Bridging the Science to Regulation Gap

An Industry Perspective

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21st Oct 2025, ASCCT 2025

Bridging the Science to Regulation Gap: Industry Perspective

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1. **Safety Science**
   a) **1980-2000**: Alternatives to Animal Testing
   b) **2000-2020**: Safety without Animal Testing
   c) **2020-2025**: Science to Regulation Gap
2. **Regulatory Science**
   a) **Consumer Safety:** BP4 ab initio case study
   b) **Occupational Safety**: SI case study
   c) **Environmental Safety**: EPAA community
3. **Next steps**
   a) **Harness AI:** democratise NGRA & build capacity
   b) **Collaborate**: Safe Spaces & Regulatory Sandboxes
   c) **Integrate:** Human & Environmental Safety

Unilever Policy & Approach

Safe & Sustainable Products without Animal Testing

What we believe

- **Every Unilever product must be safe for people and our environment**
- **Animal testing is not needed to assess ingredient & product safety** – there are a wide range of non-animal alternatives grounded in modern science and new technology

How we do it

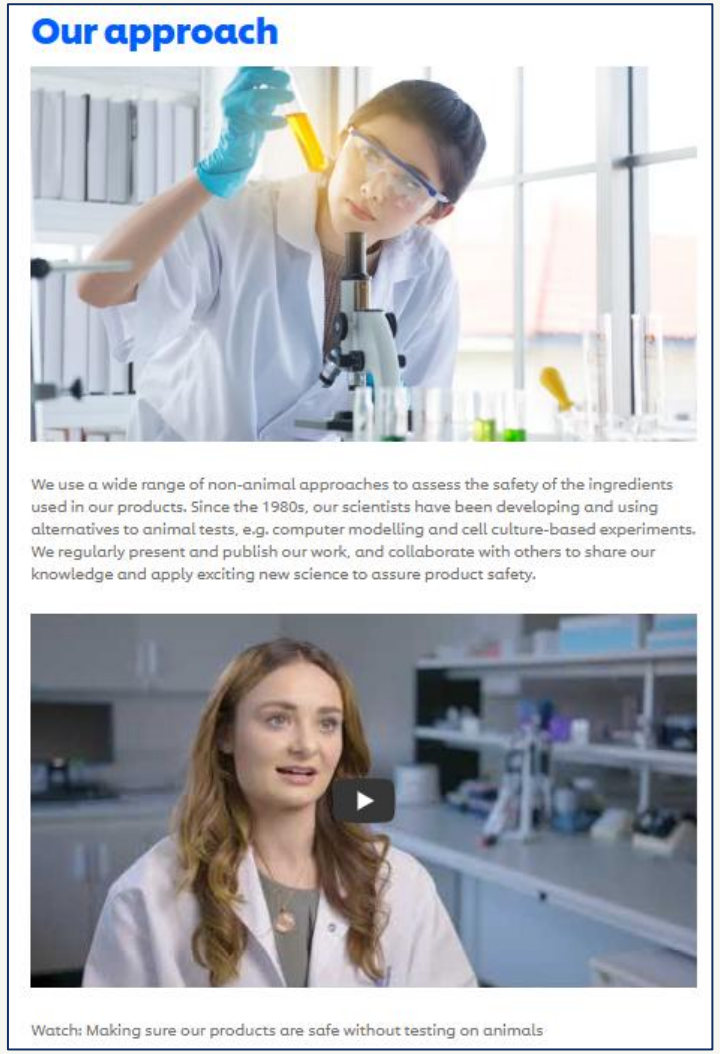
40+ years of non-animal safety science

70+ collaborations

600+ publications

1980s – 2000s: Alternatives to Animal Testing

- **Early 1980s – Ex vivo ocular methods (IRE)**: Unilever scientists helped originate and apply the *Isolated Rabbit Eye (IRE)* test for severe eye irritants
- **1990 – Cell-based in vitro screening**: Unilever reported an agarose overlay cytotoxicity assay to rank ocular irritation of detergent products, offering a rapid in vitro alternative to new Draize testing.
- **1990 – Ex vivo HET-CAM work**: Unilever researchers evaluated the HET-CAM test as a predictor of eye irritation, building the ex vivo toolbox.
- **1994–1997 – QSAR and early computational toxicology (ocular & skin)**: Unilever authors published some of the earliest QSARs linking eye-irritation potency to structure/physicochemical descriptors; similar work tied in vitro cytotoxicity to skin corrosivity prediction.
- **1999 – Early machine learning**: A Bayesian neural network (BNN) model by Unilever scientists predicted eye-irritancy of cationic surfactants—an early application of ML/NAMs in this space

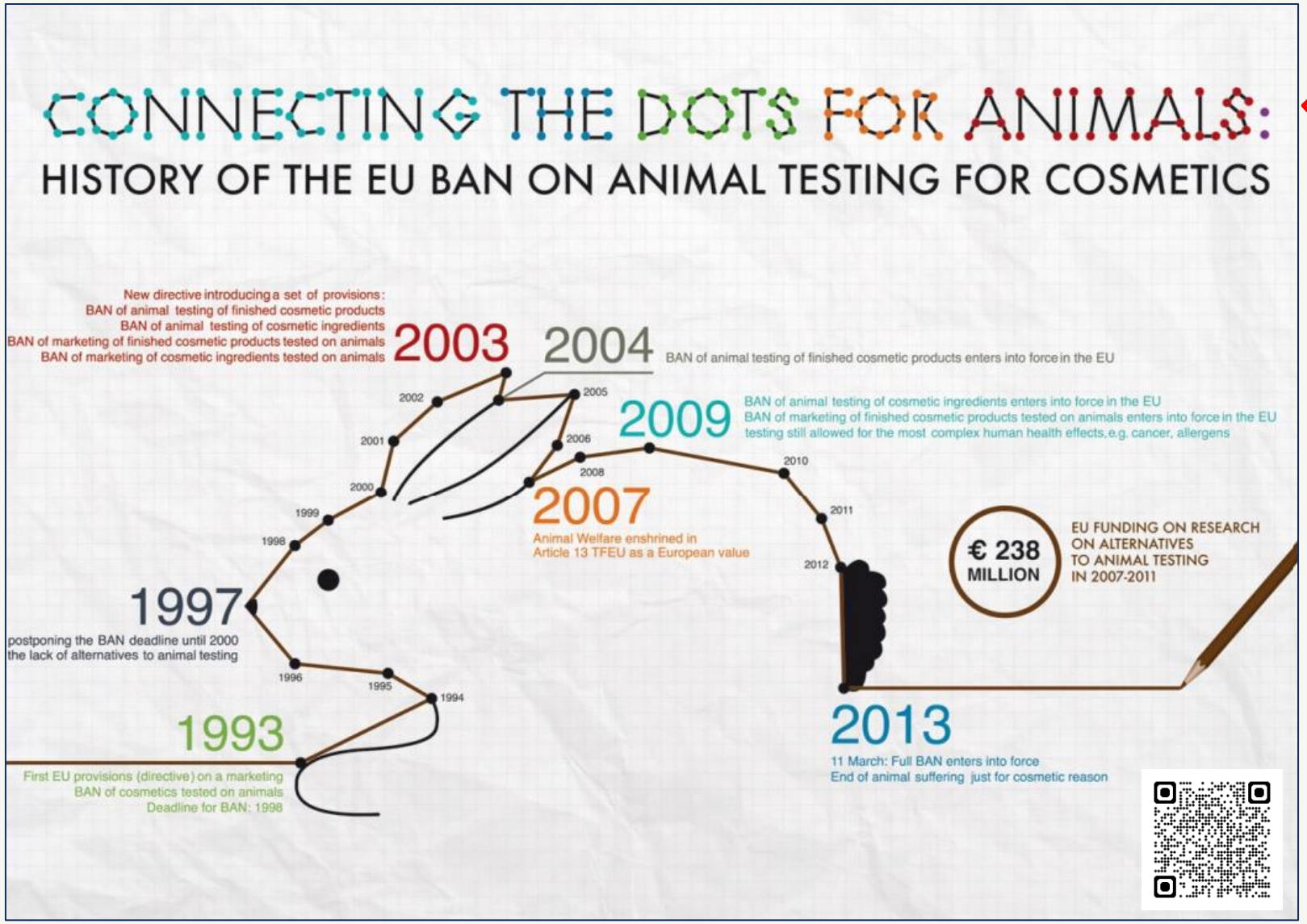


Edited ChatGPT v5 Pro summary

Alternatives to animal testing | Unilever

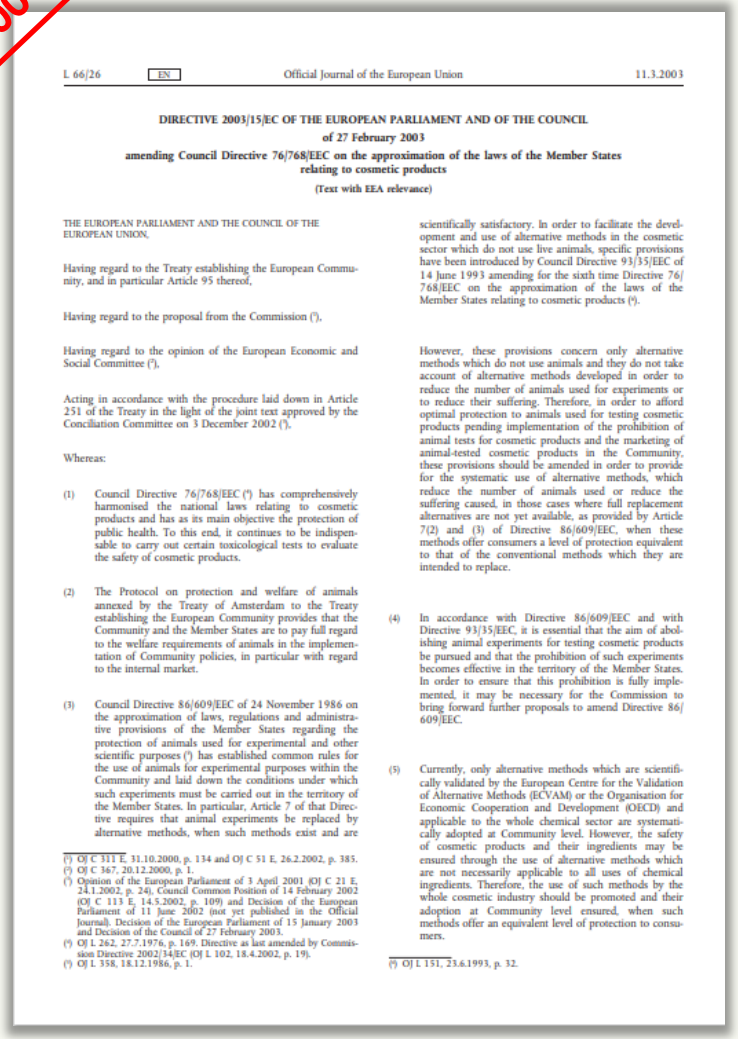
European 7th Amendment to Cosmetics Directive and resulting Animal Testing Bans drove scientific investment & replacement mindset

Unilever



7th Amendment to European Cosmetics Directive

2003



L 66/26 EN Official Journal of the European Union 11.3.2003

DIRECTIVE 2003/15/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 27 February 2003
amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products
(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 (1),

Having regard to the opinion of the European Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 251 of the Treaty in the light of the joint text approved by the Conciliation Committee on 3 December 2002 (3),

Whereas:

(1) Council Directive 76/768/EEC (4) has comprehensively harmonised the national laws relating to cosmetic products and has as its main objective the protection of public health. To this end, it continues to be indispensable to carry out certain toxicological tests to evaluate the safety of cosmetic products.

(2) The Protocol on protection and welfare of animals annexed by the Treaty of Amsterdam to the Treaty establishing the European Community provides that the Community and the Member States are to pay full regard to the welfare requirements of animals in the implementation of Community policies, in particular with regard to the internal market.

(3) Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (5) has established common rules for the use of animals for experimental purposes within the Community and laid down the conditions under which such experiments must be carried out in the territory of the Member States. In particular, Article 7 of that Directive requires that animal experiments be replaced by alternative methods, when such methods exist and are scientifically satisfactory. In order to facilitate the development and use of alternative methods in the cosmetic sector which do not use live animals, specific provisions have been introduced by Council Directive 93/35/EEC of 14 June 1993 amending for the sixth time Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products (6).

However, these provisions concern only alternative methods which do not use animals and they do not take account of alternative methods developed in order to reduce the number of animals used for experiments or to reduce their suffering. Therefore, in order to afford optimal protection to animals used for testing cosmetic products pending implementation of the prohibition of animal tests for cosmetic products and the marketing of animal-tested cosmetic products in the Community, these provisions should be amended in order to provide for the systematic use of alternative methods, which reduce the number of animals used or reduce the suffering caused, in those cases where full replacement alternatives are not yet available, as provided by Article 7(2) and (3) of Directive 86/609/EEC, when these methods offer consumers a level of protection equivalent to that of the conventional methods which they are intended to replace.

(4) In accordance with Directive 86/609/EEC and with Directive 93/35/EEC, it is essential that the aim of abolishing animal experiments for testing cosmetic products be pursued and that the prohibition of such experiments becomes effective in the territory of the Member States. In order to ensure that this prohibition is fully implemented, it may be necessary for the Commission to bring forward further proposals to amend Directive 86/609/EEC.

(5) Currently, only alternative methods which are scientifically validated by the European Centre for the Validation of Alternative Methods (ECVAM) or the Organisation for Economic Cooperation and Development (OECD) and applicable to the whole chemical sector are systematically adopted at Community level. However, the safety of cosmetic products and their ingredients may be ensured through the use of alternative methods which are not necessarily applicable to all uses of chemical ingredients. Therefore, the use of such methods by the whole cosmetic industry should be promoted and their adoption at Community level ensured, when such methods offer an equivalent level of protection to consumers.

(1) OJ C 311 E, 31.10.2000, p. 134 and OJ C 51 E, 26.2.2002, p. 385.
(2) OJ C 367, 20.12.2000, p. 1.
(3) Opinion of the European Parliament of 3 April 2001 (OJ C 21 E, 24.1.2002, p. 24), Council Common Position of 14 February 2002 (OJ C 113 E, 14.5.2002, p. 109) and Decision of the European Parliament of 11 June 2002 (not yet published in the Official Journal). Decision of the European Parliament of 15 January 2003 and Decision of the Council of 27 February 2003.
(4) OJ L 262, 27.7.1976, p. 169. Directive as last amended by Commission Directive 2002/34/EC (OJ L 102, 18.4.2002, p. 19).
(5) OJ L 358, 18.12.1986, p. 1.
(6) OJ L 151, 23.6.1993, p. 32.

https://single-market-economy.ec.europa.eu/sectors/cosmetics/ban-animal-testing_en

Safety without Animal Testing: re-framing the question to focus on the protection goal (i.e. what are you trying to prevent?)

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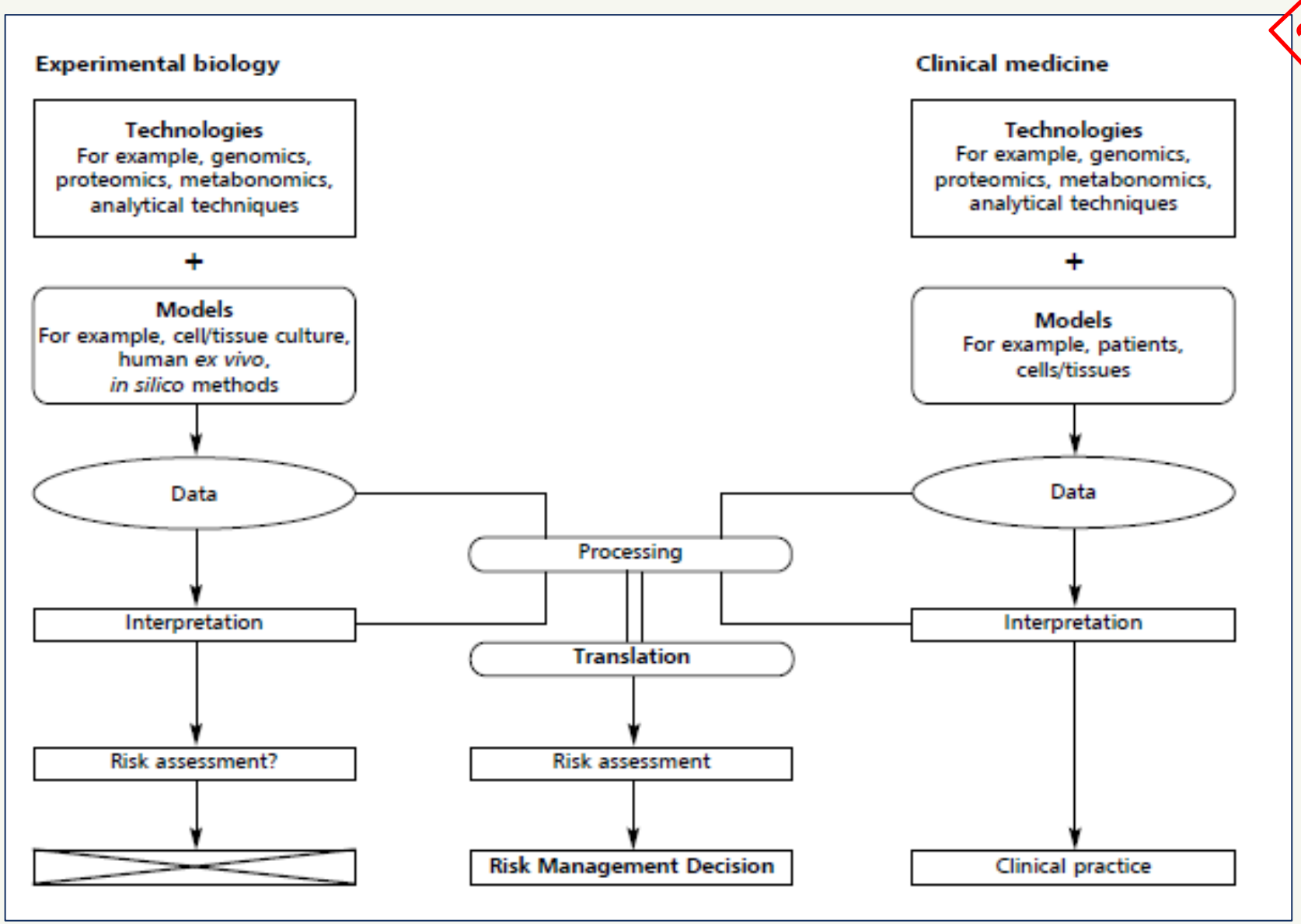

2004

ATLA 32, 617–628, 2004 617

Comment

The Feasibility of Replacing Animal Testing for Assessing Consumer Safety: A Suggested Future Direction

Julia Fentem, Mark Chamberlain and Bart Sangster

Safety & Environmental Assurance Centre, Unilever Colworth Laboratory, Sharnbrook, Bedfordshire, UK

Summary — At present, we are unable to use much of the data derived from alternative (non-animal) tests for human health risk assessment. This brief *Comment* outlines why it is plausible that new paradigms could be developed to enable risk assessment to support consumer safety decisions, without the need to generate data in animal tests. The availability of technologies that did not exist 10 years ago makes this new approach possible. The approach is based on the concept that data and information derived from applying existing and new technologies to non-animal models can be interpreted in terms of harm and disease in man. A prerequisite is that similar data and information generated in a clinical setting are available to permit this "translation". The incorporation of this additional translation step should make it possible to use data and information generated in non-animal models as inputs to risk assessment. The new technologies include genomics, transcriptomics, proteomics and metabonomics. Their application to *in vitro* and human "models" enables large amounts of data to be generated very quickly. The processing, interpretation and translation of these data need to be supported by powerful informatics capabilities and statistical tools. The use of integrated "systems biology" approaches will further support the interpretation by providing better understanding of the underlying biological complexity and mechanisms of toxicity. Clinical medicine is using the opportunities offered by the new 'omics' technologies to advance the understanding of disease. The application of these technologies in clinical medicine will generate massive amounts of data that will need processing and interpretation to allow clinicians to better diagnose disease and understand the patients' responses to therapeutic interventions. Support from clinical epidemiology will be essential. If these data and information can be made generally accessible in an ethical and legal way, they should also permit the "translation" of experimental non-animal data, so that they can then be used in risk assessment.

Key words: *alternatives, animal testing, clinical data, consumer safety, cosmetic testing, genomics, in vitro, proteomics, risk assessment, Three Rs.*

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E-mail: Julia.Fentem@unilever.com

Introduction

Products that are sold to consumers must be safe for them to use. Most countries have laws that confirm this principle and rightfully hold the manufacturer or the retailer responsible. In some cases, there are more-elaborate regulatory systems to ensure safety. These often include the need for premarket regulatory approval, such as for medicines, pesticides and functional foods.

Innovation in terms of consumer products may involve the introduction of new active ingredients, or the delivery of products in new ways, which could also include packaging. The safety of all of these new materials, or new product formats, needs to be assessed. In many cases, animal data are an integral part of the safety evaluation process.

Animal testing is a subject that often generates heated debate, since there are many different views in society as to whether or not animal testing can be morally justified. Governments, academic institutions, non-governmental organisations (NGOs), trade associations and individual companies have positions and policies explaining their views and practices regarding the use of animals for testing.

Recently, the European Union (EU) introduced the Seventh Amendment to the Cosmetics Directive (1), which includes a ban on the marketing in the EU of cosmetics with ingredients that have been tested on animals, anywhere in the world, as of 2009 (for most tests) or 2013 (for all tests). Cosmetics in this legislative context include soaps, shampoos, deodorants, antiperspirants and toothpastes, i.e. products that play an important role in personal hygiene and dental health. A consequence of the Seventh Amendment is that consumers within the EU will cease to have access to new cosmetics where innovation involves

Fentem 2004. *ATLA*. 32. 617-623

Case Study:
Skin Sensitization

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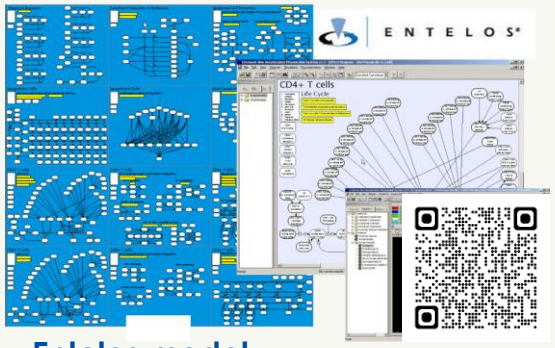
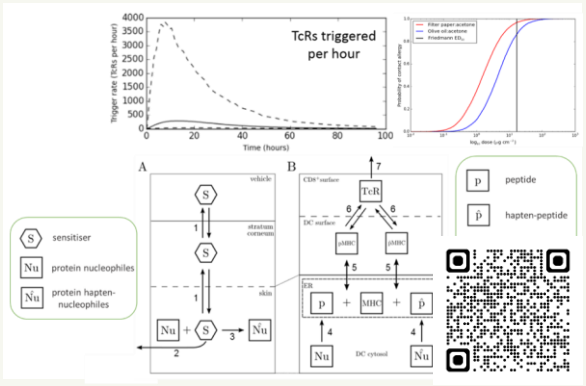


Entelos model

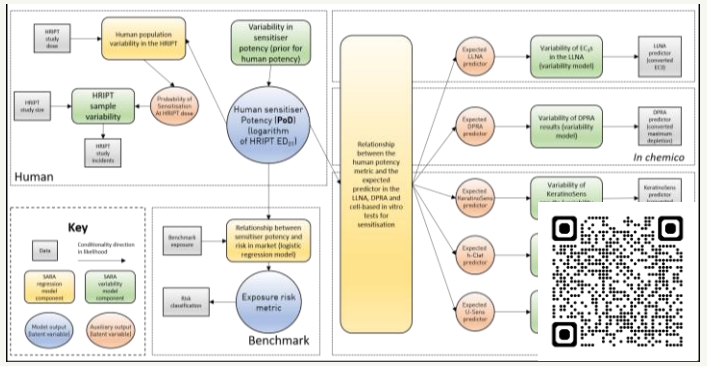
Maxwell G. & MacKay C. 2008.



SARA TKTD qAOP model

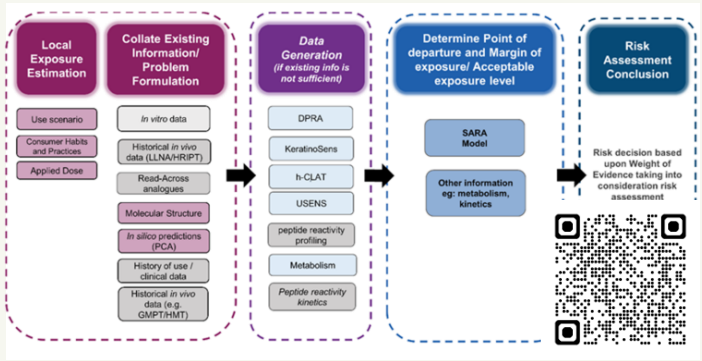
Mackay et al. 2013

SARA Defined Approach Model Structure



Reynolds et al. 2019

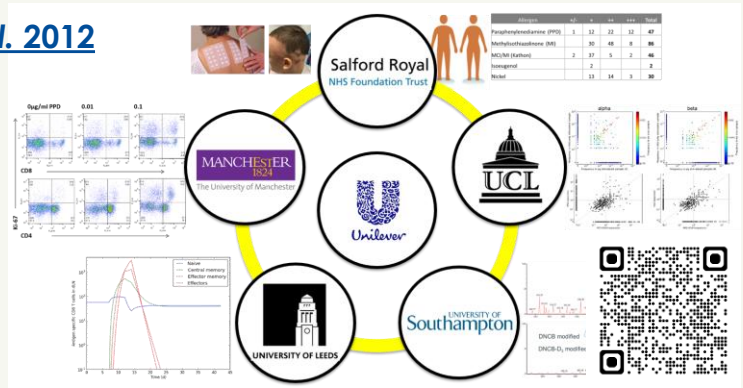
Skin Sensitisation NGRA framework



Reynolds et al. 2021

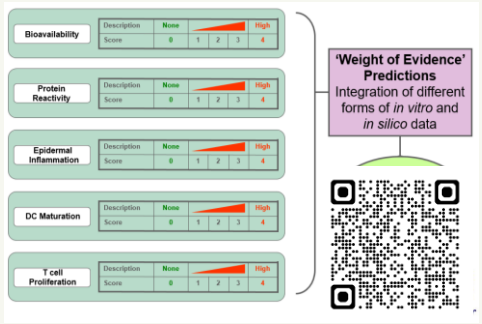
T cell Forum

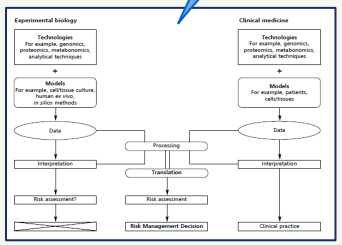
Kimber et al. 2012



Integration of non-animal data

Jowsey et al. 2006





Next Generation Risk Assessment Conceptual Frameworks

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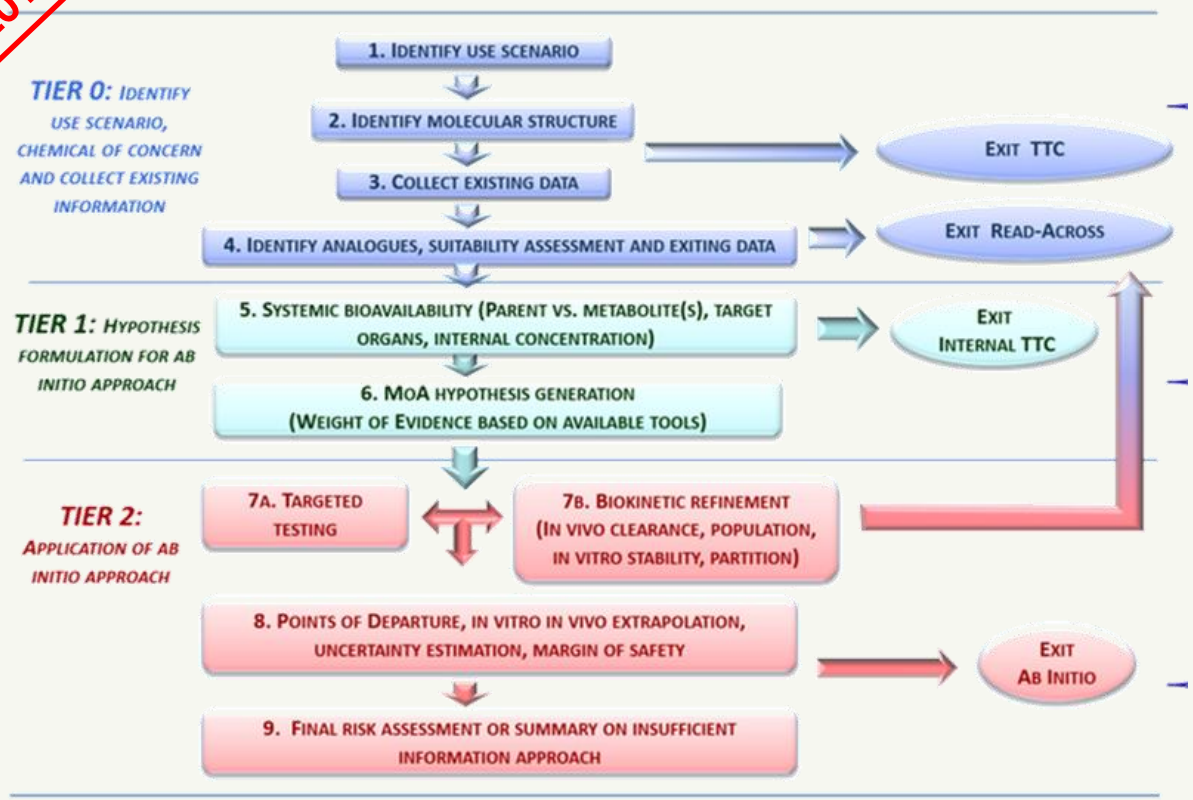
2017

SEURAT-1

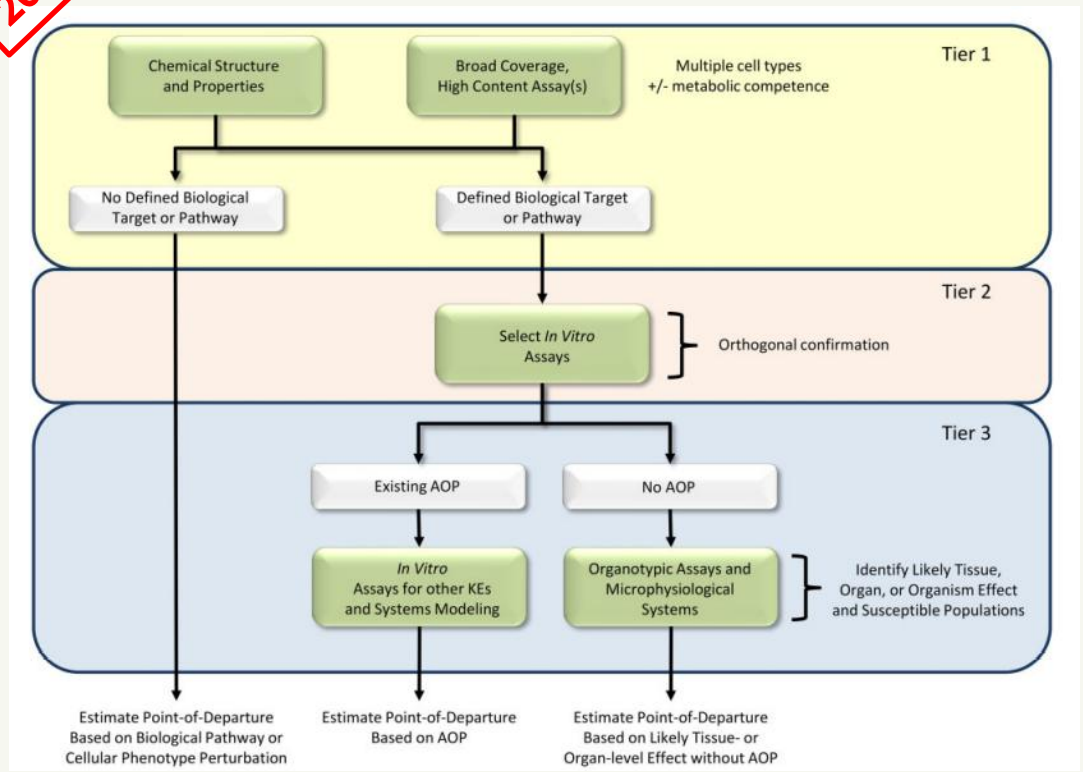


Ab initio chemical safety assessment: A workflow based on exposure considerations and non-animal methods

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

2019

EPA United States Environmental Protection Agency

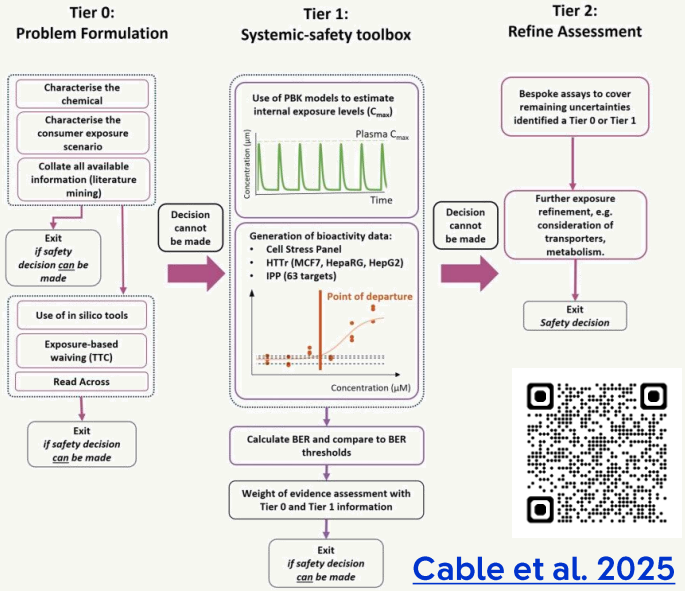


The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency

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

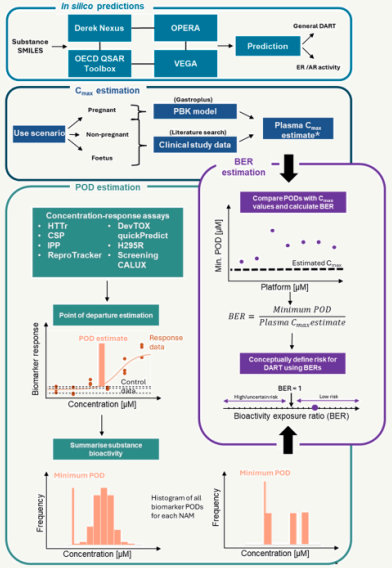
Unilever Next Gen Risk Assessment frameworks

Systemic



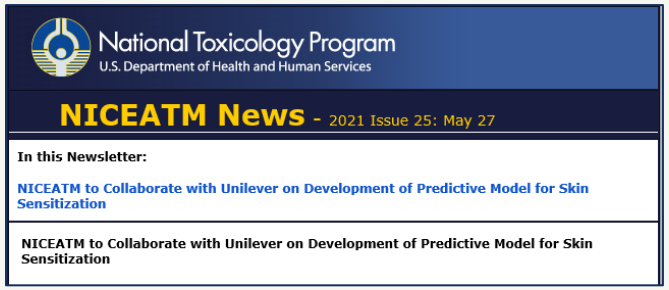
Cable et al. 2025

Developmental & Reproductive

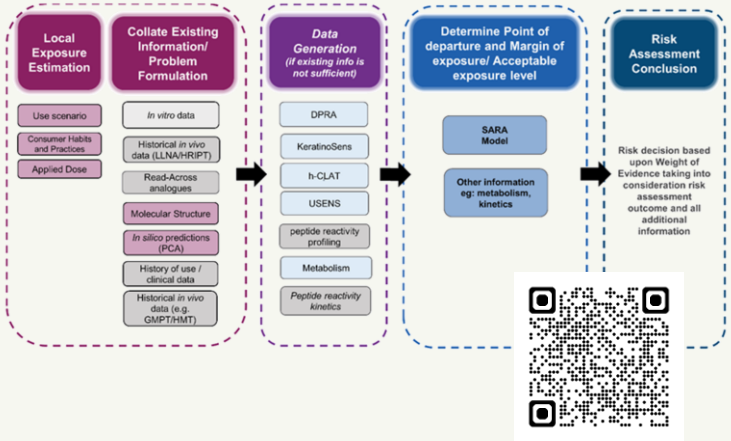


Muller et al. 2025

Ongoing Partnerships

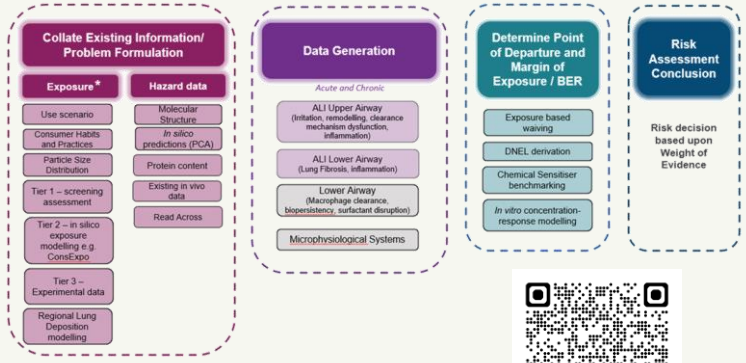


Skin Sensitization



Reynolds et al. 2021

Inhalation



de Ávila et al. 2025

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Bridging the Science to Regulation Gap: Industry Perspective

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EU REACH & CPR interface: 'Animal Testing as a Last Resort', Save Cruelty Free Cosmetics & Commission Roadmap towards phasing out animal testing

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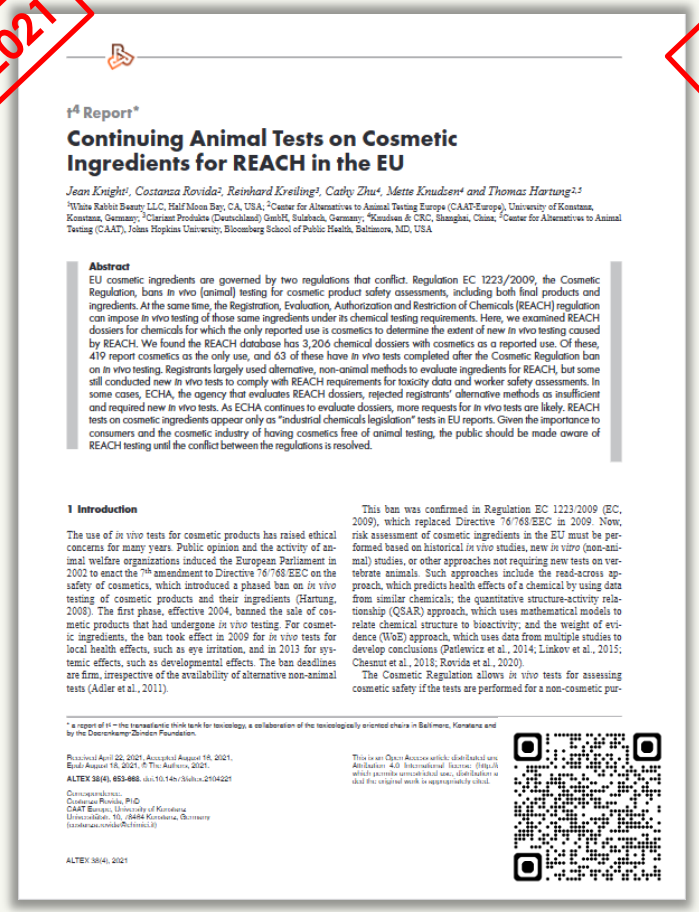
2021



t⁴ Report*

Continuing Animal Tests on Cosmetic Ingredients for REACH in the EU

Jean Knight[1], Costanza Rovida[2], Reinhard Kreiling[3], Cathy Zhu[4], Mette Knudsen[4] and Thomas Hartung[2,5]

[1]White Rabbit Beauty LLC, Half Moon Bay, CA, USA; [2]Center for Alternatives to Animal Testing Europe (CAAT-Europe), University of Konstanz, Konstanz, Germany; [3]Clariant Produkte (Deutschland) GmbH, Sulzbach, Germany; [4]Knudsen & CRC, Shanghai, China; [5]Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA

Abstract

EU cosmetic ingredients are governed by two regulations that conflict. Regulation EC 1223/2009, the Cosmetic Regulation, bans *in vivo* (animal) testing for cosmetic product safety assessments, including both final products and ingredients. At the same time, the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation can impose *in vivo* testing of those same ingredients under its chemical testing requirements. Here, we examined REACH dossiers for chemicals for which the only reported use is cosmetics to determine the extent of new *in vivo* testing caused by REACH. We found the REACH database has 3,206 chemical dossiers with cosmetics as a reported use. Of these, 419 report cosmetics as the only use, and 63 of these have *in vivo* tests completed after the Cosmetic Regulation ban on *in vivo* testing. Registrants largely used alternative, non-animal methods to evaluate ingredients for REACH, but some still conducted new *in vivo* tests to comply with REACH requirements for toxicity data and worker safety assessments. In some cases, ECHA, the agency that evaluates REACH dossiers, rejected registrants' alternative methods as insufficient and required new *in vivo* tests. As ECHA continues to evaluate dossiers, more requests for *in vivo* tests are likely. REACH tests on cosmetic ingredients appear only as "industrial chemicals legislation" tests in EU reports. Given the importance to consumers and the cosmetic industry of having cosmetics free of animal testing, the public should be made aware of REACH testing until the conflict between the regulations is resolved.

1 Introduction

The use of *in vivo* tests for cosmetic products has raised ethical concerns for many years. Public opinion and the activity of animal welfare organizations induced the European Parliament in 2002 to enact the 7th amendment to Directive 76/768/EEC on the safety of cosmetics, which introduced a phased ban on *in vivo* testing of cosmetic products and their ingredients (Hartung, 2008). The first phase, effective 2004, banned the sale of cosmetic products that had undergone *in vivo* testing. For cosmetic ingredients, the ban took effect in 2009 for *in vivo* tests for local health effects, such as eye irritation, and in 2013 for systemic effects, such as developmental effects. The ban deadlines are firm, irrespective of the availability of alternative non-animal tests (Adler et al., 2011).

This ban was confirmed in Regulation EC 1223/2009 (EC, 2009), which replaced Directive 76/768/EEC in 2009. Now, risk assessment of cosmetic ingredients in the EU must be performed based on historical *in vivo* studies, new *in vitro* (non-animal) studies, or other approaches not requiring new tests on vertebrate animals. Such approaches include the read-across approach, which predicts health effects of a chemical by using data from similar chemicals; the quantitative structure-activity relationship (QSAR) approach, which uses mathematical models to relate chemical structure to bioactivity; and the weight of evidence (WoE) approach, which uses data from multiple studies to develop conclusions (Patlewicz et al., 2014; Linkov et al., 2015; Chesnut et al., 2018; Rovida et al., 2020).

The Cosmetic Regulation allows *in vivo* tests for assessing cosmetic safety if the tests are performed for a non-cosmetic pur-

* a report of t⁴ – the transatlantic think tank for toxicology, a collaboration of the toxicologically oriented chairs in Baltimore, Konstanz and by the Doerenkamp-Zbinden Foundation.

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ALTEX 38(4), 653-668, doi:10.14573/altex.2104221

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https://www.altex.org/index.php/altex/article/view/2291/2305

2021

Comment

Upholding the EU's Commitment to 'Animal Testing as a Last Resort' Under REACH Requires a Paradigm Shift in How We Assess Chemical Safety to Close the Gap Between Regulatory Testing and Modern Safety Science

Julia Fentem, Ian Malcomber, Gavin Maxwell and Carl Westmoreland

Alternatives to Laboratory Animals 2021, Vol. 49(4) 122–132

DOI: 10.1177/02611929211040824
journals.sagepub.com/home/atl
SAGE

Abstract

Animal use for testing chemicals under REACH continues to increase, despite advances in non-animal safety science during the past 15 years. The application of modern science and technology, and the use of 'next generation' weight-of-evidence assessment approaches, are embedded in EU guidance for establishing the safety of cosmetics and foods – and of the ingredients used in these products. However, this is still not the case for the regulation of chemicals. Under the new Chemicals Strategy for Sustainability, thought leaders in human health and environmental protection are calling on the European Commission to quickly embrace the benefits of modern and innovative non-animal safety science, in place of outdated animal testing, if the EU is to be a leader in safe and sustainable innovation under the European Green Deal transformational change ambitions. The European Commission also needs to enable companies to meet their legal obligation to only conduct animal testing as a last resort, by providing a more flexible, science-based and consistent regulatory framework for assuring chemical safety, which supports the integration of data from different sources. We are at a tipping point for closing the gap between regulatory chemicals testing and modern safety science. It is time to join forces, across policy makers, scientists, regulators and lawyers, to lead the paradigm shift needed to deliver what EU citizens want – namely, chemicals and products that are safe and sustainable, without resorting to animal testing.

Keywords

alternatives, animal testing, chemical safety, new approach methodologies, next generation risk assessment, product safety, REACH, regulatory testing, safety science

Introduction

The European Union *Directive 2010/63/EU*,[1] on the protection of animals used for scientific purposes, is based on Russell and Burch's concept of the 'Three Rs' which dates back to 1959,[2] that is, the replacement, reduction and refinement of animal use. These principles have been present 'in spirit' in the EU's horizontal legislation since 1986. However, the 2010 Directive made the Three Rs a firm legal requirement: the principles must be considered systematically at all times when animals are used for scientific purposes in the EU, including where animals are used in regulatory testing.[3]

The EU Chemicals REACH Regulation (REACH; Registration, Evaluation, Authorisation and Restriction of Chemicals) came into force in 2007,[4] as the outcome of the EU Commission's 2001 White Paper on the strategy for a future chemicals policy.[5] REACH places the burden of proof on companies, who must identify and manage the risks linked to the substances they manufacture and market in the EU. They have to demonstrate how the substance can be used safely, and they must communicate the risk

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https://journals.sagepub.com/doi/pdf/10.1177/02611929211040824

2022

European Union
EUROPEAN CITIZENS' INITIATIVE

Save Cruelty Free Cosmetics

1.2M+ signatures

We call on the European Commission to do the following:

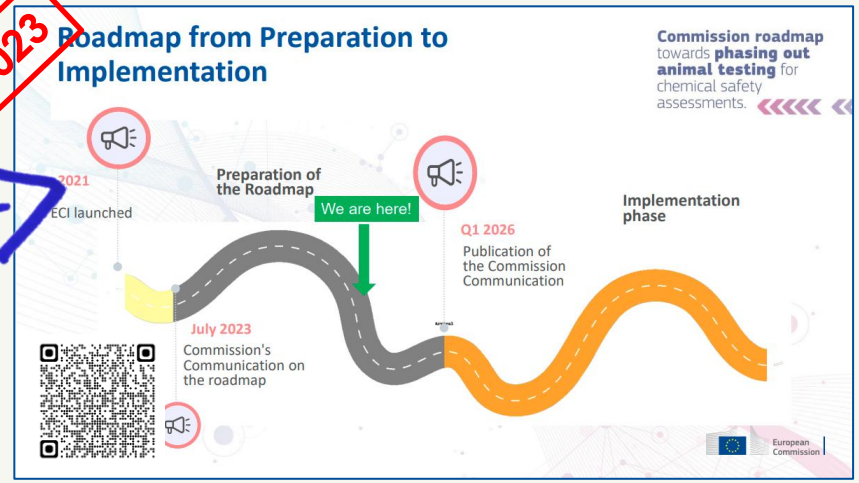
1. Protect and strengthen the cosmetics animal testing ban.
Initiate legislative change to achieve consumer, worker, and environmental protection for all cosmetics ingredients without testing on animals for any purpose at any time.

2. Transform EU chemicals regulation.
Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.

3. Modernise science in the EU.
Commit to a legislative proposal plotting a roadmap to phase-out all animal testing in the EU before the end of the current legislative term.

Save Cruelty Free Cosmetics ECI

2023



Roadmap towards phasing out animal testing

Consumer Safety: EU Scientific Committee for Cosmetics Safety (SCCS) create a 'safe space' for Benzophenone-4 (BP-4) ab initio NGRA case study

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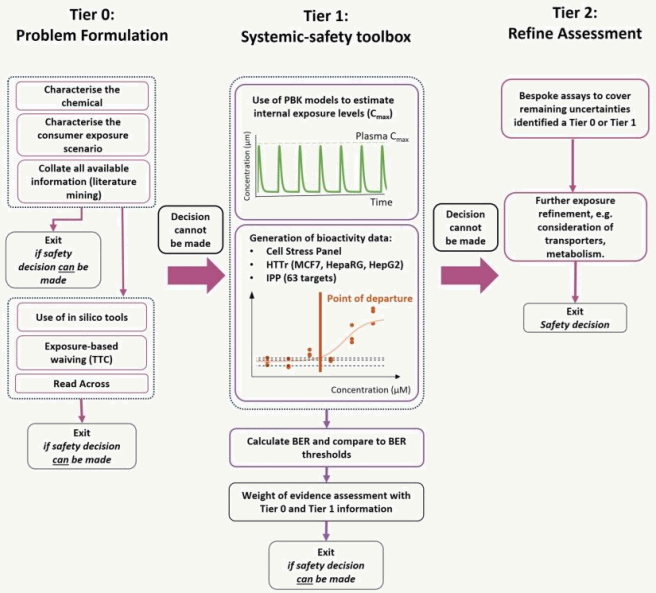
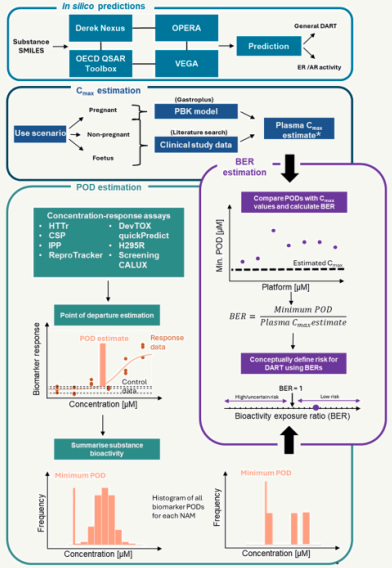
Systemic NGRA



[Cable et al. 2025]

DART NGRA



[Muller et al. 2025]

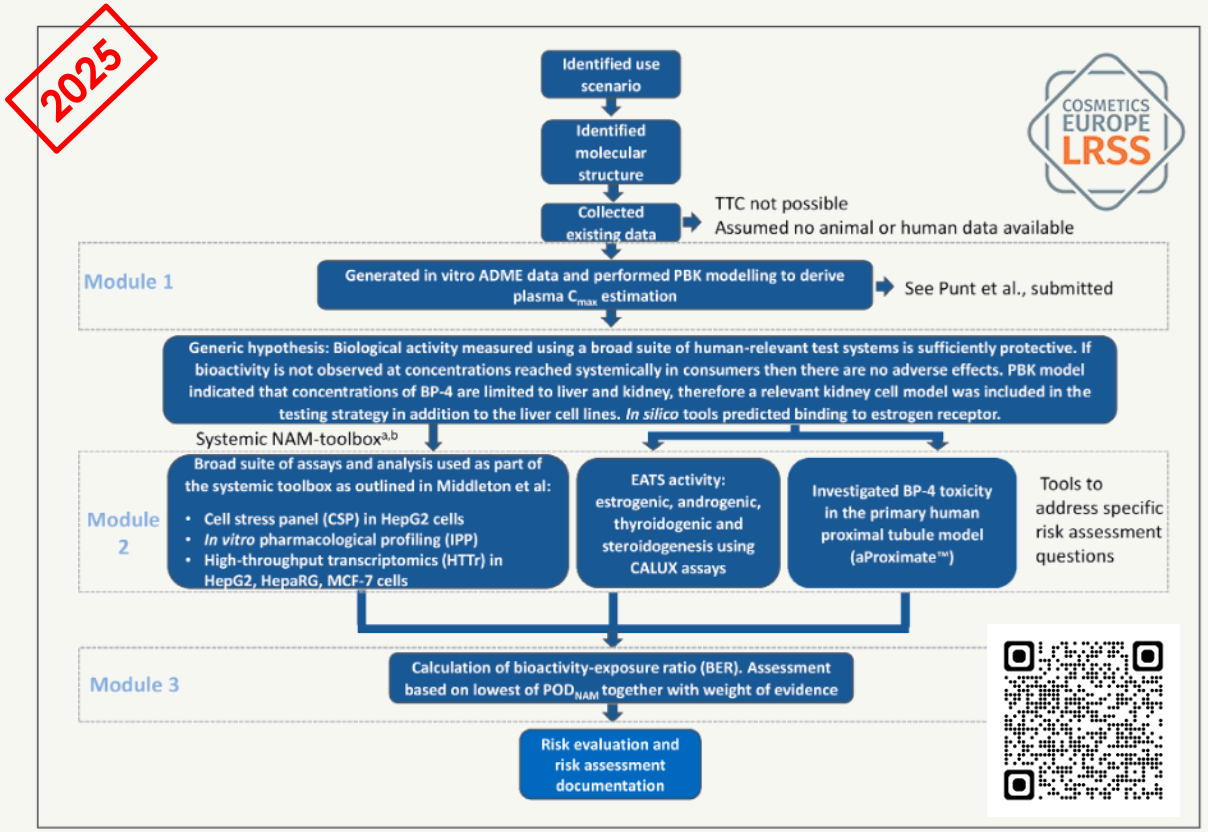
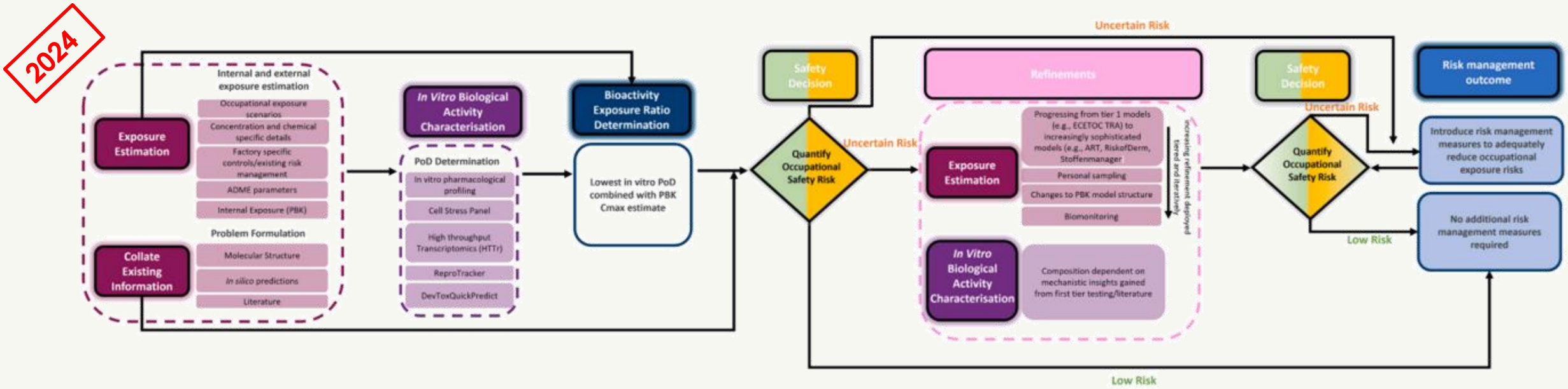


Fig. 1: NGRA case study workflow for 5% BP-4 in sunscreen body lotion
Adapted from Berggren et al. (2017) and Dent et al. (2021); [a] Middleton et al. (2022), [b] Cable et al. (2024).

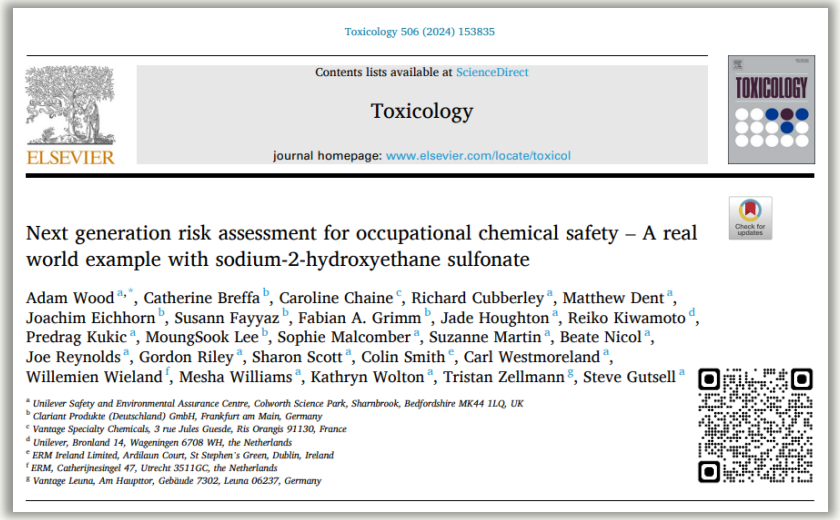
Making safety decisions for a sunscreen active ingredient using next-generation risk assessment: Benzophenone-4 case study

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

Occupational Safety: applying tiered NGRA approach to real-world sodium-2-hydroxyethane sulfonate (SI) case study



- **NGRA for worker safety assessment** developed in partnership with Clariant, Vantage, & ERM
- Consumer safety NGRA frameworks adapted & extended to enable occupational safety risks to be assessed and managed
- Such an approach could be followed to ensure that animal testing is only conducted as a "last resort" e.g. under EU REACH.


Toxicology 506 (2024) 153835

Contents lists available at ScienceDirect

Toxicology

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

Next generation risk assessment for occupational chemical safety – A real world example with sodium-2-hydroxyethane sulfonate

Adam Wood [a,*], Catherine Breffa [b], Caroline Chaine [c], Richard Cubberley [a], Matthew Dent [a], Joachim Eichhorn [b], Susann Fayyaz [b], Fabian A. Grimm [b], Jade Houghton [a], Reiko Kiwamoto [d], Predrag Kukic [a], MoungSook Lee [b], Sophie Malcomber [a], Suzanne Martin [a], Beate Nicol [a], Joe Reynolds [a], Gordon Riley [a], Sharon Scott [a], Colin Smith [e], Carl Westmoreland [a], Willemien Wieland [f], Mesha Williams [a], Kathryn Wolton [a], Tristan Zellmann [g], Steve Gutsell [a]

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[d] Unilever, Bronland 14, Wageningen 6708 WH, the Netherlands
[e] ERM Ireland Limited, Ardilaun Court, St Stephen's Green, Dublin, Ireland
[f] ERM, Catherijnesingel 47, Utrecht 3511GC, the Netherlands
[g] Vantage Leuna, Am Hauptor, Gebäude 7302, Leuna 06237, Germany

https://doi.org/10.1016/j.tox.2024.153835

Environmental safety: developing an animal-free regulatory paradigm for chemical safety assessment

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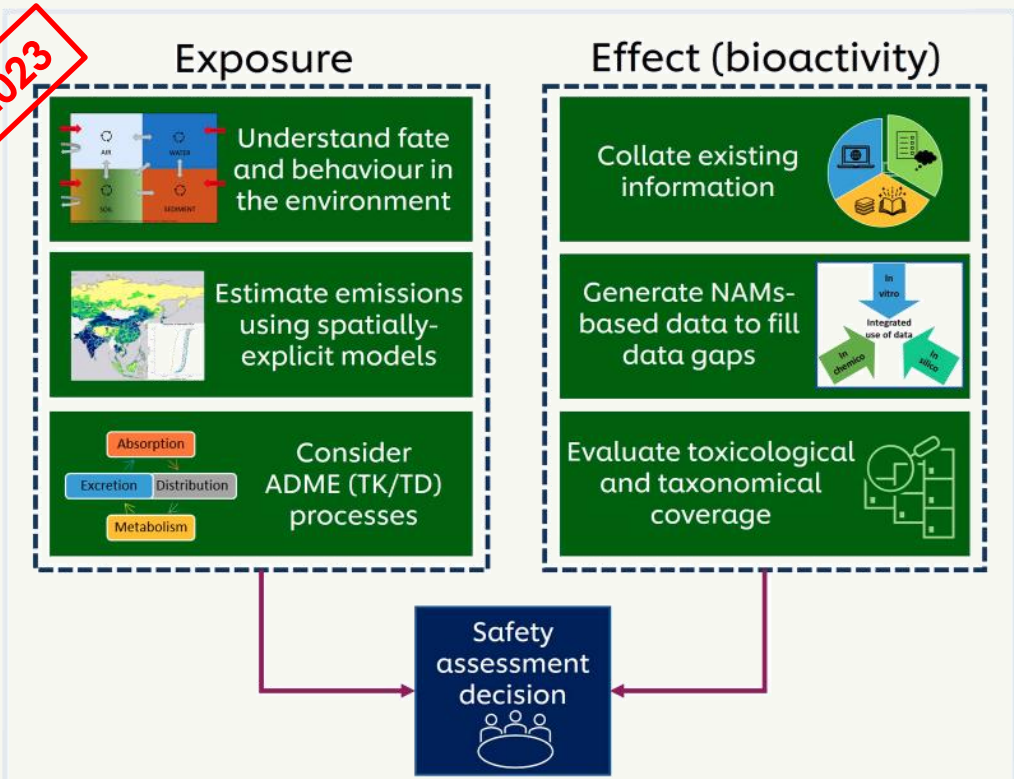
2023



Environmental NGRA conceptual framework

https://doi.org/10.1002/ieam.4763

2024

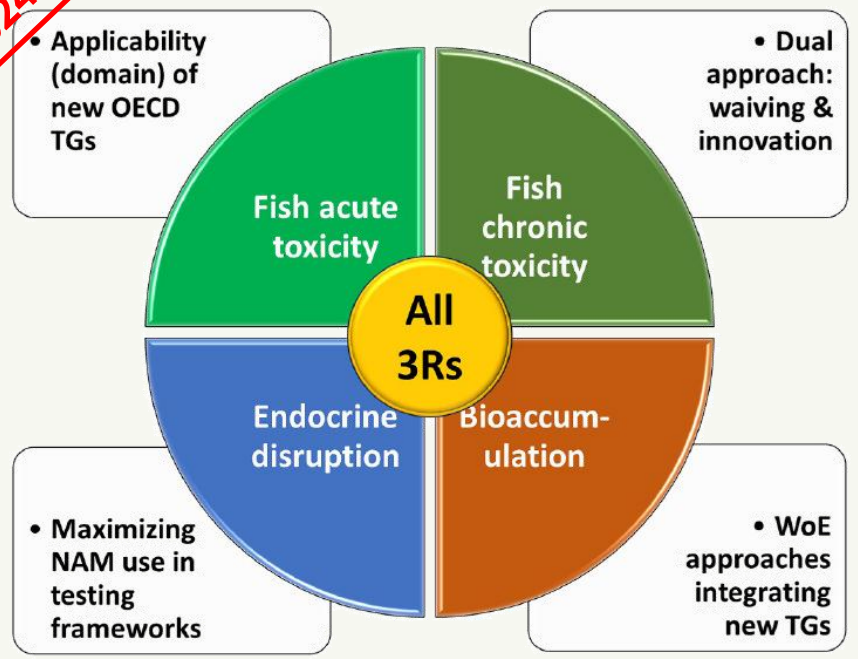


Fig. 1. Main priority areas and proposed actions, to be complemented with a long-term initiative for developing a new ESA paradigm.

EPAA Environmental Safety Assessment Team

40+ experts from across European Partnership for Alternative Approaches to Animal Testing (EPAA, including EU Commission, EU Agencies, Companies & Trade Associations) & partners

10.1016/j.yrtph.2025.105774

Bridging the Science to Regulation Gap: Industry Perspective

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1. **Safety Science**
   a) **1980-2000**: Alternatives to Animal Testing
   b) **2000-2020**: Safety without Animal Testing
   c) **2020-2025**: Science to Regulation Gap
2. **Regulatory Science**
   a) **Consumer Safety:** BP4 ab initio case study
   b) **Occupational Safety**: SI case study
   c) **Environmental Safety**: EPAA community
3. **Next steps**
   a) **Harness AI:** democratise NGRA & build capacity
   b) **Collaborate**: Safe Spaces & Regulatory Sandboxes
   c) **Integrate:** Human & Environmental Safety

Harness AI: To democratise NAMs/NGRA approaches and rapidly build global capacity

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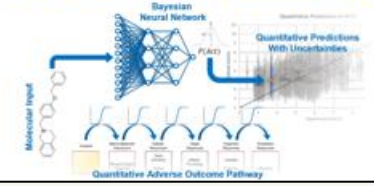
2 Identify structure

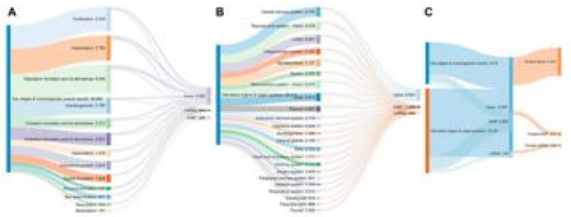
DNNs to predict chemical-protein off-target interactions



Allen et al., (2022)

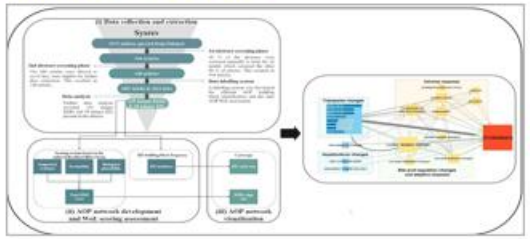
6 Mode of Action Hypothesis

NLP to understand Human Development and Reproduction

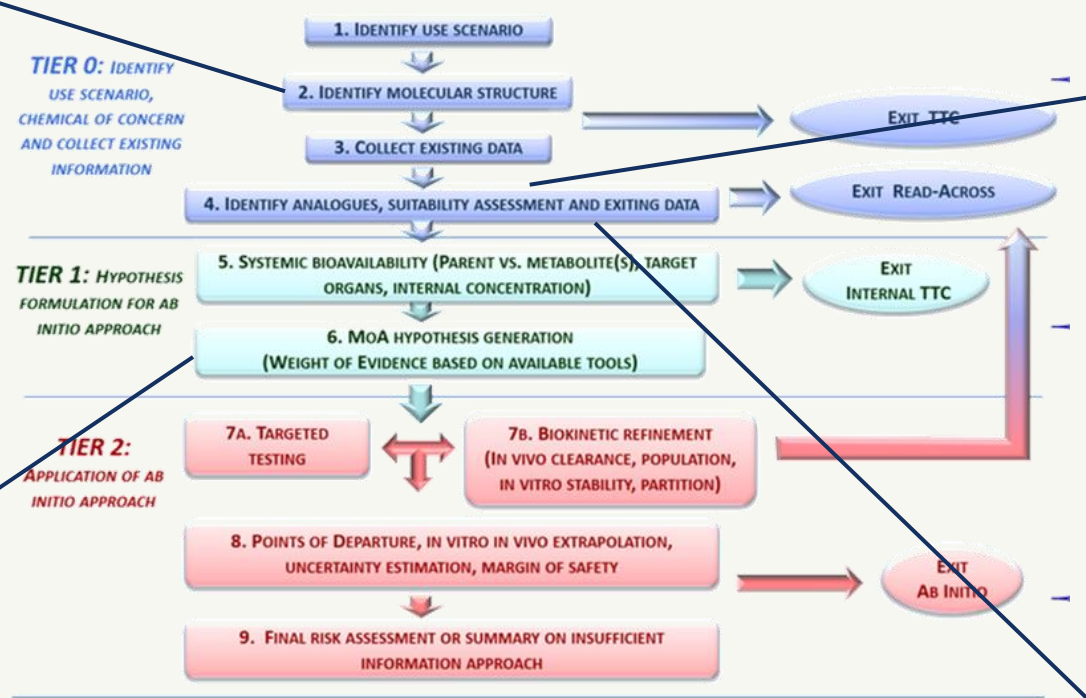


Rajagopal et al.,(2022)

NLP to create new AOPs



Ertvelde et al.,(2023)

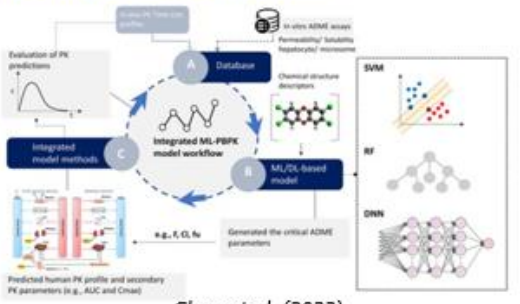


3 Collect existing data

***NLPs to automatically extract PK parameters from literature**

Bozada et al.,(2021), Hernandez et al., (2021)

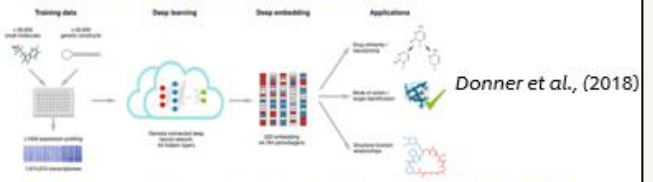
****DNNs to predict ADME properties**



Chou et al.,(2023)

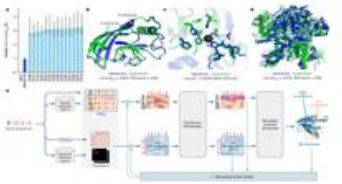
4 Identify analogues

DNNs for toxicogenomic read-across



Donner et al., (2018)

DNNs to predict protein allergenicity potential AllerCatPro



Jumper et al., (2021), Nguyen et al., (2022)

Abbreviations:

- NLP – Natural Language Processing
- DNN – Deep Neural Network

Collaborate: We need to create 'safe spaces' & strengthen 'regulatory sandboxes' to build confidence in NAMs/NGRA together

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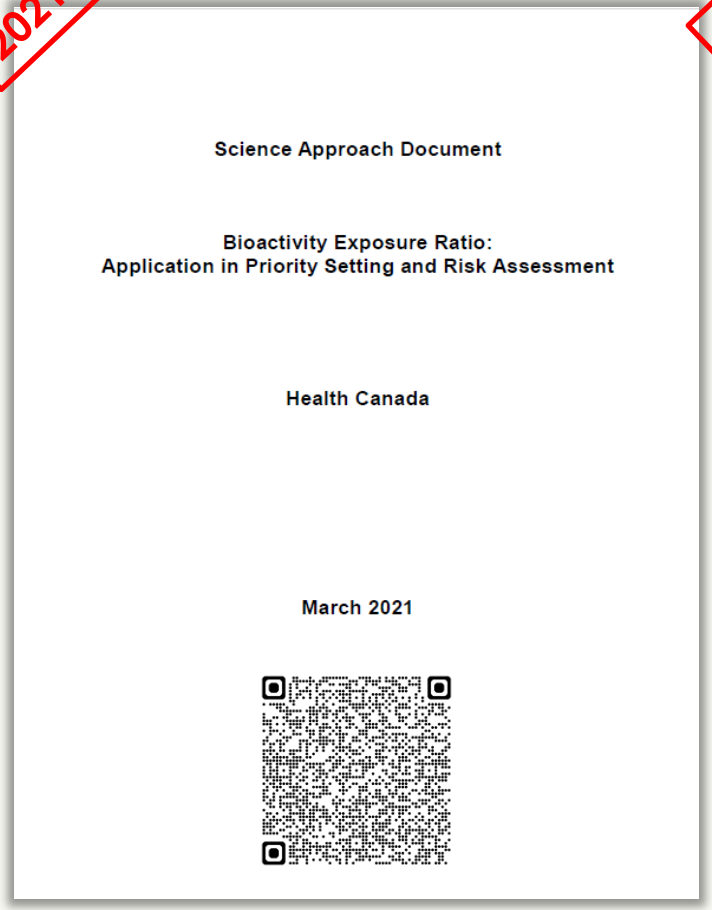
Health Canada Santé Canada

2021



Science Approach Document

Bioactivity Exposure Ratio:
Application in Priority Setting and Risk Assessment

Health Canada

March 2021

European Commission

2025

'Safe space' A forum allowing confidential data sharing with regulators to discuss the potential acceptability of a specific (set of) method(s) for a given case.				'Regulatory Sandbox' A forum where method developers and regulators would discuss more generally the regulatory needs and solutions being developed to meet them.			
Early/ Dialogue	**Qualification/ Validation**	**Scientific Advice**	**Safe Harbour**	**Identification of Gaps**	**Co-design solutions**	**Standardize for Regulatory Use**	**Regulatory Use Case Studies**
*EMA Innovation Taskforce	Innovative Medicine Methods R&D*	EMA Scientific Guidance	*EMA Data Submission	EPAA Partners Forum	EPAA NAMs Designathon	PEPPER	ASPA / ASPIS cluster
ECHA help desk		ECHA Examination of Testing Proposals	SCCS BP4 NGRA dossier	PARC task 2.1	ASPIS and PARC	NETVAL	OECD IATA
General Pre-submission Advice (GPSA)				ECHA NGO dialogue	APCRA	EFSA NAMs4NANO	EPAA NAM User Forum
					Joint exploration of NAMs in a scientific (non-binding) setting	OECD WNT	
*Regulatory acceptance of new approach methodologies (NAMs) to reduce animal use testing | European Medicines Agency (EMA)						PARERE	

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

Change Management working group overview of Safe spaces and Regulatory Sandboxes presented at 3rd Commission Roadmap workshop

Integrate: integration of human health & environmental NGRA as first step in establishing safe & sustainable by design (SSbD) frameworks

2025

Contents lists available at ScienceDirect

NAM Journal

journal homepage: www.sciencedirect.com/journal/nam-journal

Full Length Article

Unlocking the future of environmental safety: a framework for integrating new approach methodologies in decision-making

Claudia Rivetti, Jade Houghton, Maria Blanco Rubio, Danilo Basili, Predrag Kukic, Iris Muller, Geoff Hodges, Bruno Campos

ARTICLE INFO

ABSTRACT

1. Introduction

https://doi.org/10.1016/j.namjnl.2025.100028

https://doi.org/10.1016/j.namjnl.2025.100028

Integrated Human Health & Environmental NGRA framework

Tier 0- Identify use scenario and collect existing information

- Characterise exposure scenario (consumer and the environment)
- Characterise the chemical
- Use of Predictive tools (i.e. in silico)
- Collate all available information (literature and data)
- Read-across
- Use Threshold of (eco)-Toxicological Concerns

→ Exit if safety decision can be made

Tier 1- Generate data to ensure refined exposure and increase Toxicological and taxonomical coverage

- Exposure refinement, including emission, ADME and relevant PBK
- Refine chemical and biological read-across hypothesis
- Broad coverage in chemico & in vitro bioactivity panels
- Dose-response data generation and POD estimation
- Estimation of safety thresholds

→ Exit if safety decision can be made

Tier 2- Refine assessment, incl. bespoke assays to increase decision certainty

- Exposure refinement (e.g. loss processes and spatially explicit emissions, Metabolism, clearance, transporters, etc)
- Definition of Biological and toxicological coverage
- Bespoke assays to cover potential targets of concern (follow up tier 1)
- Estimation of safety thresholds

→ Safety decision or reiterate

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To bridge the science to regulation gap:

1. **Harness AI** to democratise regulatory use of NAMs/NGRA and rapidly build global capacity

2. **Create confidential 'safe spaces'** for industry: regulator scientific exchange to support new innovations

3. **Strengthen 'regulatory sandbox' platforms** to accelerate confidence-building in NAMs/NGRA use

4. **Integrate human health & environment NGRA frameworks** as first step in establishing SSbD approach

Acknowledgements:

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