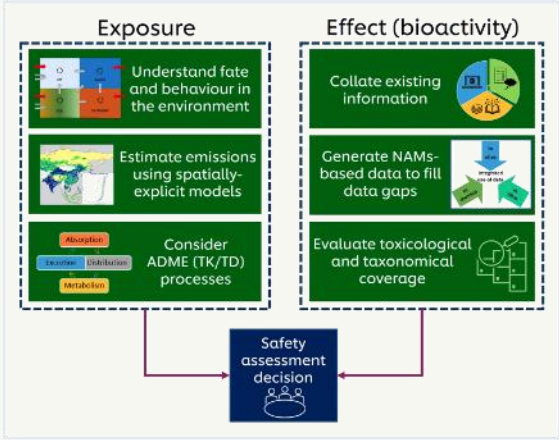
Reynolds et al. 2021

Inhalation



de Ávila et al. 2025

Environmental Safety



.Rivetti et al. 2025

Chemicals: strategies/roadmaps aim to enable widespread regulatory use of NAMs/ NGRA

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2025

Strategy to Replace, Reduce, or Refine Vertebrate Animal Testing under Canadian Environmental Protection Act (CEPA)


Strategy to replace, reduce or refine vertebrate animal testing under the Canadian Environmental Protection Act, 1999 (CEPA)

Environment and Climate Change Canada
Health Canada

July 2025

Executive summary

The Canadian Environmental Protection Act, 1999 (CEPA) recognizes the need to replace, reduce or refine the use of

[Strategy to replace, reduce or refine vertebrate animal testing under CEPA]

2025

UK Replacing Animals in Science Strategy

Note: UK strategy also addresses human and veterinary medicines

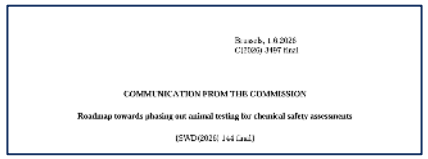

Replacing animals in science

A strategy to support the development, validation and uptake of alternative methods

[Replacing animals in science:]

2026

EU Commission Roadmap towards phasing out animal testing for chemical safety assessment


Brussels, 1.9.2025
C(2025) 3497 final

COMMUNICATION FROM THE COMMISSION

Roadmap towards phasing out animal testing for chemical safety assessments

{SWD(2025) 244 final}

[Roadmap towards phasing out animal testing for chemical safety assessments]

EUROPEAN COMMISSION

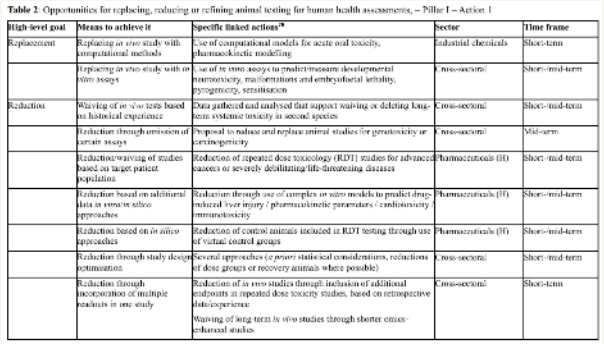


Table 2: Opportunities for replacing, reducing or refining animal testing for human health assessments, – Pillar I – Action 1

High-level goal	Means to achieve it	Specific linked actions[38]	Sector	Time frame
Replacement	Replacing *in vivo* study with computational methods	Use of computational models for acute oral toxicity, pharmacokinetic modelling	Industrial chemicals	Short-term
	Replacing *in vivo* study with *in vitro* assays	Use of *in vitro* assays to predict/measure developmental neurotoxicity, malformations and embryofoetal lethality, pyrogenicity, sensitisation	Cross-sectoral	Short-/mid-term
Reduction	Waiving of *in vivo* tests based on historical experience	Data gathered and analysed that support waiving or deleting long-term systemic toxicity in second species	Cross-sectoral	Short-/mid-term
	Reduction through omission of certain assays	Proposal to replace and replace animal studies for genotoxicity or carcinogenicity	Cross-sectoral	Mid-term
	Reduction/waiving of studies based on target patient population	Reduction of repeated dose toxicology (RDT) studies for advanced cancers or severely debilitating/life-threatening diseases	Pharmaceuticals (H)	Short-/mid-term
	Reduction based on additional data *in vitro*/*in silico* approaches	Reduction through use of samples or *in vitro* models to predict drug-induced liver injury / pharmacokinetic parameters / cardiotoxicity / immunotoxicity	Pharmaceuticals (H)	Short-/mid-term
	Reduction based on *in silico* approaches	Reduction of control animals included in RDT testing through use of virtual control groups	Pharmaceuticals (H)	Short-/mid-term
	Reduction through study design optimisation	Several approaches (*e.g.*power) statistical considerations, reductions of dose groups or recovery animals where possible)	Cross-sectoral	Short-/mid-term
	Reduction through incorporation of multiple readouts in one study	Reduction of *in vivo* studies through inclusion of additional endpoints in repeated dose toxicity studies, based on retrospective data/experience Waiving of long-term *in vivo* studies through shorter omics-enhanced studies	Cross-sectoral	Short-term
Refinement	Refinement of *in vivo* studies where not yet replaceable	Use of evident toxicity rather than lethality as endpoint in acute toxicity studies	Cross-sectoral	Short-term
Establishing an overarching, non-animal scientific assessment framework	Development of new assessment framework	Characterising protection and confidence levels of traditional assessment and non-animal-based scientific assessments based on a new scientific assessment framework	Cross-sectoral	Long-term
	Development of new assessment framework	Developing a non-animal-based classification system	Cross-sectoral[39]	Long-term
	Development of new assessment framework	Describing toxicity through changes measured at molecular level rather than adverse effects in organisms	Cross-sectoral	Long-term
	Frameworks for specific endpoints	In design (for selected endpoints below) a non-animal approach *in chemo/in silico* battery able to reliably distinguish between non-toxic and potentially toxic substances. To obtain a qualitative system with high sensitivity suitable for tiered hazard assessment and agree on characterising the endpoint, based on non-animal information leading a weight-of-evidence assessment. - Genotoxicity - Carcinogenicity - Reproductive toxicity - Endocrine disruption - Nanomaterial assessment.	Cross-sectoral	Mid-term

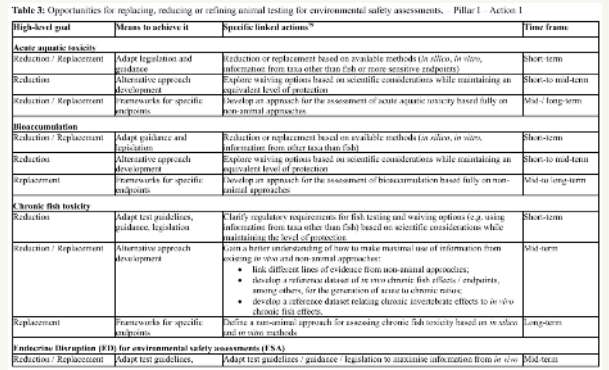


Table 3: Opportunities for replacing, reducing or refining animal testing for environmental safety assessments, – Pillar I – Action 1

High-level goal	Means to achieve it	Specific linked actions[38]	Time frame
Acute aquatic toxicity			
Reduction / Replacement	Adapt legislation and guidance	Reduction or replacement based on available methods (*in silico*, *in vitro*, information from taxa other than fish or more sensitive endpoints)	Short-term
Reduction	Alternative approach development	Explore waiving options based on scientific considerations while maintaining an equivalent level of protection	Short-to mid-term
Reduction / Replacement	Frameworks for specific endpoints	Develop an approach for the assessment of acute aquatic toxicity based fully on non-animal approaches	Mid-/ long-term
Bioaccumulation			
Reduction / Replacement	Adapt guidance and legislation	Reduction or replacement based on available methods (*in silico*, *in vitro*, information from other taxa than fish)	Short-term
Reduction	Alternative approach development	Explore waiving options based on scientific considerations while maintaining an equivalent level of protection	Short-to mid-term
Replacement	Frameworks for specific endpoints	Develop an approach for the assessment of bioaccumulation based fully on non-animal approaches	Mid-to long-term
Chronic fish toxicity			
Reduction	Adapt test guidelines, guidance, legislation	Clarify regulatory requirements for fish testing and waiving options (e.g. using information from taxa other than fish) based on scientific considerations while maintaining the level of protection	Short-term
Reduction / Replacement	Alternative approach development	Gain a better understanding of how to make maximal use of information from existing *in vivo* and non-animal approaches: • link different lines of evidence from non-animal approaches; • develop a reference dataset of *in vivo* chronic fish effects / endpoints, among others, for the generation of acute to chronic ratios; • develop a reference dataset relating chronic invertebrate effects to *in vivo* chronic fish effects.	Mid-term
Replacement	Frameworks for specific endpoints	Define a non-animal approach for assessing chronic fish toxicity based on *in silico* and *in vitro* methods	Long-term
Endocrine Disruption (ED) for environmental safety assessments (ESA)			
Reduction / Replacement	Adapt test guidelines,	Adapt test guidelines / guidance / legislation to maximise information from *in vivo*	Mid-term
Refinement	guidance, legislation	testing and use tools built for correlating on the ED properties and risk assessment	
Reduction	Validation, case studies	Validation of certain *in vitro* methods (TAMA, LATT, FETT[40] with thyroid endpoints)	Mid-term
Reduction / Replacement Refinement	Research, case studies	Gain a better understanding of how to make maximum use of information from existing non-animal approaches, including those for the assessment of human health, and by linking different information from non-animal approaches[41]	Mid- / long-term
Refinement	Research, case studies	Map mechanisms and applicability domains of elsewhere-embryo methods[42]	Mid-term
Replacement	Research, case studies	Build evidence on cross-species extrapolation by exploring key events/ adverse outcome pathways (AOPs) for different species	Mid- / long-term
Replacement	Frameworks for specific endpoints	Define a framework for assessing ED for environmental safety with a mechanism-based panel of *in silico* and *in vitro* assays taking into account knowledge of (quantitative) AOPs	Long-term
Long-term change for environmental safety assessment for all taxa (including mammals and birds)			
Replacement	Development of new assessment framework	Develop non-animal environmental NGRA and implement it for environmental safety assessments	Long-term
General		It is important to explore the links between environmental safety assessments and human health NGRA approaches under a One-Health concept to ensure the best use of data	Mid- / Long-term

Next Generation Risk Assessment:

Emerging Best Practice & Opportunities for Regulatory Use

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1. **Next Generation Risk Assessment**
   a) NGRA Paradigm Shift
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4. **Accelerating the paradigm shift**

Medicines: milestones in regulatory use of NAMs/NGRA

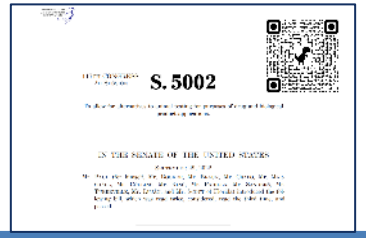
2010 - present

Micro physiological systemics (MPS) program for drug safety and efficacy assessment

NIH/NCATS, FDA, DARPA

2022

FDA Modernization Act 2.0 replaced older language referring to 'preclinical tests, including tests on animals' with 'nonclinical tests'

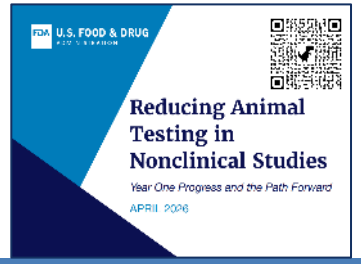


2023-present

FDA New Alternative Method Program – agency wide program to drive adoption of 3Rs methods for regulatory use

2025

FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies – stepwise strategy to reduce animal testing in preclinical safety



US FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies & NIH prioritization of human-based research technologies

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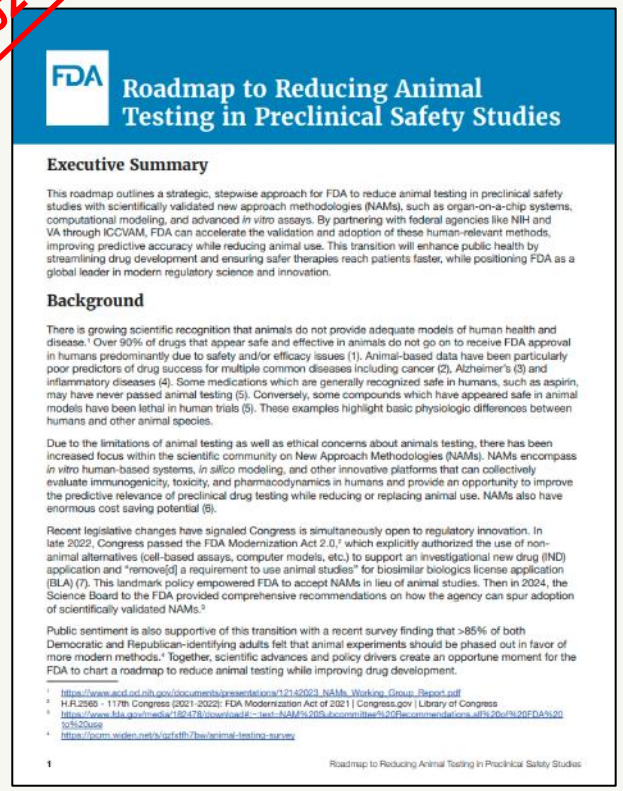
2025



FDA

Roadmap to Reducing Animal Testing in Preclinical Safety Studies

Executive Summary

This roadmap outlines a strategic, stepwise approach for FDA to reduce animal testing in preclinical safety studies with scientifically validated new approach methodologies (NAMs), such as organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays. By partnering with federal agencies like NIH and VA through ICCVAM, FDA can accelerate the validation and adoption of these human-relevant methods, improving predictive accuracy while reducing animal use. This transition will enhance public health by streamlining drug development and ensuring safer therapies reach patients faster, while positioning FDA as a global leader in modern regulatory science and innovation.

Background

There is growing scientific recognition that animals do not provide adequate models of human health and disease.[1] Over 90% of drugs that appear safe and effective in animals do not go on to receive FDA approval in humans predominantly due to safety and/or efficacy issues (1). Animal-based data have been particularly poor predictors of drug success for multiple common diseases including cancer (2), Alzheimer's (3) and inflammatory diseases (4). Some medications which are generally recognized safe in humans, such as aspirin, may have never passed animal testing (5). Conversely, some compounds which have appeared safe in animal models have been lethal in human trials (5). These examples highlight basic physiologic differences between humans and other animal species.

Due to the limitations of animal testing as well as ethical concerns about animals testing, there has been increased focus within the scientific community on New Approach Methodologies (NAMs). NAMs encompass *in vitro* human-based systems, *in silico* modeling, and other innovative platforms that can collectively evaluate immunogenicity, toxicity, and pharmacodynamics in humans and provide an opportunity to improve the predictive relevance of preclinical drug testing while reducing or replacing animal use. NAMs also have enormous cost saving potential (6).

Recent legislative changes have signaled Congress is simultaneously open to regulatory innovation. In late 2022, Congress passed the FDA Modernization Act 2.0,[2] which explicitly authorized the use of non-animal alternatives (cell-based assays, computer models, etc.) to support an investigational new drug (IND) application and "remove[d] a requirement to use animal studies" for biosimilar biologics license application (BLA) (7). This landmark policy empowered FDA to accept NAMs in lieu of animal studies. Then in 2024, the Science Board to the FDA provided comprehensive recommendations on how the agency can spur adoption of scientifically validated NAMs.[3]

Public sentiment is also supportive of this transition with a recent survey finding that >85% of both Democratic and Republican-identifying adults felt that animal experiments should be phased out in favor of more modern methods.[4] Together, scientific advances and policy drivers create an opportune moment for the FDA to chart a roadmap to reduce animal testing while improving drug development.

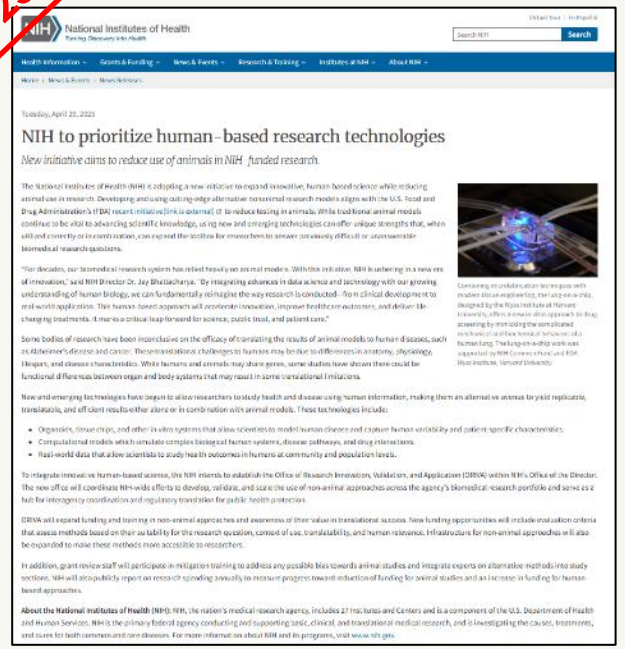
[1] https://www.acd.od.nih.gov/documents/presentations/12142023_NAMs_Working_Group_Report.pdf
[2] H.R.2565 - 117th Congress (2021-2022): FDA Modernization Act of 2021 | Congress.gov | Library of Congress
[3] https://www.fda.gov/media/182478/download#:~:text=NAM%20Subcommittee%20Recommendations.all%20of%20FDA%20to%20use
[4] https://porn.widen.net/s/qzfxtfh7bw/animal-testing-survey

1 Roadmap to Reducing Animal Testing in Preclinical Safety Studies

- **FDA Roadmap outlines strategic, approach to reduce animal testing in preclinical safety studies using New Approach Methodologies (NAMs)**:
  - organ-on-a-chip systems
  - computational modelling
  - advanced in vitro assays
- **FDA will accelerate the validation & adoption of NAMs by partnering with federal agencies like NIH & VA through ICCVAM**
- **The FDA roadmap seeks to:**
  - enhance public health
  - streamline drug development
  - ensuring safer therapies reach patients faster
  - position FDA as a global leader in modern regulatory science and innovation

[FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs | FDA]

2025



National Institutes of Health

NIH to prioritize human-based research technologies

New initiative aims to reduce use of animals in NIH-funded research

"For decades, our biomedical research system has relied heavily on animal models. With this initiative, NIH is ushering in a new era of innovation," said NIH Director Dr. Jay Bhattacharya. "

[NIH to prioritize human-based research technologies | National Institutes of Health (NIH)]

European Medicine Agency (EMA) has created ‘safe spaces’ to novel use of NAMs/NGRA approaches to reduce animal testing

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Home > Human regulatory: overview > Research and development > Ethical use of animals in medicine testing > Regulatory acceptance of new approach methodologies (NAMs) to reduce animal use testing

Regulatory acceptance of new approach methodologies (NAMs) to reduce animal use testing

Share

New approach methodologies (NAMs) refer to novel methods that are compliant with the so-called 3Rs principles for the ethical use of animals in medicine testing across the European Union (EU). '3Rs' stands for replacement, reduction and refinement of animal use. The European Medicines Agency (EMA) supports the regulatory acceptance of these new approach methodologies. This ensures NAMs are scientifically sound and can be used in regulatory decision-making.

Human | Veterinary

Briefing meetings within EMA's Innovation Task Force (ITF)

EMA holds briefing meetings with new approach methodology (NAM) developers.

Scope

These meetings host informal discussions on NAM development and readiness for **regulatory acceptance**.

They take place within EMA's Innovation Task Force (ITF). This provides developers with a forum for early dialogue with EMA on innovative medicines and **novel methodologies**.

Experts from the European medicines regulatory network also participate in these discussions.

Applications are free of charge.

Outcome

EMA shares confidential meeting minutes with participating developers.

For more information on EMA's Innovation Task Force (ITF), see:

- Supporting innovation

Scientific advice

EMA enables new approach methodology (NAM) developers to ask its Scientific Advice Working Party specific scientific and regulatory questions.

These questions can refer to the development and use of NAMs.

Scope

The scope is to consider including **NAM data** in a future clinical trial application or in marketing authorisation application (MAA) for a particular medicine.

Outcome

EMA's CHMP or CVMP issues a confidential final advice letter containing answers to the specific questions that developers raised.

For more information on requesting scientific advice from EMA, see:

- Requesting scientific advice or protocol assistance from EMA
- Scientific advice for veterinary medicines

Voluntary submission of data

Scope

Under the voluntary submission of data procedure, new approach methodology (NAM) developers can submit data obtained by using a NAM.

EMA does not use data generated with the NAM as part of its regulatory decision-making process, for instance within a MAA procedure. However, EMA evaluates these data independently.

This is for the purpose of NAM evaluation for possible future regulatory acceptance. It also aims to help EMA develop a better understanding of the potential added value of NAMs.

The voluntary submission of data procedure is also known as the safe harbour approach. This is because there is no 'penalty' in a regulatory sense for submitting the data (even if it does not concur with animal data).

Outcome

This procedure can allow the generation, compilation and review of data to help define and / or fine-tune a context of use for a NAM.

This also helps evaluate the readiness and limitations for **regulatory acceptance** of the NAM within a specific context of use.

In addition, it allows regulators to gain confidence in NAM data.

Moreover, this approach may help EMA draft qualification criteria for NAMs based on a context-of-use.

Qualification

New approach methodology (NAM) developers can apply for CHMP qualification.

Scope

They can do so if they have generated sufficient and robust **data**.This is needed to demonstrate the utility and regulatory relevance of a NAM for a specific context of use.

A **context of use** describes the circumstances under which the NAM is applied in the assessment of human or veterinary **medicines**.

A qualification team composed of EMA and experts from the European medicines regulatory network then assesses the data submitted to support the use of the NAM within medicine development.

For NAMs to be qualified in veterinary medicines development, the qualification procedure is carried out within the request for general scientific advice for veterinary medicines.

Outcome

EMA's CHMP can issue qualification advice on protocols and methods with the aim of moving towards a positive qualification opinion.

Based on CHMP's advice, EMA may propose a letter of support even when it cannot yet qualify a NAM.

This letter signals that EMA considers the preliminary data received to be promising. It can also raise awareness of the method proposed. Moreover, it can indicate EMA expectation to receive data that can further support a positive qualification opinion.

The CHMP can also issue a qualification opinion on the acceptability of a NAM within a specific context of use in drug development.

Before adopting a qualification opinion, the CHMP makes its evaluation open for public consultation by the scientific community.

To ensure public awareness, EMA publishes all qualification opinions.

Regulatory acceptance of new approach methodologies (NAMs) to reduce animal use testing | European Medicines Agency (EMA)

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   b) Where are we?
4. **Accelerating the paradigm shift**

Have we reached a tipping point wrt regulatory use of NGRA?

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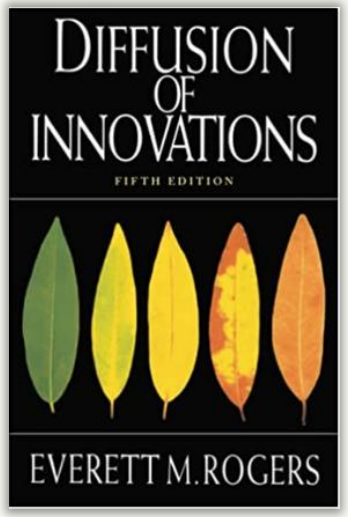
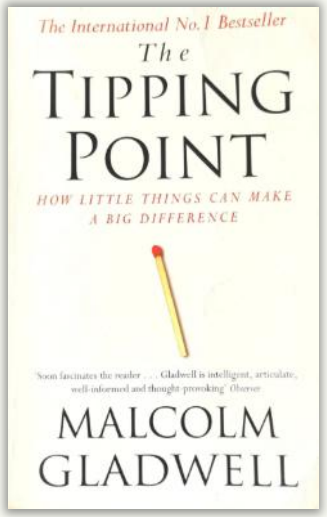
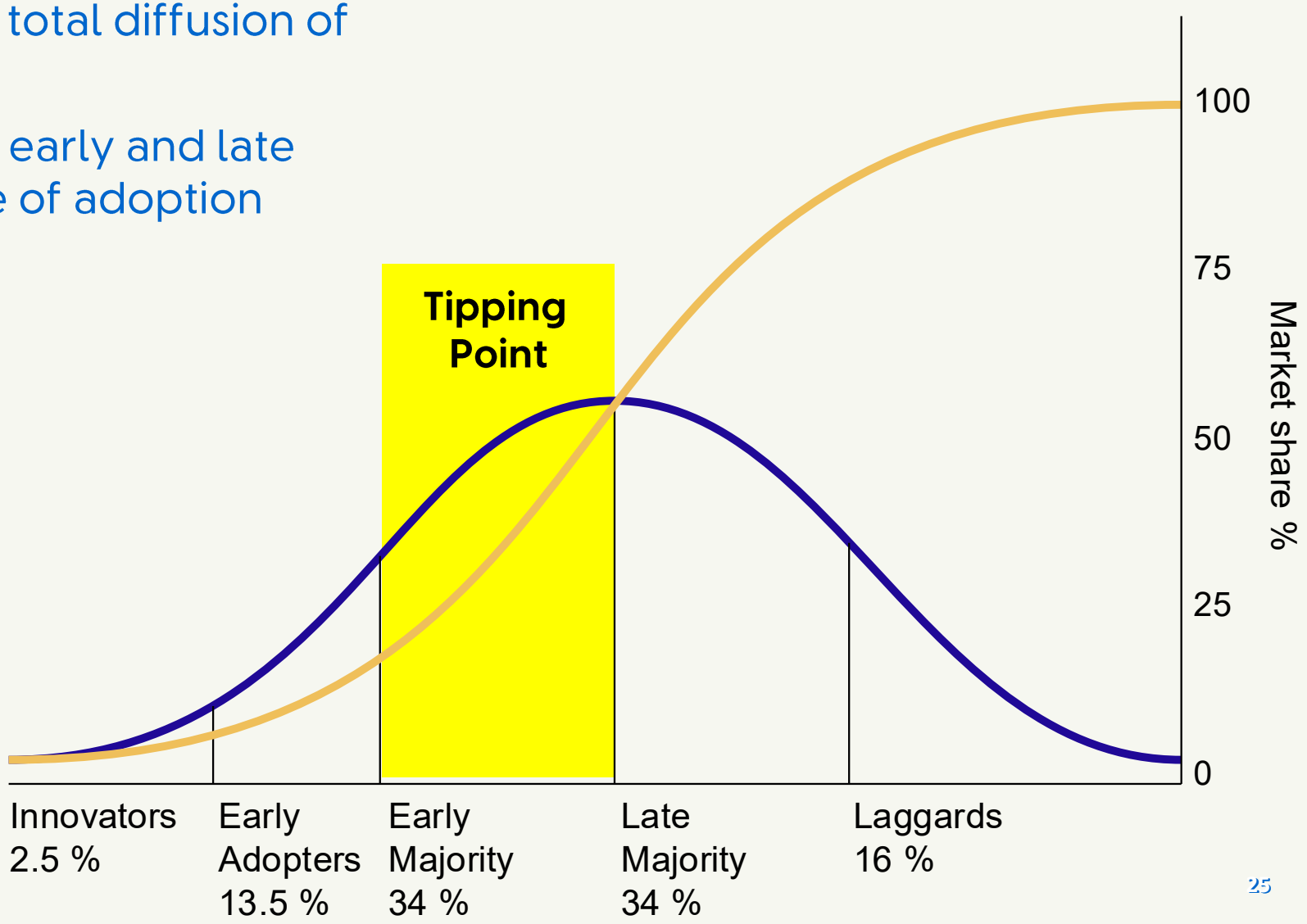
Tipping Point

- critical mass, after which the total diffusion of an innovation is likely
- inflection point between the early and late majority in the sigmoid curve of adoption





Diffusion of innovations - Wikipedia



Have we reached a tipping point wrt regulatory use of NGRA?

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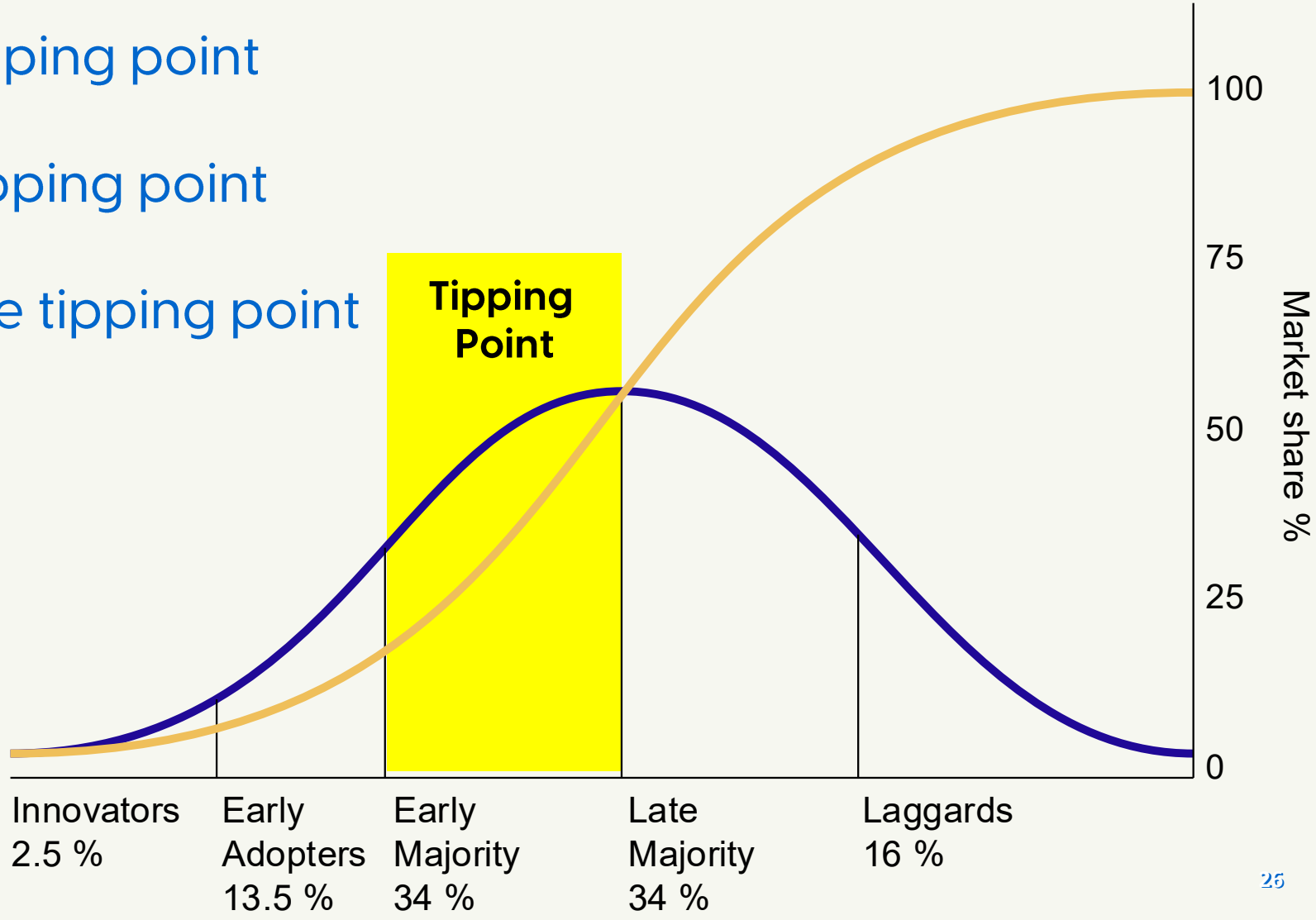
Please comment in the chat

1. We're already past the tipping point
2. We've just reached the tipping point
3. We've not yet reached the tipping point



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Accelerating the NGRA Paradigm Shift

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Confidence Building

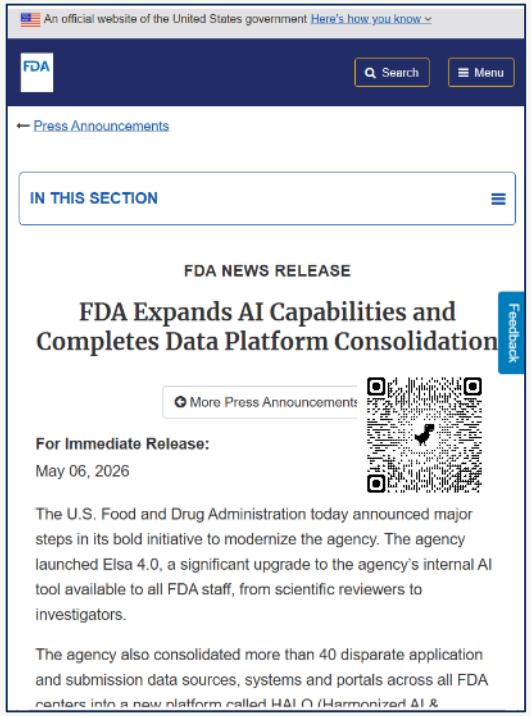
- Validation & Qualification
- NGRA / IATA case studies
- Industry-Regulator dialogue

AI-Augmentation

- Create knowledge & insights
- Enable predictive modelling
- Automate workflows

Education & Training

- Conferences & Workshops
- Continuing Education
- Webinars



Office of Research Innovation, Validation, and Application (ORIVA)

fda-expands-ai-capabilities-and-completes-data-platform-consolidation

https://www.toxicology.org/groups/ss/rass/events.asp

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