The European Partnership
for Alternative Approaches to Animal Testing

EPAA Project: Non-animal science in Regulatory Decisions for Chemical Safety

Carl Westmoreland, Charles Laroche, Catherine Mahony, Irene Manou, Gavin Maxwell and Pilar Prieto

30th August 2023

European Partnership for Alternative Approaches to Animal Testing (EPAA)

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

Non-animal science in Regulatory Decisions for Chemical Safety

- The EPAA has a long history of exploring how new science can contribute to the **3Rs in the area of safety assessment** e.g.
  - Kimber et al (2011) J Appl. Toxicol., **31**, 206-209
  - Mahony et al (2020) Regul. Toxicol. Pharmacol., **114**, 104668.

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

- Opportunities identified 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.**

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

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Hazard
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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.

and conclusions of The Eu-
aches to Animal Testing
iscussed the use of New
tory decisions for chemical
dledge gaps with regard to
ordination 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

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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

- An EPAA project was created in 2022 with two initial working groups to address the first two challenges.
  - NAMs for Classification
  - A NAMs ‘User Forum’

NAMs for new approaches to classification

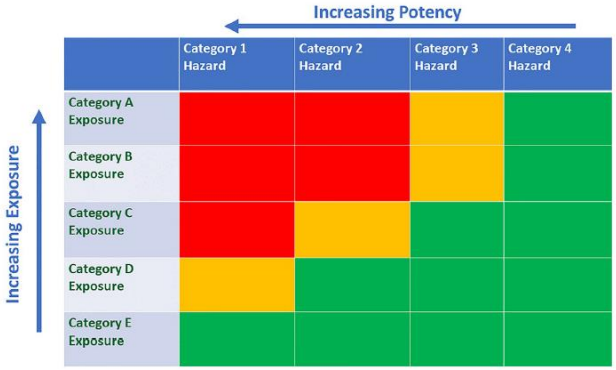
Nick Ball, **Elisabet Berggren**, Phil Botham, Marco Covaro, Stephane Dhalluin, **John Doe**, Jean-Lou Dorne, Dorothea Eigler, Rocio Garcia, Felix Kluxen, Katia Lacasse, Charles Laroche, Catherine Mahony, Irene Manou, Tina Metha, Alexander Molter, Boris Müller, **Pilar Prieto**, Frederic Schorsch, Katrin Schutte, Tomasz Sobanski, **Carl Westmoreland**, **Andrew Worth,** Ben van Ravenzwaay, **Zvonimir Zvonar**

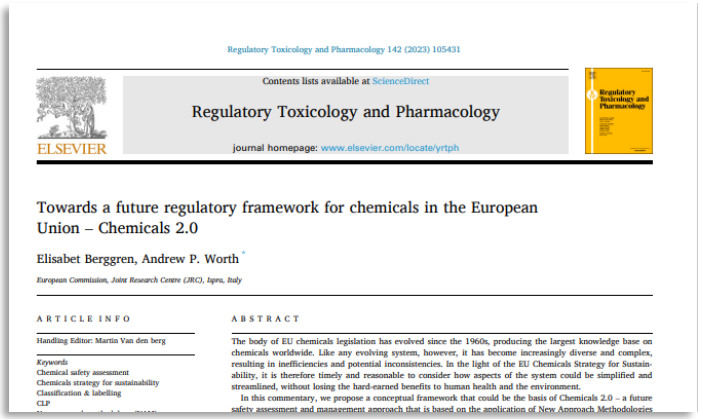
Frameworks for the use of NAMs for regulatory decisions on chemical safety

This EPAA activity is **addressing the gap between scientific research and regulatory use**

- **ECETOC framework** for chemical safety assessment
- **JRC vision** for "Chemicals 2.0"

ECETOC





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ELSEVIER

Towards a future regulatory framework for chemicals in the European Union – Chemicals 2.0

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Classification & labelling
CLP

ABSTRACT

The body of EU chemicals legislation has evolved since the 1960s, producing the largest knowledge base on chemicals worldwide. Like any evolving system, however, it has become increasingly diverse and complex, resulting in inefficiencies and potential inconsistencies. In the light of the EU Chemicals Strategy for Sustainability, it is therefore timely and reasonable to consider how aspects of the system could be simplified and streamlined, without losing the hard-earned benefits to human health and the environment.

In this commentary, we propose a conceptual framework that could be the basis of Chemicals 2.0 – a future safety assessment and management approach that is based on the application of New Approach Methodologies

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

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REGULATORY TOXICOLOGY

Check for updates

A framework for chemical safety assessment incorporating new approach methodologies within REACH

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Abstract
The long-term investment in new approach methodologies (NAMs) within the EU and other parts of the world is beginning to result in an emerging consensus of how to use information from in silico, in vitro and targeted in vivo sources to assess the safety of chemicals. However, this methodology is being adopted very slowly for regulatory purposes. Here, we have developed a framework incorporating in silico, in vitro and in vivo methods designed to meet the requirements of REACH in which both hazard and exposure can be assessed using a tiered approach. The outputs from each tier are classification categories, safe doses, and risk assessments, and progress through the tiers depends on the output from previous tiers. We have exemplified the use of the framework with three examples. The outputs were the same or more conservative than parallel assessments based on conventional studies. The framework allows a transparent and phased introduction of NAMs in chemical safety assessment and enables science-based safety decisions which provide the same level of public health protection using fewer animals, taking less time, and using less financial and expert resource. Furthermore, it would also allow new methods to be incorporated as they develop through continuous selective evolution rather than periodic revolution.

Keywords Chemical risk assessment · Toxicity · New approach methodology · Tiered assessment · Regulatory framework

		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

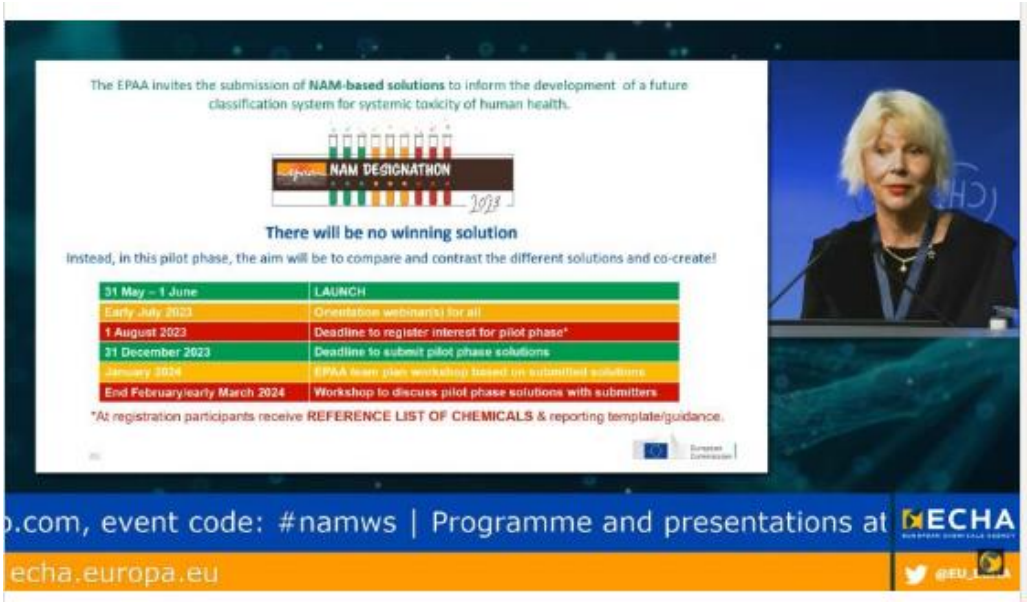
epaa

EPAA NAM Designathon 2023

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

Includes:

- Document describing the challenge
- Video of the webinar about the Designathon
- List of reference chemicals
- Reporting template



Launched: 31 May – 01 June 2023
ECHA NAMs workshop

Developing a New Classification Scheme

- Assign chemicals to groups 1-3 (low, medium & high concern)
- Existing data for already classified chemicals (high & medium concern) are used to calibrate the classification scheme resulting in **equivalent protection**

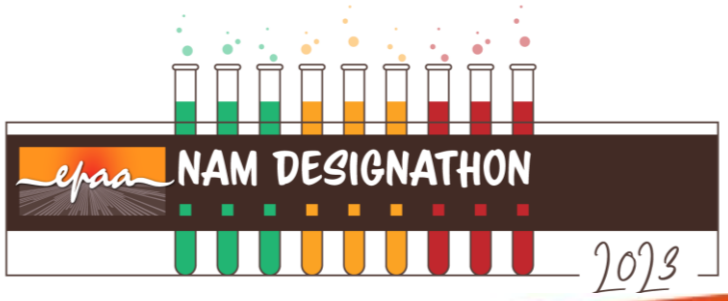
		Activity (NAM-based toxicodynamics)		
		High	**Medium**	**Low**
Potential Systemic Availability (NAM-based toxicokinetics, based on ADME properties)	**High**	H	H	M
	Medium	H	M	L
	Low	M	L	L

Challenge to the NAM development community

The EPAA invites the submission of **NAM-based solutions** to inform the development of a future classification system for **systemic toxicity** of **human health** based on the **activity and potential systemic availability of chemicals**

- The NAM-based classifications should reflect **levels of concern** related to, but not synonymous with, the current classification system addressing systemic toxicity.

- The NAMs do not need to predict the outcomes of animal studies. Nor are they expected to reproduce existing classifications.



What is the challenge about?

- To propose prototype NAM-based solutions that categorise **some or all** of the 150 chemicals on the reference list.

- In this initial prototype phase, specific **data generation** is **not necessarily required**, but rather ideas for a NAM-based classification scheme can be explored using **existing information**.

There will be no winning solution

Instead, in this pilot phase, the aim will be to compare and contrast the different NAM-based solutions and co-create!

All participants will be invited to a workshop in 2024 for this discussion

EPAA ‘NAM User Forum’

Ofelia Bercaru, **Christian Desaintes (co-chair)**, Dorothea Eigler, Marco Fabri, Irantzu Garmendia Aguire, Kirsten Gerloff, Jospeh Henriques, Georges Kass, Petra Kern, Julia Kuehnlenz, Katia Lacasse, Charles Laroche, **Gavin Maxwell (co-chair)**, Boris Müller, Gladys Ouedraogo, Pilar Prieto, Katrin Schutte, Georg Streck, Raphael Tremblay, Zvonimir Zvonar

- EPAA has provided a forum to discuss **use of NAMs for Skin Sensitisation regulatory testing** since its 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 (7^{th}-8^{th} Dec 2023, ECHA).

THANK YOU!

Find out more about EPAA