EPAA Perspective

Dr Gavin Maxwell, EPAA industry co-chair
gavin.maxwell@unilever.com

European Partnership for Alternative Approaches to Animal Testing (EPAA)

The European Partnership for Alternative Approaches to Animal Testing

Collaboration between European Commission and Industry stakeholders from 8 sectors (est. 2005)

Vision: The replacement, reduction and refinement (3Rs) of animal use for meeting regulatory requirements through better & more predictive science (e.g. New Approach Methodologies (NAMs)).

To join EPAA e-mail:

GROW-EPAA@ec.europa.eu

38 Companies (including 1 SME)

Boehringer Ingelheim, Johnson & Johnson, REVLON, L'ORÉAL, DSM, DOW, LVMH, essity, symrise, ESTĒE LAUDER, KANEBO, MERCK, MSD, SHISEIDO, Gowan, EVONIK, ADAMA, Beiersdorf, Unilever, CHANEL, COLGATE-PALMOLIVE, Henkel, BAYER, CORTEVA agriscience, P&G, Kimberly-Clark, NOVARTIS, Reckitt Benckiser, novo nordisk, zoetis, BASF, SANOFI, SOLVAY, GSK, SASOL, novozymes, stratiCELL, syngenta

European Commission

European Commission

DG GROW
DG ENV
DG SANTE
DG JRC
DG RTD

Including Partner Agencies

ECHA European Chemicals Agency, efsa European Food Safety Authority, European Medicines Agency Science Medicines Health

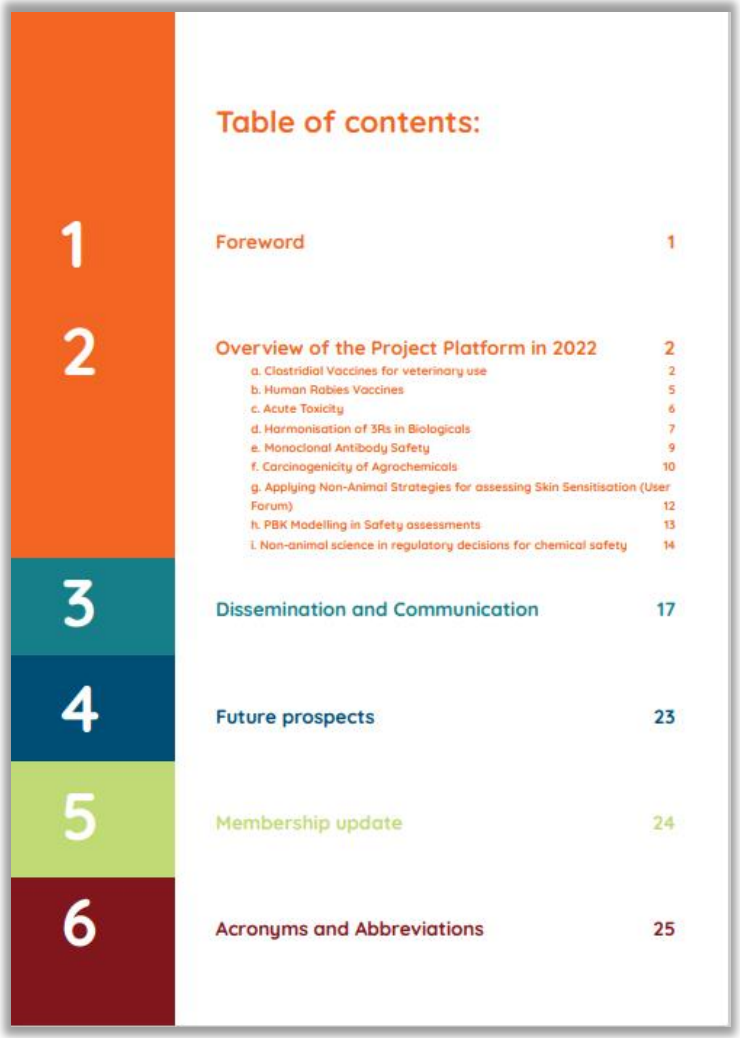
Mirror Group *(Advisory body)*

Emily McIvor (Chair), Julia Baines, Emma Grange, Tuula Heinonen, Christiane Hohensee, Monique Janssen, Helena Kandarova, Winfried Neuhaus, Sirpa Pietikaïnen (MEP), Vera Rogiers

8 Sectoral Associations

A·I·S·E, animalhealth europe, cefic, Cosmetics Europe, ifra International Fragrance Association, efpia European Federation of Pharmaceutical Industries and Associations, CropLife Europe, sme united

EPAA 2022 Annual Report



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f. Carcinogenicity of Agrochemicals
g. Skin Sensitisation Dissemination (User Forum on use of NAMs)
h. PBK Modelling in Safety assessments
i. Non-animal science (NAMs) in regulatory decisions for chemical safety

Available on EPAA website: here

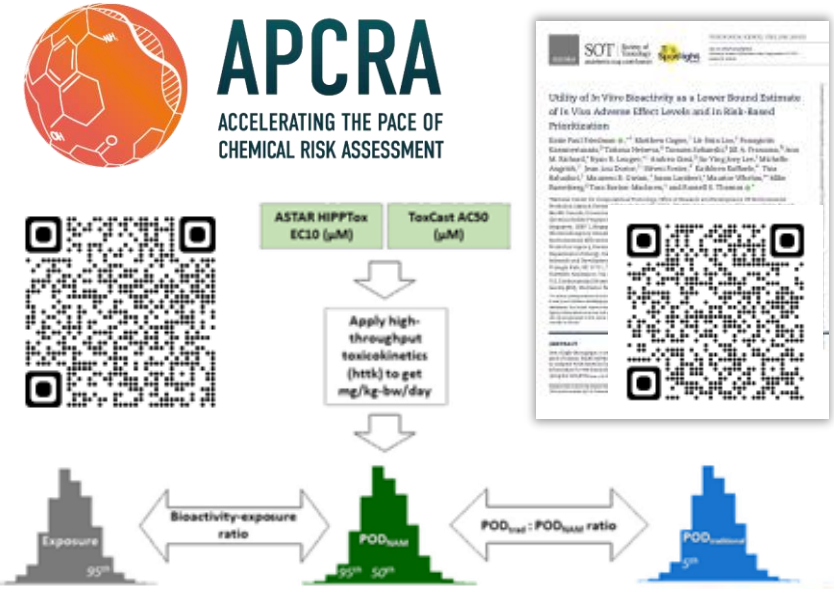
Applying NAMs to regulatory testing of chemicals: ongoing global paradigm shift

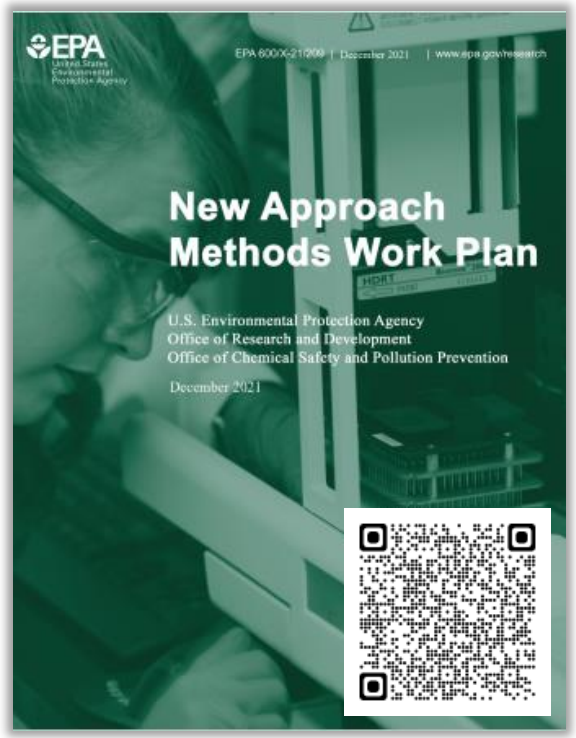
Paul Friedman et al. 2020

APCRA 'proof-of-concept' case study demonstrated the feasibility of applying a high throughput NAM-based approach for screening-level assessments

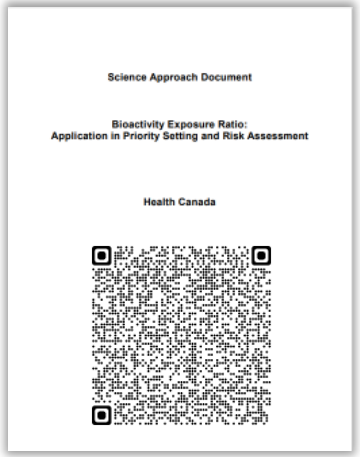
- Point of Departure (POD) $_{NAM\ 95}$ value less than or equal to the POD $_{traditional}$ value (*in vivo* tox data) value for 89% chemicals
- **Bioactivity-exposure ratio** useful metric for chemical prioritization

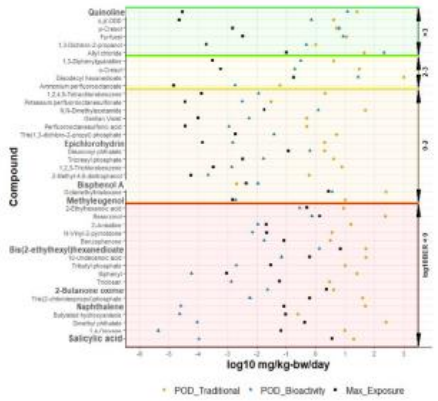
APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

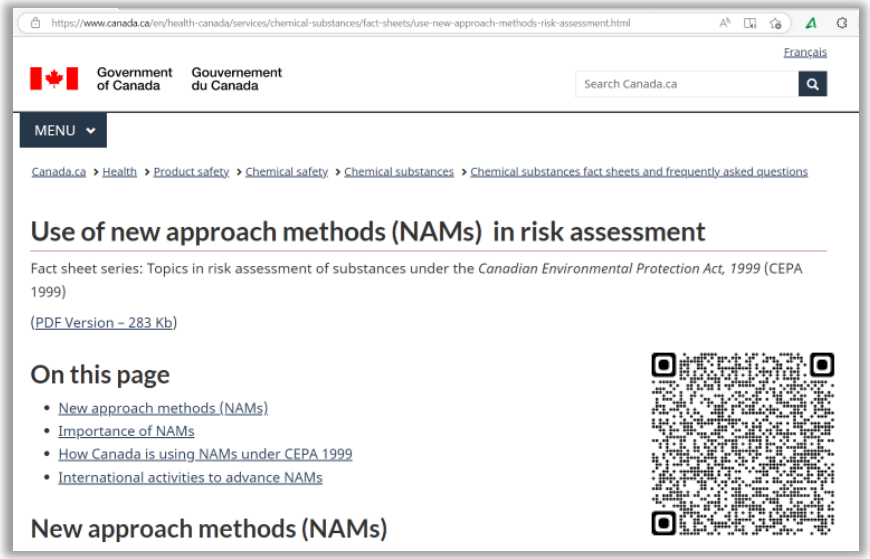




New Approach Methods Work Plan (epa.gov)







Transitioning Europe to Animal-free, Sustainable Innovation

EU Parliament resolution

On 15th Sept 2021 the EU Parliament resolution adopted to '**Accelerate a Transition to Innovation without the use of Animals in Research, Regulatory Testing and Education**' calling for an action plan with ambitious objectives, reduction targets & replacement timelines


European Parliament

2019-2024

TEXTS ADOPTED

P9_TA(2021)0387

Plans and actions to accelerate a transition to innovation without the use of animals in research, regulatory testing and education

European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education (2021/2784(RSP))

European Parliament

EU Commission response

EU Commission response to EP resolution stated that:

- '**ultimate goal of full replacement is enshrined in EU legislation**'
- 'transition to innovation without the use of animals is **best supported by focusing on & intensifying current efforts**'


Follow-up to the European Parliament non-legislative resolution on plans and actions to accelerate a transition to innovation without the use of animals in research, regulatory testing and education

1. Resolution tabled pursuant to Rules 132(2) and (4) of the European Parliament's Rules of procedure
2. Reference number: 2021/2784 (RSP) / RC9-0425/2021 / P9_TA-PROV(2021)0387
3. Date of adoption of the resolution: 16 September 2021
4. Competent Parliamentary Committee: N.A.
5. Brief analysis/assessment of the resolution and requests made in it:

The resolution recalls the objectives of the Directive on the protection of animals used for scientific purposes (2010/63/EU) and notably the replacement of procedures on live animals as soon as it is scientifically possible. It asks that those objectives be observed in all sector-specific issues of legislation that require testing (methods A and B). It stresses the

European Commission

EPAA is accelerating the transition through addressing:

1. **Scientific Research to Regulatory Use gap** by identifying NAM-based frameworks that address regulatory needs
2. **Lack of Cross-sector Scientific Consensus** by creating fora for scientific dialogue between industry & regulatory safety assessors
3. **Need for Multi-stakeholder Collaboration** by helping coordinate implementation of an EU roadmap to replace regulatory animal testing of chemicals

EPAA 'Use of NAMs in Regulatory Decisions for Chemical Safety' workshop

In November 2021, EPAA organised a deep-dive workshop on **Use of New Approach Methodologies (NAMs) in regulatory decisions for chemical safety**.

The workshop identified opportunities to advance use of NAMs through addressing the **scientific research to regulatory use gap, lack of cross-sector scientific consensus & need for multi-stakeholder collaboration.** An EPAA project was created in 2022 with two initial working groups to address the first two challenges.

Science

a) Building trust through defining criteria for robust, reliable and reproducible use of NAMs and level of acceptable variability
b) Sharing NAMs experience for a wide coverage of substances / exposure situations
c) Increasing applicability and reliability of *in vitro* ADME and QIVIVE.
d) Defining curated data sets that could be used to evaluate the performance of NAMs including qualitative/ quantitative human data
e) Taking advantage of human-based NAMs across appropriate doses vs. predicting NOAELs/LOAELs from animal studies
f) Developing a transparent scientific approach to characterise sensitivity/specificity and avoid potential over/under-classification with NAMs
g) Better defining exposure information across the lifecycle of chemicals and progressing work on exposure classification
h) Building on achievements of use of NAMs (link to survey) and addressing complex areas that currently have fewer NAM approaches (e.g., DART)
i) Ensuring new approaches provide Points of Departure for risk assessments AND hazard classification schemes, including repurposing existing NAM data
j) Consider applicability domain for NAMs-based approaches including future chemical classes (e.g., nanomaterials, polymers)

Regulatory Frameworks

a) Existing regulation could be revised to further explore tiered schemes that include exposure and NAMs without seeing animal studies as the gold standard.
b) Increasing opportunities to use NAMs that are fit for regulatory needs (e.g. Annexes of REACH) such as sharpening the text to better facilitate the use of NAMs
c) Striving to seek balance between flexibility/adaptation and prescribing defined test approaches in regulations, retaining the goal of protecting humans and the environment
d) Ensuring that scientifically valid NAMs/strategies are horizontally applied across different legislative frameworks
e) Exploring whether a cross-sector approach for use of NAMs is conceivable for OSOA
f) Increasing formal channels for scientific dialogue between decision-making regulators and industry on bespoke use of NAMs for filling information requirements

Education & Training

a) Raise awareness and provide relevant expertise and training
b) Industry and regulators to find ways to explore more NAM assessments in regulatory submissions to increase confidence in use of NAMs in regulatory discussions
c) Build common understanding with other stakeholders: NGOs, wider society – role for EPAA
d) Identify opportunities to leverage NAMs for the EU Chemicals Strategy for Sustainability

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Use of New Approach Methodologies (NAMs) in regulatory decisions for chemical safety: Report from an EPAA Deep Dive Workshop

Carl Westmoreland [a], Hans J. Bender [b], John E. Doe [c], Miriam N. Jacobs [d], George E.N. Kass [e], Federica Madia [f], Catherine Mahony [g], Irene Manou [h], Gavin Maxwell [a], Pilar Prieto [f], Rob Roggeband [i], Tomasz Sobanski [j], Katrin Schütte [k], Andrew P. Worth [f], Zvonimir Zvonar [h], Mark T.D. Cronin [c,*]

[a] SEAC, Unilever, Colworth Science Park, Sharnbrook, Bedfordshire, MK44 1LQ, United Kingdom
[b] Peter Schwingen 6, D 53177, Bonn, Germany
[c] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom
[d] Radiation, Chemical and Environmental Hazards, UK Health Security Agency, Harwell Science and Innovation Campus, Chilton, OX11 0RQ, United Kingdom
[e] European Food Safety Authority, 43126, Parma, Italy
[f] European Commission, Joint Research Centre (JRC), Ispra, Italy
[g] Procter & Gamble Technical Centre Ltd, United Kingdom
[h] EPAA Industry Secretariat, Avenue Herrmann-Debroux 40, 1160, Brussels, Belgium
[i] Procter & Gamble, Temselaan 100, 1853 Strombeek-Bever, Belgium
[j] Computational Assessment Unit, European Chemicals Agency, Telakkakatu 6, Helsinki, Finland
[k] European Commission, DG Environment, Brussels, Belgium

ABSTRACT

New Approach Methodologies (NAMs) are considered to include any *in vitro*, *in silico* or chemistry-based method, as well as the strategies to implement them, that may provide information that could inform chemical safety assessment. Current chemical legislation in the European Union is limited in its acceptance of the widespread use of NAMs. The European Partnership for Alternative Approaches to Animal Testing (EPAA) therefore convened a 'Deep Dive Workshop' to explore the use of NAMs in chemical safety assessment, the aim of which was to support regulatory decisions, whilst intending to protect human health. The workshop recognised that NAMs are currently used in many industrial sectors, with some considered as fit for regulatory purpose. Moreover, the workshop identified key discussion points that can be addressed to increase the use and regulatory acceptance of NAMs. These are based on the changes needed in frameworks for regulatory requirements and the essential needs in education, training and greater stakeholder engagement as well the gaps in the scientific basis of NAMs.

This report describes the main findings and conclusions of The European Partnership for Alternative Approaches to Animal Testing (EPAA) 'Deep Dive Workshop', which discussed the use of New Approach Methodologies (NAMs) in regulatory decisions for chemical safety. The EPAA seeks to bridge the knowledge gaps with regard to replacing animal testing and to facilitate coordination and cooperation via its partners and project platforms. The workshop was held virtually on 23–24 November 2021. The EPAA 'Deep Dive Workshop' provided a platform to exchange information between EPAA partners regarding how NAMs are being applied and/or considered for regulatory use in safety assessment and registration of new and existing substances. The workshop was opened by Mrs Sirpa Pietikäinen, Member the European Parliament, who stated that there must be an overall commitment to the safety of consumers and workers, but also to use the best science to achieve this goal. She recognised that the traditional animal tests may

* Corresponding author.
E-mail addresses: carl.westmoreland@unilever.com (C. Westmoreland), bender.hj@hotmail.de (H.J. Bender), j.e.doe@ljmu.ac.uk (J.E. Doe), Miriam.Jacobs@phe.gov.uk (M.N. Jacobs), georges.kass@efsa.europa.eu (G.E.N. Kass), 2fedemadia@gmail.com (F. Madia), mahony.c@pg.com (C. Mahony), irene.manou@epaaind.eu (I. Manou), Gavin.Maxwell@unilever.com (G. Maxwell), pilar.prieto-peralta@ec.europa.eu (P. Prieto), roggeband.r@pg.com (R. Roggeband), Tomasz.SOBANSKI@echa.europa.eu (T. Sobanski), katrin.schutte@ec.europa.eu (K. Schütte), andrew.worth@ec.europa.eu (A.P. Worth), zvonimir.zvonar@epaaind.eu (Z. Zvonar), m.t.cronin@ljmu.ac.uk (M.T.D. Cronin).

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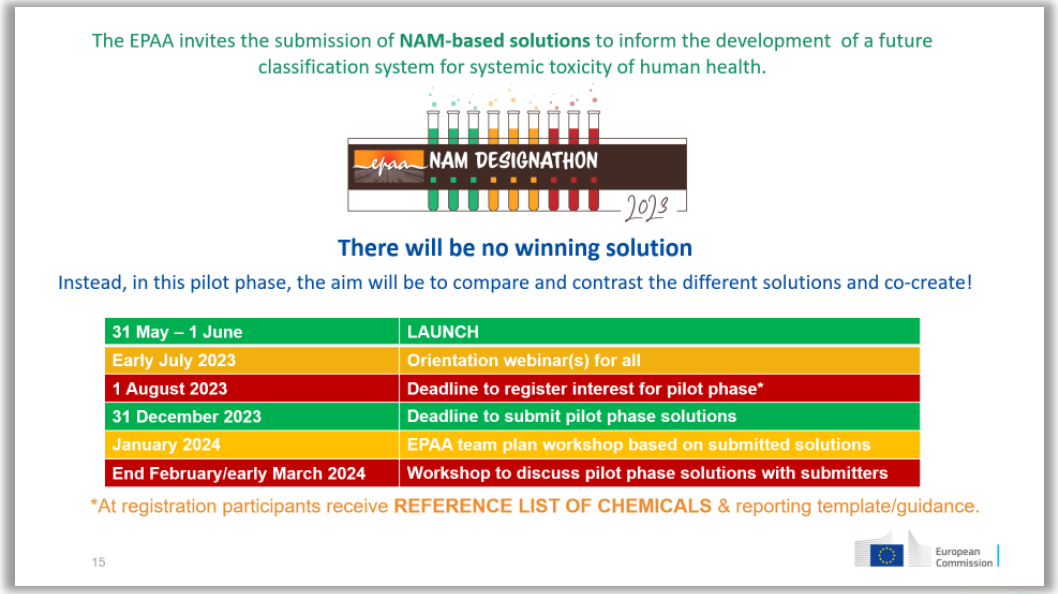
Available online 11 September 2022

EPAA ‘Non-animal science (NAMs) in Regulatory Decisions for Chemical Safety’

EPAA NAM project working group 1 have focussed on **addressing the scientific research to regulatory use gap** identified during the workshop by reflecting on how to implement the conceptual ECETOC framework for chemical safety assessment incorporating NAMs within REACH.

EPAA ‘NAM Designathon 2023’ Challenge for human systemic toxicity seeks to identify classification systems capable of categorising chemicals based on the intrinsic toxicodynamic & toxicokinetic properties.



		Activity (NAM-based toxicodynamics)		
		High	Medium	Low
Potential Systemic Availability (NAM-based toxicokinetics, based on ADME properties)	High	H	H	M
	Medium	H	M	L
	Low	M	L	L

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

ecetoc

EPAA 'Non-animal science (NAMs) in Regulatory Decisions for Chemical Safety'

EPAA NAM project working group 2 have focussed on addressing the **lack of cross-sector, scientific consensus on NAM use for chemical regulatory testing** identified during the EPAA NAM deep-dive workshop.

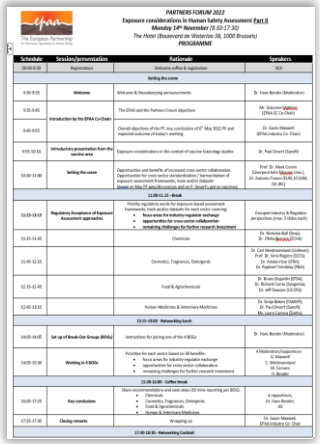
EPAA has provided a forum to discuss **use of NAMs for Skin Sensitisation regulatory testing** since it's inception – running a series of knowledge sharing workshops that have evolved into the ongoing **Skin Sensitisation NAM User Forum.**

EPAA will expand the **NAM User Forum** to allow scientific, case study-led discussions on **use of NAMs to address priority regulatory testing requirements for chemicals**, starting with a kick-off workshop (7th-8th Dec 2023, ECHA).

EPAA Partners Fora: Exposure (2022) & Environmental Safety (2023)

EPAA Partners Fora are annual events that allow the membership to review a priority topic or theme to identify opportunities for EPAA to advance use of the 3Rs through:

- identifying priority research gaps/challenges
- facilitate industry: regulator dialogue
- foster cross-sector collaboration



Last year EPAA held two partners fora on '**Exposure considerations for Human Safety Assessment**' (6th May & 14th Nov 2022) that identified several opportunities to standardise use of exposure information, tools and exposure-based safety assessment frameworks across sectors to enable greater use of NAMs (manuscript in prep).

This year EPAA will discuss '**Use of NAMs in Environmental Safety Assessment**' (13th-14th Nov 2023) to identify where EPAA can help accelerate the adoption of Environmental NAMs. Forum will be hosted by CEFIC and organised in partnership with SETAC, ECETOC & ICCS.

EU Replacement Roadmap for Regulatory Animal Testing of Chemicals

In 2022, EFSA published their '**Development of a Roadmap for Action on NAMs in Risk Assessment**' scientific report and hosted the **One Conference** (21st-24th June 2022) to discuss the recommendations.

ECHA's '**Towards an animal-free regulatory system for industrial chemicals**' workshop has broadened the scope of the scientific discussion and increased momentum.

We now need to work together to implement an **EU replacement roadmap for regulatory animal testing of chemicals**.

EXTERNAL SCIENTIFIC REPORT

APPROVED: 2 May 2022

doi:10.2903/sp.efsa.2022.EN-7341

Development of a Roadmap for Action on

New Approach Methodologies in Risk Assessment

Sylvia E. Escher[1], Falko Partosch[1], Sebastian Konzok[1], Paul Jennings[2], Mirjam Luijten[3], Anne Kienhuis[3], Victoria de Leeuw[3], Rosmarie Reuss[4], Katrina-Magdalena Lindemann[4], Susanne Hougaard Bennekou[5]

[1] Fraunhofer ITEM, [2] Vrije Universiteit Amsterdam, [3] National Institute for Public Health and the Environment, [4] Eura AG, [5] The National Food Institute Denmark

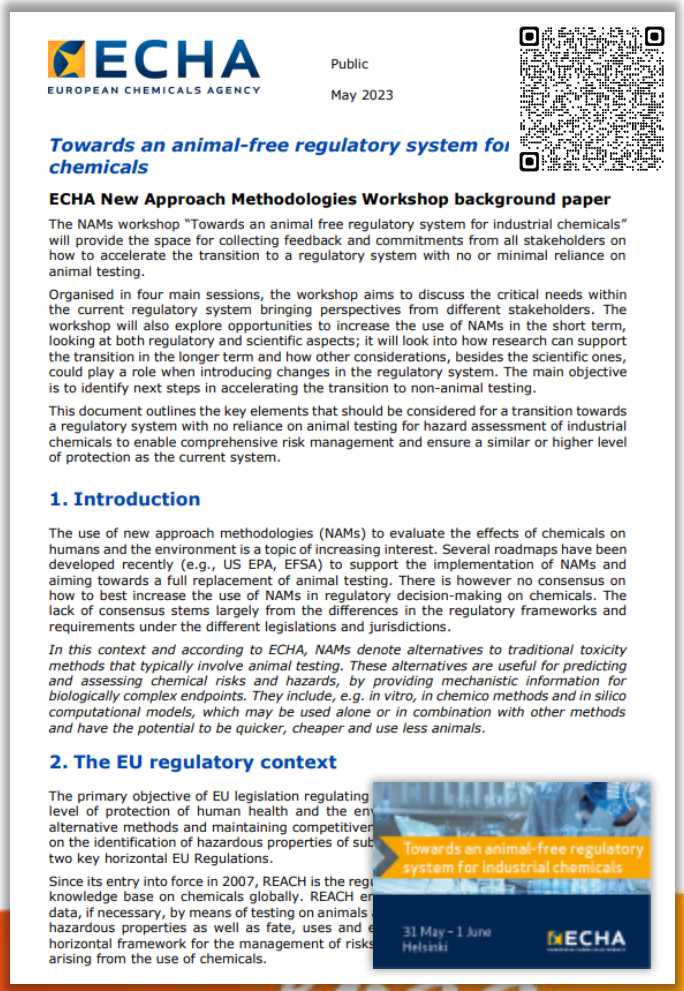
Abstract

While whole animal studies have their place in risk assessment of food and feed components, it is thought that more modern approaches such as human focused new approached methodologies (NAMs) would bring advantages including a greater focus to the human species, a focus on molecular mechanism and kinetics and the possibility of addressing susceptible populations. This report outlines the thinking from the authors and culminates in activity proposals in seven distinct but interacting scientific areas i.e. development of additional AOPs/AOP networks (AOPs), advanced cell culture models including Organ on a chip (OoC), toxicokinetic assessment with a focus on physiological based kinetic modelling (PBK), exposome, human susceptibility, data integration and new concepts in human risk assessment. Furthermore, the development of a Forum is proposed to facilitate the implementation of new approaches and concepts in risk assessment. The report was compiled by the project team, renowned experts in the various areas, and recommendations were discussed with EFSA and further refined following consultation with external experts via a dedicated workshop. The authors are convinced that if the recommendations are taken up, there will be a significant impact in the field, resulting in increasing the uptake and utilisation of these emerging technologies by all stakeholders involved.

Key words: Next Generation Risk Assessment, Ne

Question number: EFSA-Q-2022-00231

Correspondence: SPIDO@efsa.europa.eu



ECHA EUROPEAN CHEMICALS AGENCY

Public

May 2023

Towards an animal-free regulatory system for chemicals

ECHA New Approach Methodologies Workshop background paper

The NAMs workshop "Towards an animal free regulatory system for industrial chemicals" will provide the space for collecting feedback and commitments from all stakeholders on how to accelerate the transition to a regulatory system with no or minimal reliance on animal testing.

Organised in four main sessions, the workshop aims to discuss the critical needs within the current regulatory system bringing perspectives from different stakeholders. The workshop will also explore opportunities to increase the use of NAMs in the short term, looking at both regulatory and scientific aspects; it will look into how research can support the transition in the longer term and how other considerations, besides the scientific ones, could play a role when introducing changes in the regulatory system. The main objective is to identify next steps in accelerating the transition to non-animal testing.

This document outlines the key elements that should be considered for a transition towards a regulatory system with no reliance on animal testing for hazard assessment of industrial chemicals to enable comprehensive risk management and ensure a similar or higher level of protection as the current system.

1. Introduction

The use of new approach methodologies (NAMs) to evaluate the effects of chemicals on humans and the environment is a topic of increasing interest. Several roadmaps have been developed recently (e.g., US EPA, EFSA) to support the implementation of NAMs and aiming towards a full replacement of animal testing. There is however no consensus on how to best increase the use of NAMs in regulatory decision-making on chemicals. The lack of consensus stems largely from the differences in the regulatory frameworks and requirements under the different legislations and jurisdictions.

In this context and according to ECHA, NAMs denote alternatives to traditional toxicity methods that typically involve animal testing. These alternatives are useful for predicting and assessing chemical risks and hazards, by providing mechanistic information for biologically complex endpoints. They include, e.g. in vitro, in chemico methods and in silico computational models, which may be used alone or in combination with other methods and have the potential to be quicker, cheaper and use less animals.

2. The EU regulatory context

The primary objective of EU legislation regulating
level of protection of human health and the en
alternative methods and maintaining competitiver
on the identification of hazardous properties of sub
two key horizontal EU Regulations.

Since its entry into force in 2007, REACH is the regu
knowledge base on chemicals globally. REACH en
data, if necessary, by means of testing on animals
hazardous properties as well as fate, uses and e
horizontal framework for the management of risks
arising from the use of chemicals.

EPAA EU Parliament events

Last year EPAA held a lunch debate in the EU Parliament with key MEPs to discuss EPAA's contribution to '**Accelerating the transition to animal-free, sustainable innovation**' (13th Sept 2022).

This year a range of EPAA partners will hold a follow-up **EU Parliament exhibition** to share progress & discuss opportunities / challenges (12th Sept 2023).

PARC Synergy Network

Partnership for the Assessment of Risks from Chemicals (PARC) is a collaborative network of 200 partners /28 EU countries that aims to develop Next Gen chemical risk assessment to protect human health and the environment.

EPAA is proud member of PARC's Synergy Network (SYNet), a programme designed to facilitate collaboration and knowledge sharing with other initiatives.

Summary: EPAA is accelerating the transition to animal-free, sustainable innovation through addressing:

1. **Scientific Research to Regulatory Use gap** by identifying NAM-based frameworks that address regulatory needs

   EPAA NAM Designathon Challenge 2023

2. **Lack of Cross-sector Scientific Consensus** by creating fora for scientific dialogue between industry & regulatory safety assessors

   EPAA NAM User Fora

   EPAA Partners Fora

   - Exposure
   - Env. Safety

3. **Need for Multi-stakeholder collaboration** by helping coordinate implementation of EU roadmap to replace regulatory animal testing of chemicals

   EFSA ONE conference

   ECHA NAM workshop

   EU Parliament events

   PARC SYNet

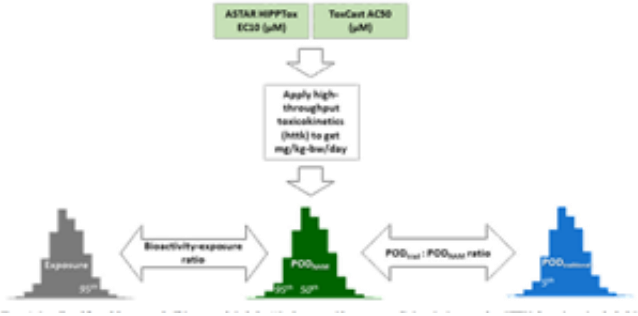
Goal: Safe & Sustainable Chemicals without Animal Testing

Chemical regulatory testing can evolve…

A paradigm shift in chemical regulatory testing is underway.

New tiered, chemical safety assessment frameworks ensure animal testing is a 'last resort' through early use of NAMs.

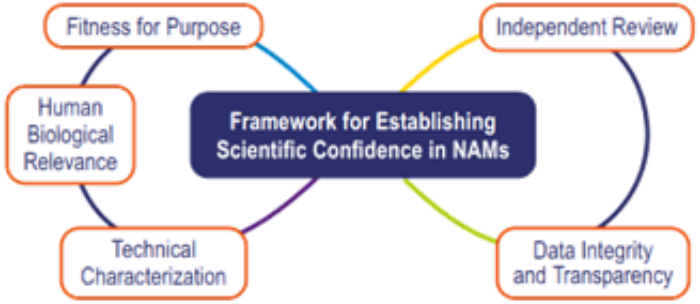
Let's use NAMs to reduce and replace chemical regulatory animal testing.



…to better protect people & our planet

Increased use of NAM data, exposure information and/or computational approaches should allow us to set, and assess against, more meaningful human health & environmental protection goals.

Let's use NAMs to strengthen confidence in chemical safety.



…and support new chemical innovation

Work is ongoing to update our chemical safety frameworks to better assess green chemistry / sustainable chemicals.

Let's use NAMs to ensure new chemicals are Safe & Sustainable by Design without Animal Testing.

Thank you – EPAA partners, collaborators & secretariat

38 Companies (including 1 SME)

European Commission

DG GROW
DG ENV
DG SANTE
DG JRC
DG RTD

@EPAA3Rs

Including Partner Agencies

Mirror Group *(Advisory body)*

Emily McIvor (Chair), Julia Baines, Emma Grange, Tuula Heinonen, Christiane Hohensee, Monique Janssen, Helena Kandarova, Winfried Neuhaus, Sirpa Pietikaïnen (MEP), Vera Rogiers

8 Sectoral Associations

EPAA website: https://ec.europa.eu/growth/sectors/chemicals/epaa_en
E-mail: GROW-EPAA@ec.europa.eu