ECHA
EUROPEAN CHEMICALS AGENCY

Report on the European Chemicals Agency's "New Approach Methodologies Workshop: Towards an Animal Free Regulatory System for Industrial Chemicals"
31 May – 1 June 2023, Helsinki, Finland

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Executive Summary

This report presents the main findings from the European Chemical Agency's (ECHA's) New Approach Methodology (NAM) workshop "*Towards an Animal-Free Regulatory System for Industrial Chemicals*" (31 May – 1 June 2023). The aim of the workshop was to discuss how to support the transition to an animal-free regulatory system for chemical safety assessment. Over 500 delegates attended the workshop, either in person (ECHA, Helsinki) or on-line, representing all relevant stakeholders. Recordings of all presentations and discussions, and the slides presented are made available[1].

NAMs include *in vitro* and *in chemico* methods, as well as *in silico* computational models, that could be integrated into IATAs (Integrated Approaches to Testing and Assessment) and DAs (Defined Approaches). Such NAMs are seen as the most promising tools to ultimately replace the use of animals in chemical safety. All stakeholders demonstrated a strong commitment towards the use of NAMs to achieve the goal of animal-free chemical safety assessment. It was, however, realised that the transition to animal free chemical safety assessment will depend on the endpoint (and its complexity) and the acceptance of the NAMs. A number of examples of NAMs were presented to the workshop, demonstrating the breadth of possibilities in using different technologies, models, and methods, e.g., *in vitro* assays to replace animal models, use of omics to support chemical grouping and the development of various frameworks, IATAs and DAs utilising NAMs.

The workshop revealed strong motivations and, often related to them, considerable advantages in the use of NAMs in chemical safety assessment. The clear driver to the use of NAMs is the realisation of the ultimate aim to phase out animal testing. Other motivations and advantages include the possibility to capitalise on progress made in molecular biology, mechanistic toxicology, big data and artificial intelligence (amongst many other areas). Other benefits include the possibility of lowering costs and increasing throughput of testing. As such NAMs can provide more timely information in a flexible manner that will support the implementation of changes to chemicals' legislation.

Regulatory acceptance of NAMs is seen as crucial to their success in chemical safety assessment. Gaining regulatory acceptance of NAMs relies on the demonstration of the confidence in their use and understanding their limitations. Case studies to illustrate the applicability of NAMs are essential. Also improving the quality and accessibility of data was flagged as a necessary to support informed regulatory decisions making, help developing test methods, and improve protection levels. The use of NAMs is also intrinsically linked to adaptation of regulatory frameworks, with progress in the revision on the REACH legislation, and to CLP, being highlighted. Validation of NAMs potentially leading to internationally accepted test guidelines was noted as necessary to acceptance, with adaptations of the current validation process envisioned. Other crucial factors include legal certainty when a NAM is used for a particular purpose and the extension of the principle of Mutual Acceptance of Data to NAMs. For full uptake of NAMs, there will need to be training and education for all stakeholders and capacity building. Significant funding and investment in many areas is required. Defining the process of acceptance of NAMs, within a roadmap towards replacing animal testing, with goals and milestones, was suggested as a way to encourage and measure progress.

[1] https://echa.europa.eu/-/new-approach-methodologies-workshop-towards-an-animal-free-regulatory-system-for-industrial-chemicals

Abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
APCRA	Accelerating the Pace of Chemical Risk Assessment
C&L	Classification and Labelling
CLP	Classification, Labelling and Packaging
CSS	Chemicals Strategy for Sustainability
DA	Defined Approach
DNT	Developmental Neurotoxicity
ECHA	European Chemicals Agency
ECI	European Citizens' Initiative
EFSA	European Food Safety Authority
EPAA	European Partnership for Alternative Approaches to Animal Testing
EU	European Union
GD	Guidance Document
GHS	Globally Harmonised System
GLP	Good Laboratory Practice
IATA	Integrated Approaches to Testing and Assessment
MAD	Mutual Acceptance of Data
MATCHING	MetAbolomics ring-Trial for CHemical groupING
NAM	New Approach Methodology
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Cooperation and Development
POD	Point of Departure
PPR	Plant Protection Products and their Residues
QSAR	Quantitative Structure-Activity Relationship
SIR	Standard Information Requirement
TG	Test Guideline
UN	United Nations

1. Introduction and Aim of the Workshop

1.1 Introduction to the Workshop

This report summarises the main topics of discussion and conclusions from the European Chemicals Agency's (ECHA's) New Approach Methodology (NAM) workshop "*Towards an Animal-Free Regulatory System for Industrial Chemicals*". The workshop was held as a hybrid event both at ECHA (Helsinki, Finland) and on-line over two days, 31 May – 1 June 2023. Over 500 delegates attended and contributed to the workshop, bringing together scientists from regulatory agencies, industry, non-governmental organisations (NGOs) and academia, as well as EU competent authorities.

The aim of the workshop was to discuss how to support the transition to an EU animal-free regulatory system for chemical safety assessment. The workshop provided an opportunity to bring stakeholders together and develop a common understanding of what NAMs can achieve in the short and long term, identifying challenges and solutions.

The workshop was opened by Dr Sharon McGuiness, the Executive Director of ECHA, and Ms Tilly Metz, Member of the European Parliament, who emphasised the timeliness and importance of the topic. The workshop included sessions on:

- Hazard assessment for industrial chemicals: regulatory landscape and identifying critical needs
- Opportunities for increasing the use of NAMs under the current chemical regulatory systems
- Looking beyond current regulatory settings for a completely animal-free system

The topics included contributions from experts representing governmental and regulatory agencies, industry, NGOs and academia. In total, 27 oral presentations were made at the workshop, along with five panel discussions. Delegates were provided the opportunity to comment and ask questions both in person and through the on-line platform and polling system (a selection of results from the on-line polls are presented in Annex 1). All presentations, discussions and slides are available at ECHA's website[2].

1.2 Definition of NAMs

Multiple speakers in the workshop acknowledged that there is no formal and legally agreed definition of a NAM. In order to provide context and guidance to attendees, prior to the workshop, in their Background Paper[3], ECHA provided the following statement as a working definition:

> "*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.*"

ECHA definition was in-line with the variety of other definitions provided in the workshop. Whilst there were a range of opinions, most speakers and delegates agreed that NAM is a broad term encompassing any methodology, technology or approach providing information on hazard or risk assessment of chemicals that at a minimum contribute to refine, reduce or replace animal testing. All speakers and delegates agreed that NAMs include the use of *in silico*, *in chemico* and *in vitro* approaches. The use of Integrated Approaches to Testing and Assessment (IATA) and Defined Approaches (DA) was also highlighted.

[2] https://echa.europa.eu/-/new-approach-methodologies-workshop-towards-an-animal-free-regulatory-system-for-industrial-chemicals
[3] https://echa.europa.eu/documents/10162/21184118/2023_06_01_nam_workshop_background_note_en.pdf

1.3 Vision for NAMs Captured in this Report

The workshop heard from all speakers an agreement that NAMs are essential to achieve animal-free assessment of chemical safety. This report does not provide a detailed account of all the findings and deliberations of the workshop, these are captured on-line at the workshop page of the ECHA web-site[1]. Rather, this report attempts to set out the motivations to moving towards NAMs, the advantages of NAMs, as well as establishing how on-going efforts can provide solutions to the challenges faced by NAMs to become an alternative to animal testing in the regulatory context. The report supports ECHA's promotion of animal-free chemical testing in an attempt to understand what is achievable in the short, medium and long term. Key amongst the requirements for the move towards animal-free chemical testing are increasing confidence in NAMs and gaining acceptance for the intended purpose. The considerable work and progress by numerous stakeholders since the first ECHA NAMs workshop in 2016 (ECHA, 2016) is acknowledged.

2. Motivations, Examples and Needs for the Implementation of NAMs

All speakers and delegates at the Workshop agreed on a strong need, motivation and willingness to implement NAMs in chemical safety assessment. Section 2 provides a summary of the main motivations for implementing NAMs in chemical risk assessment, along with their advantages and examples of their use. It draws from the knowledge and expertise of all speakers and delegates who made presentations and/ or comments in the workshop.

2.1 Motivations for the Implementation of NAMs

Many speakers and delegates articulated a number of motivations for the implementation of NAMs in animal-free chemical safety assessment. A number of these are summarised in Table 1 along with the advantages associated with NAMs and cover the ethical, scientific and legal aspects of safety assessment. The workshop was also reminded of the public commitment to replacing animal testing in the European Union as well as of the recent European Citizens' Initiative (ECI) "*Save Cruelty Free Cosmetics – Commit to a Europe Without Animal Testing*" (EU, 2023).

Table 1. A summary of the main advantages and motivations in the move towards NAMs identified in the workshop, as presented by various different contributors and delegates. These represent the variety of views and positions expressed at the workshop.

Advantage in the use of NAMs over traditional animal methods	Details and motivations
Realising the ultimate aim to phase out animal testing	NAMs are key for the replacement of animal testing
Scientific	NAMs will capitalise on scientific progress, e.g., in molecular technologies, big data, artificial intelligence etc.
Cost	NAMs have the potential to be cheaper than the tests they could potentially replace

Throughput	NAMs allow for greater numbers of compounds to be tested compared to the current assays
Timeliness of decision	NAMs allow for rapid responses to emergencies, contamination etc.
Flexibility	NAMs can provide a flexible means of assessing safety, which may be tailored to new concerns or specific issues e.g., organ level toxicity
Use of exposure information	NAMs can assist in the better and more rapid assessment of systemic bioavailability following a specific dose or exposure scenario
Legal	NAMs will assist in compliance with EU Directive 2010/63/EU, in addition to chemical specific legislation, e.g., REACH, where animal testing is considered as a last resort
Changing regulation	NAMs can adapt to the requirements of legislation

2.2 Advantages in the Uptake of NAMs in Chemical Safety Assessment

Many advantages to the use of NAMs in chemical safety assessment were identified within the workshop, these are, of course, closely related to the motivations described in Section 2.1. The advantages, which are also considered to be the most important drivers for implementation, can be broadly considered to be based around reduction in animal use, more efficient chemical regulation, responding to regulation and improved use of resources. Along with the motivations for the use of NAMs, the advantages are summarised in Table 1.

2.3 Examples of NAMs

Many examples of NAMs that are currently applied, or have the possibility of being applied in the near future, in chemical safety assessment were presented to the workshop. This report does not constitute a full review of the use of NAMs for chemical safety assessment (the reader is referred elsewhere e.g., Westmoreland et al. (2022)). However, it was recognised that NAMs may be appropriate across the breadth of endpoints required for safety. To illustrate this, a number of examples of NAMs were presented to the workshop including those from human health and environmental assessment such as the Accelerating the Pace of Chemical Risk Assessment (APCRA)[4] case study (Paul Friedman et al., 2020); the MetAbolomics ring-Trial for CHemical groupING (MATCHING)[5], related to rodent (sub-)chronic toxicity; IATA case studies on developmental neurotoxicity (DNT) risk assessment (EFSA PPR Panel, 2021); the ECETOC Framework (Ball et al., 2022); amongst others. In total, the types of NAMs presented described spanned the full range of approaches including various *in silico*, *in chemico*, *in vitro* and omics assays. In addition, NAMs are being applied in a variety of ways from direct predictions of activity or Point of Departure, to their implementation in tiered strategies.

[4] https://www.apcra.net/
[5] https://cefic-lri.org/projects/c8-assessing-the-repeatability-of-metabolomics-within-a-regulatory-context-through-a-multi-laboratory-ring-trial/

3. State of the Art of NAMs and Solutions to the Needs for Their Implementation in Chemical Safety Assessment

Section 3 provides an overview of the current state of the art of NAMs in relation to the relatively large number of definable needs to secure their implementation in animal-free safety assessment. In addition, Section 3 summarises, where possible, further requirements and opportunities for the implementation of NAMs. The consensus from the workshop was that the required process for the implementation of NAMs will require some, or all, of the following steps: a global vision for the use of the NAM and a defined need; a innovation stage to allow for the design and development of the assay; pre-validation (usually by the developers); validation (which may require external input, allowing for possible acceptance for regulatory use). Should the NAM be suitable for a particular purpose, training and capacity building will be necessary.

The overwhelming needs for the implementation of NAMs are to gain scientific confidence and understanding of their purpose, leading ultimately to acceptance in their use in specific regulatory application. The workshop recognised that to increase the pace of progress towards the implementation of NAMs there is a need to collaborate at a number of levels, e.g., all stakeholders working together, across sectors and geographical regions, in partnership to produce a "global vision" (Section 3.1). There is a need to identify key questions, characterise and address critical needs (some of which are described in Sections 3.2 – 3.7) and recognise and coordinate the concerted effort of all stakeholders. Amongst these recognised needs should be capacity building (Section 3.8) and the definition of achievable timelines and expectations in a roadmap to realise the process for the implementation of NAMs (Section 3.9).

3.1 Need to Provide a Global Vision to Overcome Objections or Reluctance for the Implementation of NAMs

The workshop recognised that there is, on occasions, reluctance to change in the stakeholders involved in chemical safety assessment. This reluctance may be as a result of a lack of trust in new, non-animal methods, to replace well-used, understood and conservative approaches to safety assessment. As such, many speakers and delegates spoke of the need to provide a global vision with realistic expectations from NAMs and to demonstrate confidence in their use.
The workshop appreciated the challenges laid out by, amongst other policies and initiatives, the goals of the European Union's Chemicals Strategy for Sustainability (CSS), namely to increase information requirements for low tonnage chemicals and to identify the most harmful substances (such as endocrine disruptors). These challenges can only be met by existing, and yet to be developed, NAMs. Many speakers and delegates recognised the need for a flexible approach to the implementation of NAMs, with an emphasis on batteries of NAMs potentially organised within testing strategies or tiered approaches. The vision for NAMs to replace animals should form an integral part of the roadmap for implementation (Section 3.9).

3.1.1 Expectations from NAMs: Short to Long Term Goals

The complete move towards animal-free chemical safety assessment will not be achieved "overnight", with speakers and delegates having different opinions of when this may ultimately be realised. It is important, therefore, that realistic expectations are presented. The workshop heard a number of such expectations. Firstly, with the exception of a small number of endpoints, NAMs should not be seen as a one-to-one replacement for a particular test. For complex toxicological assays, this is likely to be a battery approach, incorporating many NAMs with a range of methods and complexity, potentially incorporating both absorption, distribution, metabolism and excretion (ADME) and toxicodynamic considerations as well as hazard assessment. NAMs may represent a single, or multiple, mechanism(s) of action (or part of an Adverse Outcome Pathway). The battery approach may be organised into tiers of tests and

decision points, with increasing complexity in the NAMs being required for the most difficult endpoints and exposure scenarios.
A number of speakers expressed opinions as what may be achievable in the short, medium and longer term. Uptake of NAMs will occur at different rates, depending on the endpoint and the stage of development and validation of assays. Short term goals could include the refinement of tests and overall reduction of animals for toxicological testing. Existing NAMs that may be of use should be identified and, if not already done so, entered into pre-validation. Exposures considerations could also be used in specific regulatory contexts.
A number of on-going activities demonstrated that data being generated under the current regulatory framework continues to hold in the short term the potential to accelerate the transition to non-animal testing, and maximising its use could be further explored.
The long term goals are clearly the replacement of the current animal tests with accepted NAMs, preferably with an Organisation for Economic Cooperation and Development Test Guideline (OECD TG). The short to long term goals should form part of the roadmap described in Section 3.9.

3.1.2 Importance of Case Studies to Achieve the Implementation of NAMs

Achieving the global vision for the use of NAMs will require valid and illustrative examples of their strengths and limitations. To reach this goal the workshop reinforced the value of case studies to demonstrate the use of, and increase confidence in, the application of NAMs in animal—free chemical safety assessment. There is a need for well-designed future case studies to achieve these goals across the range of endpoints and available NAMs.

3.2 Technical Needs for the Implementation of NAMs

Understanding and overcoming the technical challenges to the implementation of NAMs is fundamental to their success. The workshop heard that the innovation process is well established, with many NAMs available. However, the process of moving to stable and reproducible approach is more costly and difficult to achieve. This latter process is vital to the development and ultimate acceptance of NAMs. Without robust and reproducible outputs from NAMs, there is no possibility of success. A number of technical challenges were identified within the Workshop:

- Once developed, a NAM will need to be standardised. There were several calls for standardisation to be at the level of an OECD TG, if possible. However, it is appreciated that standardisation to OECD TG may not be possible for a number of reasons, e.g., time, cost, lack of facilities, etc., therefore other means of demonstrating standardisation are required.
- There is a need to demonstrate confidence in the NAMs to all stakeholders. A significant part of this was the recognition of validation of NAMs and the need to develop novel approaches to achieve this, as described in Section 3.6. As part of this there is a need to demonstrate accuracy and relevance of a NAM, this relates in part to the performance criteria that will be considered as part of the validation process. Several proposals and recommendations were made in the workshop. Firstly, some speakers acknowledged that NAMs should be protective and not aim for predictivity, thus direct comparison with animal data may not always be relevant. Instead, the consistency of a NAM, and its capability to identify known positive and negative chemicals should be demonstrated.
- As a further part of the validation of a NAM, there is also a need to place a greater emphasis on demonstrating biological relevance, reproducibility and fitness for purpose. This will require well-designed training and transfer studies, as well as proficiency testing. An example of how this may be achieved is the EU-NETVAL Thyroid Validation Study (Bartnicka et al., 2021). This focussed on optimising *in vitro* methods, their transferability, and demonstration of their reproducibility and relevance.
- NAMs are frequently seen as being able to identify hazard, but more work is required to demonstrate the reliable identification of an absence of hazard. In addition, it will be very

difficult to find a single mechanism of action for a non-specific chemical using mechanistic NAMs. The concept of "general non-selectivity" was introduced and will remain a challenge for NAMs, particularly those for assessment of chemicals of no or low toxicity.
- Data sharing was raised as a challenge by several speakers and delegates. This may require bespoke platforms and is related to the Mutual Acceptance of Data, as described in Section 3.7.
- Improving the quality and accessibility of data was flagged as a critical need for improving protection levels, target testing needs and support informed regulatory decisions making

3.3 Acceptance of NAMs

The acceptance, in a regulatory context, of the data from NAMs for chemical safety assessment is fundamental to their implementation. Acceptance of a NAM is the process with which confidence in its use can be demonstrated and documented, with significant examples already available in areas such as eye irritation and skin sensitisation. Overall acceptance of NAMs is likely to be a time-consuming process and can be seen as a gradual transition.
The workshop recognised the need for further work on what constitutes regulatory acceptance, with the dependence on regulatory context appreciated. In essence, acceptance is the process by which there may be evidence, or a formal statement, of when NAM data are good enough for a particular purpose. There is no one piece of evidence that can support acceptance, rather it is based on a demonstration of the standardisation of an assay, consistent repeated studies, confidence, legal certainty etc., which are discussed elsewhere in Section 3. The concept of building flexible frameworks for the acceptance of NAMs was proposed.
The critical elements for the international acceptance of NAMs were outlined by the OECD. These include the development of common definitions and understanding in the NAM; standards for evaluating suitability which should demonstrate reproducibility and relevance in terms of the currently applied tests; clear demonstration of context of use across a variety of regulatory scenarios; and the identification of aspects of the NAM that can be standardised including the need for guidance.
It was emphasised that acceptance must include an understanding of regulatory needs, resulting in TGs incorporating individual, or batteries, of NAMs that are fit for purpose. It is also recognised that for acceptance, NAMs may need to be integrated into IATA and DA. Ideally acceptance should aim for international harmonisation (or international harmonisation should be a driver for acceptance) allowing for the mutual acceptance of data.

3.4 Adaptation of Regulatory Frameworks

To facilitate the use of NAMs, there will be a need to modify existing regulatory frameworks, or take the opportunity to implement changes in planned updates to frameworks. It was acknowledged that developing, agreeing and sharing criteria for NAMs in regulatory applications is key for wider acceptance. The need to be dynamic and flexible in development of NAMs, and the regulatory frameworks to apply them, was seen as being essential for implementation.
The adaptation of regulatory frameworks to accommodate NAMs is seen as a long-term aim which will require the input of all stakeholders. ECHA proposed a way forward based on a number of key steps:
- Identification of critical needs for animal-free testing to direct development of NAMs. This should allow for the demonstration that NAMs can derive protection levels comparable to those currently applied. NAMs should be capable of hazard identification, i.e., NAMs have the ability to allow a conclusive outcome on the (lack of) hazardous properties for a given regulatory endpoint. With regard to hazard characterisation, NAMs should be able to reliably identify hazard based on changes at the molecular/cellular level instead of observed adversity in an organism. In addition, NAMs should be able to reliably convert nominal concentrations measured or predicted into external doses used to set safety levels and to allow for the communication of the hazard to assess the risks, (i.e. allow

for extrapolation of doses and observed effects to the whole organism).

- NAMs that are already available should be applied, where practicable, under current regulatory systems. It is recognised that there is currently significant potential for refinement and reduction, using NAMs and other tools already available in a number of areas. For lower tier endpoints, this may include *in silico* methods (e.g., quantitative structure-activity relationships (QSARs)) with good predictive capability and broad applicability domains for hazard and risk assessment. For higher tier endpoints 'omics enhanced *in vivo* studies could be considered to generate molecular data in an entire biological system. In addition, there could be better utilisation of NAMs to support read-across and grouping.
- There should be a longer-term redefinition of regulatory systems for chemical safety assessment. Potential areas for consideration and further development are: the derivation of reference values for risk assessment from molecular data (as opposed to adverse effects); the calibration of NAMs against expected and well-defined protection goals; revision, or development, of C&L criteria which are suitable for NAMs; the overall throughput and performance of a NAM as well as its cost.

Desirable characteristics for a future regulatory system based on NAMs were proposed (Berggren and Worth, 2023). These state that a future chemical system should: be applicable to all substances on the market; provide an equivalent level of protection as under the current legislation; provide regulatory certainty and guide innovation; and maintain current C&L conclusions. In addition, regulatory implementation of NAMs would implicitly incorporate the principle of equivalent protection, namely that the same risk management decisions would be obtained using NAMs rather than animals.

Whilst not a formal regulatory proposal and rather theoretical and exploratory, a new classification scheme was proposed, based on the use of toxicokinetic and toxicodynamic properties (which could potentially be derived from NAMs). Additional to this, the European Partnership for Alternative Approaches to Animal Testing (EPAA) "NAM Designathon" was announced. The purpose of the Designathon was to present a hypothesis to enable the classification of 150 chemicals, or a fraction thereof, into a category of low, medium or high concern. The Designathon[6] is to be initiated in July 2023 and results published in early 2024.

3.4.1 Revision to REACH

The on-going revisions to the REACH legislation were viewed as an opportunity to incorporate further NAMs, specifically in the revision of the standard information requirements (SIR). The proposals presented (although not yet accepted) included potential deletions of information requirements, or inclusion of NAMs, in Annexes VII, VIII, IX and changes to Annex XI. The changes to Annex XI, in particular, have at least two ambitions, firstly to incentivise the greater use of NAMs for adaptations; and secondly to increase legal clarity regarding what the adaptation needs to provide. It will be important to describe how an adaptation can provide an equivalent predictive capacity to the information that would be obtained from the study normally required. This may require more guidance to be developed per endpoint. Further, there will be additional information on what characterises a valid *in vitro* method or DA, and ensure that the results from NAMs will be adequate for the purpose of classification and risk assessment.

The current revision to REACH will not be the last; there was a feeling that such revisions should (or will) be more frequent. Further, it was acknowledged that adaptations for a NAM SIR will remain possible, and could include *in vivo* testing as a last resort.

[6] https://single-market-economy.ec.europa.eu/calls-expression-interest/epaa-launches-designathon-human-systemic-toxicity_en

3.4.2 Classification, Labelling and Packaging (CLP) Regulation

The possibilities to use NAMs for the classification and labelling of chemicals were mentioned by many delegates and speakers. The use of NAMs for CLP is considered to be one of the crucial means to reducing and/or phase out animal testing globally. It is recognised that the use of NAMs for hazard identification and subsequent classification through CLP will require co-ordination through the United Nations (UN) Globally Harmonised System of classification and labelling (GHS). GHS harmonises globally classification criteria and communication tools on chemicals. Therefore, it is important to make progress at the UN GHS level for changing classification criteria to allow for the introduction of NAMs.

3.5 Legal Certainty

The workshop recognised that the implementation of NAMs for animal-free chemical safety assessment will require legal certainty in the application of NAMs, i.e., that they comply with the relevant legislation. In some cases, e.g., the REACH adaptation as described in Section 3.4.1, this may require greater understanding in terms of the meaning of legal certainty. Thus, it was noted that clarity in legal certainty is required in a number of areas, e.g., industry on how to fulfil their obligations and the conditions for acceptance by authorities (information requirements, waivers and adaptations, testing proposals etc.). Clarity is also required for authorities to ensure that NAM data fulfil requirements and to facilitate the checking of compliance and enforcement.

3.6 Validation of NAMs

The workshop recognised the essential role the validation of NAMs plays in their acceptance for a particular purpose and to build confidence in their use. Validation is essential to facilitate acceptance and ensure sound science-based decisions. It is also an important process to maintain scientific integrity, credibility and usefulness of NAMs. Despite its importance, validation is currently recognised as one of the limiting factors in the use of NAMs. The current validation procedure has failed to keep pace with rapid scientific progress in, e.g., the emergence of DAs and data integration, computational models, and new technologies such as organ-on-a-chip, etc.

The current validation principles (as defined by OECD Guidance Document (GD) 34) state "*the validation process should be flexible and adaptable*", performance must be "*demonstrated using a series of reference chemicals*", and "*evaluated in relation to existing relevant toxicity data*" (OECD, 2005). These principles are recognised as still being valid and should form the basis for future validation principles, although their implementation does not reflect the state of the art of NAMs or their requirements for use.
A number of speakers and delegates noted the desired properties of a validation system for NAMs. An updated validation, or qualification, process should evolve to be flexible and performance-based. Validation should acknowledge and address uncertainty in current data and future scientific methods, specifically comparing uncertainty in current data with future NAMs. With regard to this aspect, validation can be seen as a process to characterise and reduce uncertainty, replacing the explicit needs for a ring trial to demonstrate "toxicological equivalence". In addition, it is important to characterise the (human) relevance as part of the validation process.

The National Academies of Sciences, Engineering, and Medicine (2017) report also recognised the upcoming issues with the validation of NAMs. The report identified a number of key areas to be considered in validation emphasising the importance in defining the purpose and scope of the NAM. It also noted challenges in validating a NAM where there is no "gold standard" or against assays that have not themselves been validated. It recognised that the current ring-trial design

is not necessary for all purposes, and may not be appropriate for many NAMs, instead suggesting the establishment of performance standards for data quality. It also confirmed the need for reporting standards and transparency in the description of NAM technologies and results.
It was reported to the workshop that OECD GD 34 is currently under revision. The purpose of the revision is to take account of the changing landscape in chemical safety assessment. Much of the revision to OECD GD 34 will be a consideration of the framework for establishing confidence in NAMs described by van der Zalm et al. (2022). The van der Zalm et al. (2022) framework incorporates five key principles: data integrity and transparency; independent scientific review; human biological relevance; fitness for purpose; and technical validation of mechanistic NAMs.

3.6.1 Non-Standard Data

Related to the issue of validation, several speakers mentioned the potentially useful nature of non-standard data. These could include so called "academic data" which can be used to support TG and regulatory data. Frameworks for assessing the validity of non-standard data, and their utility for regulatory decisions, are required.

3.7 Mutual Acceptance of Data (MAD)

Mutual Acceptance of Data (MAD) from NAMs should be seen as essential as it will allow for the use of common data across jurisdictions. However, the workshop appreciated that NAMs may challenge the current paradigm for MAD as it requires the same data requirement in each regulation. To achieve MAD, effort will need to be placed under the auspices of the OECD, specifically that NAMs should be harmonised internationally. Other practical aspects were noted, such that to facilitate data sharing, reporting of data should also be harmonised. A data sharing platform would encourage this and ultimately support MAD.

3.8 Training and Capacity Building

A number of delegates highlighted the need to increase awareness and capacity of NAMs. The necessity for training was highlighted, which will be vital for implementation and use of new methods. Similarly, education and awareness is required within all stakeholder groups. It will be vital to gain the understanding and support of consumers. Related to this, there is a need to communicate the shortcomings of the current paradigm of animal testing. There is also a requirement and opportunity to integrate NAMs into basic scientific training, especially in university graduate and post-graduate courses.

3.9 Need for a Roadmap Towards Replacing Testing on Animals

The prerequisite for an EU roadmap to identify critical needs and timelines necessary for the implementation of NAMs to replace testing on animals was recognised by the workshop. Any roadmap is likely to include many, or all, of the steps identified in Section 3. Examples of roadmaps, i.e., definable goals and dates towards the goals of animal free chemical safety testing, were provided. These included EFSA's "*Development of a Roadmap for Action on NAMs in Risk Assessment*" (Escher et al., 2022). In addition, the European Partnership for the Assessment of Risks from Chemicals (PARC) Task 2.2 is developing NGRAroute, itself a roadmap activity towards NAM-based Next Generation Risk Assessment (NGRA).

3.9.1 Funding and Investment

Implementation of NAMs will undoubtedly require appropriate funding and investment. Strategic funding is required at all stages of the implementation of NAMs. Fundings sources such as those provided by the European Union Framework programmes have proven key for innovation.

However, a number of speakers and delegates also mentioned the need for further funding in the pre-validation and validation stages of NAM development (see Section 3.6).

4. Conclusions

ECHA's New Approach Methodologies Workshop "*Towards an Animal Free Regulatory System for Industrial Chemicals*" demonstrated a strong commitment from all stakeholders for the implementation of NAMs in chemical risk assessment to ultimately replace animal testing. Clear motivations and advantages to the use of NAMs were articulated. To achieve the goal of animal free testing, three critical needs to regulatory acceptance (hazard identification, hazard characterisation and extrapolation) were identified. In addition, there was a common understanding of the challenges ahead, notably with the proposal of objectives for the short and medium term, better use of data being generated, refinement of tests and overall reduction of animals for toxicological testing. Gaining regulatory acceptance of NAMs through increasing confidence in their use and appropriate validation is vital. It was also agreed that a roadmap (towards replacing testing on animals) identifying key steps to achieving acceptance, although the format was not defined, would encourage faster progress. The roadmap will require dialogue with all stakeholders across industry / governmental sectors and geographical regions.

5. References

Ball N et al. (2022) A framework for chemical safety assessment incorporating new approach methodologies within REACH. *Arch. Toxicol*. 96: 743–766. doi: 10.1007/s00204-021-03215-9
Bartnicka J et al. (2021) *Towards animal-free in vitro methods in the Thyroid Validation Study*. EUR 30818 EN, Publications Office of the European Union, Luxembourg. ISBN 978-92-76-41164-2. doi: 10.2760/544332, JRC125904

Berggren E, Worth AP (2023) Towards a future regulatory framework for chemicals in the European Union – Chemicals 2.0. *Regul. Toxicol. Pharmacol*. 142: 105431. doi: 10.1016/j.yrtph.2023.105431

ECHA (European Chemicals Agency) (2016) *New Approach Methodologies in Regulatory Science. Proceedings of a Scientific Workshop. Helsinki, 19–20 April 2016*. ECHA-16-R-21-EN, ECHA, Helsinki, Finland. ISBN: 978-92-9495-397-1. doi: 10.2823/543644. Available from: https://echa.europa.eu/documents/10162/21838212/scientific_ws_proceedings_en.pdf/a2087434-0407-4705-9057-95d9c2c2cc57 (accessed 3 August 2023).

EFSA PPR Panel (European Food Safety Authority Panel on Plant Protection Products and their Residues) (2021) Hernández-Jerez A et al. Scientific Opinion on the development of Integrated Approaches to Testing and Assessment (IATA) case studies on developmental neurotoxicity (DNT) risk assessment. *EFSA J*. 19: 6599. doi: 10.2903/j.efsa.2021.6599

Escher SE et al. (2022) Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment. *EFSA Supporting Publications* 19(6). doi: 10.2903/sp.efsa.2022.EN-7341
EU (European Union) (2023) *European Citizens' Initiative: Save Cruelty Free Cosmetics – Commit to a Europe Without Animal Testing.* Commission Registration Number: ECI(2021)000006. Available from: https://europa.eu/citizens-initiative/initiatives/details/2021/000006_en (accessed 3 August 2023).

Paul Friedman K et al. (2020) Utility of *in vitro* bioactivity as a lower bound estimate of *in vivo* adverse effect levels and in risk-based prioritization. *Toxicol. Sci*. 173: 202-225. doi: 10.1093/toxsci/kfz201

National Academies of Sciences, Engineering, and Medicine (2017) *Using 21st Century Science to Improve Risk-Related Evaluations*. The National Academies Press, Washington DC, USA. doi:

10.17226/24635

OECD (Organisation for Economic Co-operation and Development (2005) *Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment.* OECD Series on Testing and Assessment 34. ENV/JM/MONO(2005)14. OECD, Paris, France. Available from: https://one.oecd.org/document/ENV/JM/MONO(2005)14/en/pdf (accessed 3 August 2023).

OECD (Organisation for Economic Co-operation and Development (2021) *Test No. 249: Fish Cell Line Acute Toxicity – The RTgill-W1 Cell Line Assay.* OECD Guidelines for the Testing of Chemicals, Section 2. OECD Publishing, Paris. doi: 10.1787/c66d5190-en

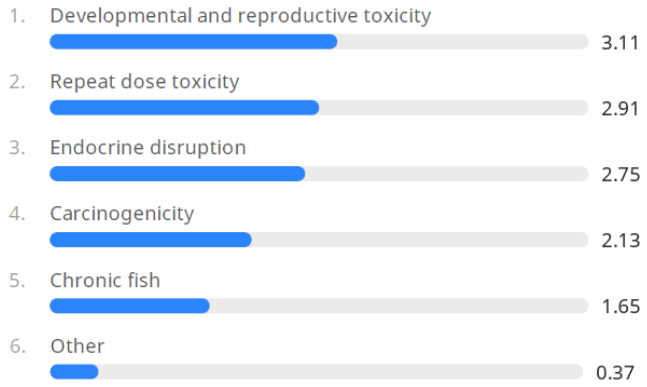
van der Zalm AJ et al. (2022) A framework for establishing scientific confidence in new approach methodologies. *Arch. Toxicol.* 96: 2865–2879. doi: 10.1007/s00204-022-03365-4

Westmoreland C et al. (2022) Use of New Approach Methodologies (NAMs) in regulatory decisions for chemical safety: Report from an EPAA Deep Dive Workshop. *Regul. Toxicol. Pharmacol*. 135: 105261. doi: 10.1016/j.yrtph.2022.105261

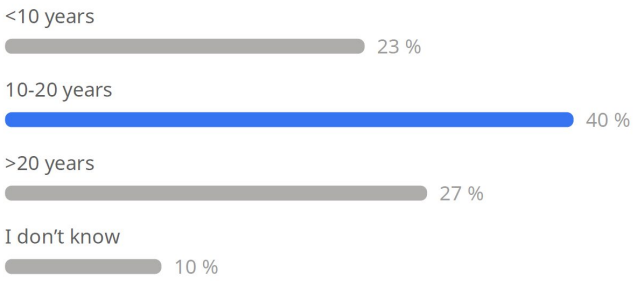
Annex I - Slido Poll results and responses from delegates at the ECHA NAMs workshop (31 May – 1 June 2023)

Number of respondents: 134

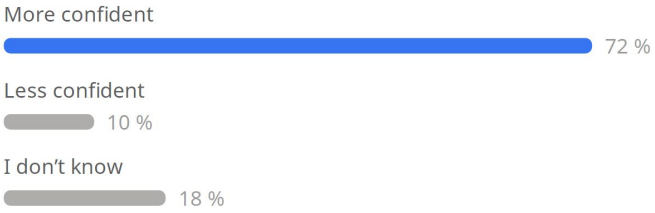
1. Which endpoint would you prioritise for new approach methodology development?



2. How long will it take to fully replace animal testing to assess industrial chemical hazards?



3. After the workshop, how confident are you that we can move forward with the replacement of animal testing?



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