PRECISIONTOX

D6.3 REPORT ON SOLUTIONS TO EXISTING ROADBLOCKS FOR USAGE OF NAMs IN REGULATION (ACTION PLAN)

2024

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Acronyms	
3Rs	Replace, reduce, or refine animal testing
AOP	Adverse Outcome Pathway
ASPIS	Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies.
CARACAL	Competent Authorities for Registration, Evaluation, Authorisation and restriction of CHemicals (REACH) and Classification, Labelling and Packaging
CLP	Regulation (EC) No 1272/2008 on the Classification, Labelling, and Packaging of substances and mixtures
CMR	Carcinogenic, germ cell mutagenic, and reproductive toxicants
DA	Defined Approach
DNT IVB	Developmental Neurotoxicity In Vitro Battery
ECHA	European Chemicals Agency
EU	European Union
EURL ECVAM	EU Reference Laboratory for alternatives to animal testing
GFRB	Group First, Regulate Better
GLP	Good Laboratory Practice
JRC	Integrated Approaches to Testing and Assessment
MS	Member State

NAM	New Approach Methodologies
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Co-operation and Development
PBPK	Physiological Based Pharmacokinetic modelling and simulation approach
PBT	Persistent, Bioaccumulative, and Toxic
PoD	Point of Departure
QSAR	Quantitative Structure-Activity Relationship model
QIVIVE	Quantitative In-Vitro to In-Vivo Extrapolation
REACH	Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation, and Restriction of Chemicals
SME	Small and Medium-sized Enterprises
WoE	Weight of Evidence
WP	Work Package

EXECUTIVE SUMMARY

The goal of PrecisionTox is to advance the safety assessment of chemicals without the use of animal testing. As a first phase in the project for Work Package 6 (WP6 - Regulatory Analysis and Application), the project team undertook a comprehensive study of the sociotechnical barriers to new approach methodologies (NAMs) across a range of stakeholder groups. The project team has now examined options to overcome these barriers by deploying the Delphi research method to determine the level of consensus for particular policy options. By discovering points of agreement, broad themes of solutions have been built upon so that refined actions have now been identified. A table of the Delphi questions, solution consensus, and actions is provided below.

The research analysed policy solutions that are applicable to NAMs in general and that could be applied broadly across sectors. Where there is broad consensus, we have been able to outline concrete measures. These relate to the regulatory use of data; education and training strategies; and routes towards validation. With regards to the remaining areas of moderate and indeterminate consensus, we instead suggest further enquiry to enable the questions at issue to be refined and so better determine what actions are needed for greater acceptance of NAMs for regulatory purposes. Thematically, these enquiry areas relate to meeting protective aims; enhancing the assessment of risk; the domain of application of NAMs; enabling the broader adoption of NAMs; utility of the wider NAM community; engagement with the debate on NAM use; regulator-industry dialogue; and the evaluation of the role of soft law guidance. Additionally, this report identifies actions of relevance to the activities of specific Work Packages within PrecisionTox.

EXECUTIVE SUMMARY

Table of Delphi Questions, Solution Consensus, and Actions
Industry is making use of NAMs but not necessarily for regulatory approval purposes. Would it be beneficial to have access to such data? If so, how might this be achieved? **Broad Consensus** • Create tools and guidance for regulatory use of academic and industry data. • Develop incentives and risk mitigations for data sharing. • Establish an EU data repository.
Are there other ways in which data from NAMs can be provided by independent studies, to reduce concerns of bias and promote familiarity with NAMs? **Indeterminate Consensus: Multiple Views** • Further research on the utility of the wider NAM community, including the means of effective collaboration, ensuring regulatory relevance of studies, accreditations, and MS validation funding.
Do we need a wider debate about the use of animal testing and the status of NAMs? How might these issues be communicated to the public, and be made accessible? **Indeterminate Consensus: Opposing Views** • Whether there is a need for a wider debate on the use of NAMs requires redefining to separate the scientific community from wider society, and the scope and aims of such action.
Is there a need for opportunities for regulators to dialogue with industry about the existing prescribed regulatory process? If so, can and should this be built into the process itself? **Indeterminate Consensus: Opposing Views** • Further research on regulator-industry dialogue, including characterising existing engagement and investigating the consequences of further engagement.

EXECUTIVE SUMMARY

Table, Continued
Is there a need to create a structured platform of education and training on NAMs? If so, how and where could this be created? **Broad Consensus** • Identify leadership and funding for coordinated educational platforms. • Identify the multiple audiences for tailored training. • Deploy European Education Area.
Can we make better use of soft law guidance issued by regulators to offer clearer information about their interpretation of legislation, decision-making, and risk assessment criteria? If so, how might this be mobilised? **Indeterminate Consensus: Opposing Views** • Further enquiry on the provision of soft law guidance, including evaluating its current effectiveness to identify whether and where to prioritise improvements.
What are the greatest opportunities for NAMs to be used strategically in chemicals risk assessment? Can you provide examples? **Indeterminate Consensus: Multiple Views** • Further investigation on the application of NAMs, including investigating areas of improvement in existing guidance, understanding of context of use, and analysing success criteria of previous NAM acceptance.
Where do you see the earliest adoption of NAMs occurring? How can such incremental take-up be facilitated? **Indeterminate Consensus: Multiple Views** • Further enquiry to define and prioritise multiple aspects associated with enabling the adoption of NAMs, including collaboration, capacity building, and case studies.

Table, Continued
Does validating a NAM necessarily involve comparison with in vivo data, or is there room for approaches that speak more to human biology? **Broad Consensus** • Identify sources of human data and disease progression knowledge. • Establish acceptance criteria for combining methods whose regulatory outcomes are consistent. • Determine the potential for comprehensively connecting tools. • Create an accessible and comprehensive NAM inventory.
Are regulatory structures based on predicting hazard by reference to stated endpoints helpful? Or can you envisage structures that could accommodate more complex indications of adverse outcomes where these might enhance levels of protection? **Moderate Consensus** • Further enquiry on meeting protective aims, including reviewing legislation interpretation, NAM expectations, information gaps, and cost-benefit analysis.
How well do you feel tonnage serves as a surrogate for exposure under REACH? If you feel tonnage is an insufficient approach to exposure, how else might exposure be addressed? **Moderate Consensus** • Further investigation on enhancing the assessment of risk, including the feasibility of incorporating further exposure and supply-chain information, the use of REACH waivers, and evaluating the effectiveness of current requirements.

1. BACKGROUND

The goal of PrecisionTox is to advance the safety assessment of chemicals without the use of animal testing. As a first phase in the project, the project team of Work Package 6 (WP6 - Regulatory Analysis and Application) has undertaken a comprehensive study of the barriers to new approach methodologies (NAMs), which was submitted in January 2024 (Barriers Report). This study draws upon interviews with 32 stakeholders involved in the risk assessment and management of chemicals. The participants represented three main groups who are broadly involved in the regulatory process, including industry, regulators, and policy makers. Despite the fact that considerable progress has been made in developing new methods for use in chemical risk assessment by employing in vitro, in silico, and in chemico approaches to uncover the potential adverse effects of chemicals on human health and the environment, the study concludes that limited progress has been achieved in developing and utilising NAMs for regulatory purposes.

The barriers to the uptake of NAMs identified in the above study are not merely technical, but predominantly involve a range of social barriers, which have led to dependency on existing (and typically mammalian) methods and an apparent resistance to technological transition. The report discussed some of the following key barriers to NAMs across different jurisdictions and encompassing different forms of NAMs (Table 1).

BACKGROUND

Table 1: Barriers to the Uptake of NAMs	
Theme	**Sub-Theme**
Views of regulatory science and the legislative framework	Regulatory culture: • Acceptance of NAMs by regulators • Familiarity and confidence in animal studies • Lack of trust between actors in the regulatory process
Validation and standardisation	• Time to achieve consensus • Human relevance of NAMs
Expertise and resources	• Pressure on regulatory capacity • Unfamiliarity / lack of expertise with NAMs
Regulatory objectives	• Differences between jurisdictions that lead to different approaches and levels of acceptance of NAMs • Principles of exposure versus hazard that underpin the legal framework on industrial chemicals
Social perceptions	• Public unaware of NAMs • Fears of diluting chemical safety
Scientific development	• Lack of comprehensive biological coverage of NAMs for complex endpoints • Understanding and acceptance of mechanisms of adverse outcomes rather than visible apical harms

2. METHODOLOGY

In consideration of the range of barriers identified in the first report by stakeholders across different jurisdictions, the project team examined policy solutions raised by respondents, or which otherwise became apparent through the interviews. As these options may have wider stakeholder consensus, the project experts consequently deployed the Delphi research method (in this case comprising of a questionnaire and a discussion group) as an appropriate method to examine the level of consensus that may exist for particular policy options in greater depth. The initial policy solutions as identified from the Barriers Report data that informed the Delphi questionnaire are discussed in section 3.

The Delphi method is a long-standing method that has been in use since the 1950s. It is particularly suitable to the question of NAM development as this method allows for the examination of long-term and challenging issues, as well as prospective research questions, to gather views on what future projections or scenarios may look like. Equally, it is an iterative process that permits the building of consensus among participants on issues considered.

Our study involved several phases: the identification and selection of experts; the design and distribution of the questionnaire; the design and running of the discussion group; followed by the data analysis, as presented in this report.[1] These phases are further described below.

Identification and Selection of Experts

As with the report on sociotechnical barriers (D6.1), participants came from the same three groups of stakeholders of industry, regulators, and policy makers. However, for this study in searching for solutions for the European market, we focused on participants operating within Europe, rather than, for example, regulators from other jurisdictions as was the case in undertaking the barriers study.

We approached the participants by email and shared with them the project information, consent form, and provided a link to the Barriers Report. Participants were assured that their comments to the questionnaire would remain anonymous, and that the later discussion group was to be conducted under the ‘Chatham House’ rule. We provided a link to the questionnaire upon their confirmation that they were willing and able to participate, and we managed further rounds of invitations until the desired number of stakeholders had confirmed their participation. We deliberately chose a smaller number of participants to contribute to the questionnaire (n11), than had been interviewed for the barriers study (n32). This was to allow us to dwell more deeply in the discussion group on questions that may generate high levels of consensus. This is aligned with the Delphi technique, where the number of respondents is smaller, as there is no intention in employing this method to produce statistically significant results.

Design and Distribution of the Questionnaire

The development of the questionnaire was informed by the above-mentioned list of policy recommendations, which had been identified with the help of the study on barriers to NAMs, and that had been identified from scholarship (described further in section 3). After careful thematic analysis, we refined these options down to eleven questions that formed the questionnaire, and which are listed in Table 3 (section 4) and in the Executive Summary. The survey link was distributed electronically to the identified expert stakeholders, and responses were anonymous.

Design and Running of the Discussion Group

We analysed the data from the first phase of the Delphi study (Questionnaire) to identify areas of initial consensus among the stakeholders. This informed the sequence of policy options to be discussed at the subsequent second phase of the Delphi (Discussion Group). The group was drawn from participants who responded to the questionnaire. The results of these discussions and analysis of the extent of consensus are provided at section 5.

‘Chatham House’ rule: Under this rule, participants in a meeting are free to use information received in that meeting but neither the identity nor the affiliation of any participant in the meeting, including the speaker providing the information may be disclosed.

3. SCHOLARSHIP RESEARCH & STAKEHOLDER RECOMMENDATIONS

The empirical study that identified the socio-technical barriers to the uptake of NAMs (PrecisionTox Deliverable D6.1) also identified wide-ranging policy recommendations derived from the initial conversations with stakeholders. These were outside the scope of that initial report on barriers and were therefore not included in the Deliverable 6.1, but they were significant for this project deliverable of examining policy solutions for the better uptake of NAMs. Additionally, the literature review undertaken as a part of Deliverable 6.1 also identified scholarship proposing solutions to overcome the barriers to the uptake of NAMs.

Some of this literature had identified areas of NAM science that need to be addressed and had suggested that advantage could be taken from developments in, for example, quantitative in-vitro to in-vivo extrapolation (QVIVE) and points of departure (PoD). This may be facilitated by data accessibility, standardisation, and sharing, which will also help to build trust. Additionally, there is an identified need for greater understanding of exposure, which might herald changes to regulatory regimes for chemical testing. Legislative change would require greater political involvement, and there were calls for alternatives to be promoted, such as through the Chemical Strategy for Sustainability (CSS) and globally. Communication, training, and dialogue, including at the international level, were also commonly identified, along with the need for improvements to validation. Soft law guidance and case studies were also recognised as being important agents of change.

There is a generally acknowledged need to build capacity and confidence in NAMs, and scholarship tends to view solutions in terms of such thematic ‘needs.’ In contrast to the debate focused narrowly on the science of NAMs, our research has explored these wider needs through a sociotechnical lens to understand how it is that solutions can develop. A significant part of this is understanding where the current potential in acceptance lies, which is identified through seeking areas of consensus.

Together, the scholarship and recommendations from the Deliverable 6.1 interviews provided the starting point from which we built the Delphi methodology, which underlies the findings of this report on solutions for utilising NAMs. The recommendations were evaluated and grouped under strategic themes, noting that some echoed the solutions in scholarship. These identified themes are titled strategic and policy reform; legal and regulatory changes; enhancement for implementation; and communication and education strategies. The recommendations are summarised in Table 2 and described in detail further below, grouped in their themes.

Table 2: Recommendations from interviews on barriers to the uptake of NAMs, grouped thematically	
Strategic and Policy Reform • Clearer policy direction • Enhancing dossier quality • The role of compliance checks • Consideration of exposure • Outcome-based approach • Sustainable designs	**Legal and Regulatory Changes** • REACH revisions • Review of soft law instruments • Mapping of the potential for regulatory deployment of NAMs
Enhancement for Implementation • Existing REACH adaptations • Screening and prioritisation • Validation and standardisation • Dialogue across stakeholders • Industry (SME) capabilities	**Communication and Education Strategies** • Value proposition of NAMs • Sharing and using information • Education and training

Strategic and Policy Reform

Clearer policy direction

The political steer has an important effect both on regulators and industry and could nudge stakeholders to embrace NAMs more forcefully. It was suggested that there is a need for a different policy steer, such as that found in cosmetics regulation: instead of gradually introducing NAMs, a ban of animal testing is the only way forward for compliance with 3Rs in the short to medium term. Other recommendations noted that the science of NAMs allows greater mechanistic understanding of toxicity, which could allow for decisions to be made based on the early signs of toxicity rather than being satisfied only with the endpoint itself being observed.

Enhancing the quality of submitted dossiers

Three options were put forward here:

- **Incentives**

Bearing in mind the incompleteness of some submissions under REACH, it was recommended that improved submissions should be incentivised.

- **Submitting NAM data in parallel with standard information derived from animal tests**

This will drive the acceptance of innovation and demonstrate how new approaches can be used, in comparison to the in vivo data provided. This does require additional resources (time, money) as well as the development of definitions and standards prior to asking for NAMs as part of the submission process. Without clear definitions and standards, submissions risk being of poor-quality data and the extensive array of NAM types may create further resistance to NAMs among regulators.

- **Greater use and commissioning of independent / collaborative studies**

There was discussion about making use of the more independent studies, such as industry collaboration with competent authorities and research institutes, thereby building trust by reducing the concern of bias.

Better consideration of exposure

As an important element of safety assessments, hazard and exposure should be considered together, with the consideration of exposure going beyond tonnage bands. As with cosmetics, understanding consumer uses will allow for potentially applying an exposure-based approach to industrial chemicals. This will allow appropriate and effective risk management measures to be applied at all levels of use.

Developing an outcome-based approach

What constitutes ‘harm’ should be considered more widely, such as immunotoxicity and neurotoxicity. This contrasts with a prescriptive approach, which is based on requirements to replicate complete biology or to observe a specific endpoint.

Sustainable designs

Pre-regulatory steps to aid safe and sustainable by design were proposed. A sustainable chemical industry and sustainable chemical products require input from different stakeholders; consideration of chemical life cycles; and an understanding of the impacts of and on the industry.

Legal and Regulatory Changes

Revisions around REACH and soft law amendments

As a corollary of the finding that law can act as a barrier, possibilities regarding the revision of EU chemicals law were suggested. Depending on the scale of change and willingness of policy makers and regulators to apply NAMs more forcefully, different changes to REACH have been suggested, such as revising REACH and measures such as moving away from tonnage as a surrogate for exposure (see above).

Soft law amendments

There were proposals for less radical reform by exploring the scope to promote greater deployment of NAMs within regulatory decision-making using changes to soft law instruments, such as guidance. The revision and better use of soft law by developing further NAM-specific guidelines was recommended.

Mapping the regulatory application of NAMs

Given the ubiquity of chemicals in a huge variety of products, many of which are subject to some form of regulation before being placed on the market, there was a view that a mapping exercise across these many areas of regulation (pharmaceuticals, food, pesticides, etc.) might be of assistance. This could actively explore areas in which there was scope for the regulatory application of NAMs, without the requirement of wholescale legal reform. Context-specific guidance could then provide confidence in the application of specific NAMs to meet defined requirements.

Enhancement for Implementation

Better use of existing adaptations in REACH

Without necessarily amending the EU law, better use of existing mechanisms has been suggested. Under REACH's Annex XI, adaptations such as in vitro, grouping and read across, and weight of evidence (WoE) are available. However, their acceptance by regulators is reported to be low, such that steps to remedy this were proposed so that methods to avoid animal testing can be used to their greatest potential. Deploying WoE approaches involves some qualitative judgement with which regulators may feel uncomfortable and hence improved guidance and support is required.

Prioritisation of chemicals

Considering the number of chemicals that are under-evaluated, it was suggested that a more realistic and pragmatic system of screening and prioritisation using NAMs is needed. Here, more efficient grouping of substances using NAMs may assist.

Enhancing validation and standardisation

As validation is one of the key barriers, a recommendation was to have a simplified validation strategy to accelerate the acceptance of NAMs. Performance is not to be assessed against existing animal studies but rather on scientific merits. Funding and incentives are also needed. The harmonisation of risk assessment methodologies was also suggested.

Better dialogue with stakeholders, especially regulators

Enhancing the dialogue between the industry and regulators will be a multifaceted endeavour: it will help address uncertainties and levels of confidence with regulators, as well as clarifying gaps regarding NAMs; and it will help boost trust among different stakeholders.

Developing industry capabilities/resources, especially with SMEs

Capacity building will assist in strengthening the capabilities of smaller companies, which are not incentivised to invest in NAMs. However, this activity is highly dependent on clearer policy direction in the EU and better acceptance of mechanisms that facilitate NAMs, such as grouping for read across and WoE.

Communication and Education Strategies

Defining the value proposition of NAMs

As limited progress has been achieved with NAMs, one of the key recommendations was to take stock of the current progress and evaluate what NAMs can offer. An important aspect of this is for a time and cost comparison of NAMs against traditional toxicology. However, it should also include the assessment of the wider economic landscape of whether there could be a NAM-based industry and whether this has growth potential, which is relevant for companies and governments, while carrying societal benefits.

Enhanced sharing and use of information from NAMs

With low levels of trust between stakeholders and limited understanding of collaborations and dialogue, openness and transparency will both contribute to building confidence. This involves several important measures:

- **Presenting data in a digestible and approachable manner, tailored by audience**. As NAMs will not replace animal tests 1:1, with many 'types' of NAMs and a range of scientific disciplines involved, it is important that information is clearly and openly presented for a range of audiences. Increasing transparency and understanding will assist in building confidence and trust.
- **Creating a better platform for engagement.** As communication with different parts of society is at times disparate, it was recommended to launch a structured platform for engagement.
- **More and better engagement with the public.** The public is not necessarily familiar with NAMs and are of the impression that robust chemical risk assessment is undertaken for each chemical. Different forms of engagement need to be considered and launched. Greater public knowledge of and confidence in NAMs is likely to aid the policy making process.
- **Creating a new mindset.** Undoubtedly it will take time to create a new mindset among stakeholders. The primary aim is to create new ways of thinking about health risks, which is aided by having dialogue with risk managers, industry, the public health sector, and civil society.
- **Case studies.** It is important to demonstrate how NAMs support safety assessments and improve understanding. Case studies may assist here to capitalise on such learning, and these should be incentivised.

Education and training

This recommendation applies to a variety of stakeholders. The primary aim is to improve the knowledge of regulators about different NAMs, which is largely considered to be a generational issue whereby younger toxicologist have a better understanding of NAMs, unlike longer established staff. This also applies to industry, as there are different levels of knowledge and application of NAMs here. Additionally, there is a need to improve the public knowledge of NAMs, which requires working with NGOs as well.

4. SOLUTIONS REFINED - 1

Delphi Questionnaire: Phase 1

From the information obtained from the empirical study on barriers, we refined these points to 11 questions. We considered this to be a reasonable number of questions for the questionnaire, considering we were seeking expansive, qualitative data from respondents, rather than multiple choice or other quantitative returns.

The list of question that populated the questionnaire in the first phase of the Delphi study are provided in Table 3.

Table 3: List of Questions, Delphi Questionnaire
1. Industry is making use of NAMs but not necessarily for regulatory approval purposes. Would it be beneficial to have access to such data? If so, how might this be achieved?
2. Are there other ways in which data from NAMs can be provided by independent studies, to reduce concerns of bias and promote familiarity with NAMs?
3. Do we need a wider debate about the use of animal testing and the status of NAMs? How might these issues be communicated to the public, and be made accessible?
4. Is there a need for opportunities for regulators to dialogue with industry about the existing prescribed regulatory process? If so, can and should this be built into the process itself?
5. Is there a need to create a structured platform of education and training on NAMs? If so, how and where could this be created?

Table 3: Continued
6. Can we make better use of soft law guidance issued by regulators to offer clearer information about their interpretation of legislation, decision-making, and risk assessment criteria? If so, how might this be mobilised?
7. What are the greatest opportunities for NAMs to be used strategically in chemicals risk assessment? Can you provide examples?
8. Where do you see the earliest adoption of NAMs occurring? How can such incremental take-up be facilitated?
9. Does validating a NAM necessarily involve comparison with in vivo data, or is there room for approaches that speak more to human biology?
10. Are regulatory structures based on predicting hazard by reference to stated endpoints helpful? Or can you envisage structures that could accommodate more complex indications of adverse outcomes where these might enhance levels of protection?
11. How well do you feel tonnage serves as a surrogate for exposure under REACH? If you feel tonnage is an insufficient approach to exposure, how else might exposure be addressed?

The analysis of survey data from the first Delphi phase exposed different levels of agreement among the stakeholders as to whether the proposed topics were indeed issues that needed to be addressed, and if so, how this might be done. In certain instances, there was broad agreement both about the relevance of the question posed as well as the ways of addressing it (termed ‘broad consensus’). In other cases, there was broad agreement of the issue raised but the stakeholders had different views and suggestions as to the precise cause of the problem or how it should be addressed (termed ‘moderate consensus’). Finally, in some cases a range of responses were received (termed ‘indeterminate consensus’), which did not allow for consensus to be generated.

5. SOLUTIONS REFINED - 2

Delphi Discussion: Phase 2

Having analysed and categorised the responses on the basis of the degree of consensus, this categorisation was used to form the agenda of the online group discussion for the second phase of the Delphi. Starting with items of broad agreement, we used the group discussion to further refine the consensus, and then moved on to areas where there was less apparent agreement, to seek the generation of points of consensus. It is worth noting that when it comes to issues generating 'broad consensus', this classification does not entail absolute unanimity, but rather it is a position that accommodates the views and interests of the group. With moderate consensus and opposing views, there was less room for consensus. All questions are summarised below, according to their consensus grouping.

The outcomes of the Delphi method have been used to generate the action plan in the conclusion. Where lack of consensus remains, we have documented views for information and to form an agenda for further action (section 6).

5.1 Broad Consensus

Industry is making use of NAMs but not necessarily for regulatory approval purposes. Would it be beneficial to have access to such data? If so, how might this be achieved?

This question generated a very high level of consensus among participants during the first Delphi phase and further discussions during the workshop assisted in fleshing out the practical approach to deployment of industry data for regulatory purposes. There is no doubt that having access to industry data would be beneficial. This may not only improve the quality of dossiers but would also have positive ramifications for validation. It will also help in addressing the issue of trust in data provided by industry. However, there are certain caveats that are worth considering regarding the implementation of this recommendation into practice. As one of the participants suggested, 'it feels like we've got this NAM airplane, and we don't have a landing strip.[2]

There is an issue of commercial confidentially and business competitiveness that is difficult to overcome. Moreover, there must be careful consideration of data that is available because not all data would be useful for regulatory purposes. Some testing by industry may be a result of efforts to improve efficiency or for screening purposes, rather than to improve the safety of products. Furthermore, there is a wider question of the best ways to incentivise industry to submit NAMs data, as they are already obliged to submit relevant data. Wider discussion often mentioned creating a safe harbour for industry to submit data, but it is not clear what this would entail in practice. These challenges may be overcome by having provisions in place that would require a priority evaluation of NAMs data, but this would need to be aligned with the REACH procedure. Finally, the most important issue focuses on how relevant data should be generated and evaluated, which is a separate question from the access to data. There was unanimous agreement that this would require the development of reporting criteria and templates that would facilitate use of industry data. The idea of a repository of data under the 'FAIR' data principles could be useful in thinking about making such data available.

Linked to this discussion, the participants in the workshop also reflected on the academic research data that could be equally beneficial to the regulator. Even where such data are included in academic papers, which is often not the case, the data are not necessarily produced in a manner that could be employed for regulatory purposes as it may not have been generated with a regulatory context of use as a focus of the outcome. Thus, this is also an important endeavour that could improve the quality of data available, which would also be aided by determining the quality of study design, execution, and analysis. There are some positive examples already, such as the 'RIVER NC3R' initiative in the UK.[3] It was recommended that academic associations as well as academic publishers have an important role to play in facilitating this exercise.

The following policy steps have been identified:

- **Create tools and guidance to help regulators better identify and use industry and academic data, including clarity of what is of regulatory use in terms of data and its generation and evaluation. This extends also to academic associations and publishing companies.**
- **Develop incentives and risk mitigations to enable industry and academia to share their data.**
- **Establish a repository of data that would be managed at the EU level.**

Is there a need to create a structured platform of education and training on NAMs? If so, how and where could this be created?

There was consensus among stakeholders about the need for education provision focusing on NAMs. Data demonstrated a broad range of issues that need to be further resolved. Certain examples of education and training provision were identified by participants, such as the NICEATM webinars,[4] and the JRC summer school.[5] However, there is a general agreement that existing provisions are not structured and are not designed to cover the range of different audiences that might require NAM related education. It was noted that there are different audiences, such as industry practitioners, risk assessors, and managers, some of whom are already familiar with NAMs and need support for understanding how NAMs should be used post-validation, whereas others are much less familiar with some of the technology. At the same time, we have some novices in this area who would require more comprehensive training. It was also pointed out that education should start from an earlier age, and this may even start in secondary schools and provide more comprehensive education at the university. One of the main caveats is the fact that education policy does not fall within exclusive and shared competences of the EU, but it is regarded as a supporting competence, which limits the extent of the EU's action.

Moreover, there are important cost and funding issues, coupled with a wider question as to how responsibility and delivery of training can be better structured and offered across the EU. The JRC was mentioned as a possible provider, though further and more coordinated training in Member States (MS) would be required. Thus, it would be advisable to carefully think about having several structured platforms to be effective in addressing the needs of different audiences. With regards to funding and mindful of the fact that education is a supporting competence, funding may come through various sources across MS, such as for the UK the NC3Rs and BTS.[6] No less important is the provision of training in different languages, as aligned with the EU multilingualism policy. Finally, the content of the educational provision was identified as an issue to consider, and this will depend on the levels of training and target audience. Of particular importance is to demonstrate the relevance of science behind NAMs for regulatory purposes.

The following policy steps have been identified:

- **Identify the leadership, funding, and development of structured and coordinated educational platforms or inventory of providers.**
- **Identify the multiple audiences that would benefit from tailored forms and levels of further education and training, which should be provided in different languages across various governance levels (EU; MS) and settings (formal education; staff development).**
- **Deploy European Education Area to identify technologies such as NAMs as an area for collaboration; to strengthen links with academic institutions across the EU who have the potential to offer training; and to utilise Horizon to develop research-led teaching and training.**
- **Utilise ASPIS both in terms of its educational offerings and as a model for the research-led educational approach.**

Does validating a NAM necessarily involve comparison with in vivo data, or is there room for approaches that speak more to human biology?

There was resounding support that NAMs should be validated alongside consideration of human biology. It was noted that the OECD are providing leadership in utilising human data in validation through their revision of Guidance Document 34, the authority of which is therefore building on this approach, and discussions on developing the Roadmap have also touched on this. Currently though, it is felt that the availability of human data is limited and so the ability to validate solely on such data is the exception rather than the rule. Therefore, other means of validation that move away from in vivo data were discussed, such as combining different data and seeking consistency in regulatory outcomes across different methods. Tools on their own, such as the Adverse Outcome Pathway (AOP) framework, were seen as limited but helpful when positioned alongside others, such as IVIVE and physiological based pharmacokinetic modelling and simulation (PBPK) approaches. Discussions served to highlight, as well, that scientific knowledge of human biology, disease progression, and the range of possible adverse effects is still developing. Along with questions of relevance, it was reaffirmed as important that methods should be reproducible.

The following policy steps have been identified:

- **Identify sources of human data and disease progression knowledge.**
- **Establish alternative means for the EU acceptance of methods where human data is not available, such as the development of criteria for combining methods whose regulatory outcomes are consistent.**
- **Determine the potential for comprehensively connecting tools, such as AOP frameworks with IVIVE and PBPK knowledge.**
- **Create an accessible and comprehensive NAM inventory, which can be regularly updated and informs on relevance and reliability.**

5.2 Moderate Consensus

This section evaluates those questions that revealed only moderate consensus following the two stages of the Delphi. The degrees of consensus were variable depending on the question, but in all cases, these were areas where definitive action could not be discerned.

Are regulatory structures based on predicting hazard by reference to stated endpoints helpful? Or can you envisage structures that could accommodate more complex indications of adverse outcomes where these might enhance levels of protection?

The first phase of the Delphi (questionnaire) identified a split in respondents between those who felt the current endpoint-focused regulations are sufficiently protective, and others concerned about the close association between these endpoints and animal tests. In the second stage, this discussion became more nuanced, in that there was a general feeling that the association of NAMs and human relevance is the future direction of travel. Discussions around this question focused on mechanistic information and changes to soft law guidance to better define how the existing endpoints are met using NAMs. Having said that, it was claimed that the limiting issue is ultimately the interpretation of the Classification, Labelling, and Packaging (CLP) regulations, which might be seen as holding back the use of NAMs.

The wide-ranging discussions reflected the complexity and interconnectedness of what is being asked while regulating and how this can be demonstrated. Discussions ranged widely from questioning whether the need is to be protective rather than predictive. Examples of this included the role of dose levels in testing; the potential of the approaches being proposed in the EPAA 'Designathon;' exposure versus hazard-based regulation and the utility of NAMs to each; identifying priority endpoints and organ systems as led by science; and the importance of in silico NAMs including artificial intelligence (AI).

While the general mood was that protection must be maintained, whether specified endpoints are helpful or not is inextricably linked with wider questions of implementation. Additionally, it was thought that any way forward must still be cost-effective and proportionate, and any move towards flexibility must consider how such an approach can be applied across a large number of substances.

Further enquiry agenda:

- **Review of legislative requirements (priority: CLP) to understand where policy and interpretation changes can benefit the uptake of NAMs (especially regulating on mechanisms of action), thereby making it clear where hard law changes will then be needed.**
- **Clearly define and draft guidance on what is expected of NAMs: is this to reproduce all aspects of an animal test?**
- **Review of legislative endpoints to understand gaps in protection.**
- **Undertake a cost-benefit analysis of NAMs and the potential of their application to thousands of chemicals.**

How well do you feel tonnage serves as a surrogate for exposure under REACH? If you feel tonnage is an insufficient approach to exposure, how else might exposure be addressed?

There was broad agreement that tonnage is not the best surrogate for exposure, though it is regarded as a rough indication, particularly for exposure in the environment. Still, there was a general agreement that, thus far, tonnage has served a purpose, and it is useful for screening purposes. The lack of exposure information in REACH and the difficulty in understanding routes of exposure through the supply chains has resulted in a focus on hazard. Yet, for protection the need is to improve risk assessment, which is the equation of hazard and exposure. To highlight the issue with tonnage being a proxy of exposure for human health, the majority of participants agreed that exposure for cosmetics (in, for example, small but consistent applications direct to the skin) is different such that making comparisons with industrial chemicals may not be very helpful.

Despite the agreement that tonnage is not an ideal approach, and unanimous agreement that we have multiple gaps in knowledge about use and exposure, there was little agreement on what an effective replacement might look like. For industrial chemicals there are claims that all uses are not known down the supply chain and concerns of hazard can lead to perceived unnecessary limitations in industrial use. It is apparent there is a need to improve exposure science because of the presence of chemicals for which we have little knowledge of their application. Therefore, there was thought to be a place for exposure modelling that will take into account physical chemical properties and patterns of use with tonnage level emission data. It was also noted that REACH waivers (Annex XI, s3) could perhaps be used more widely than they currently are.

Having said that, protective mechanisms are in place, as it was noted that substances meeting the criteria of being toxic (carcinogens, germ cell mutagens, and reproductive toxicants (CMRs)) are under a regulatory restriction at some concentrations under lines 28-30 of Annex XVII of REACH for supply to the general public and under the persistent, bioaccumulative, and toxic (PBT) criteria of Annex XIII substances. However, outside of this, before substances are considered for regulatory risk management of authorisation or restriction, and considering the large number of under-evaluated substances, the risk management measures are the responsibility of industry to propose. Additionally, below the lowest tonnage bands, no reporting is required, or only limited knowledge of health effects at the lower tonnage bands. There were some calls for a broader assessment of harm to be more widely applied. NAMs were considered to play an important role in assessing exposure through modelling, which was considered to inevitably lead to a reduction of animal testing over time.

However, caution was raised in terms of proportionality in the level of information that is sought from industry, particularly from small and medium-sized enterprises (SMEs) and the resulting risk of reducing the economic viability (and potential hampering of innovation) when producing low volume substances.

An agenda for further investigation:

- **Investigate how better to incorporate exposure information and manage risk, particularly under industrial chemical risk assessments, and the extent to which animal testing will be reduced as a result.**
- **Consider the feasibility and usefulness of requiring full supply-chain-use information, and the extension of requirements to lower tonnages.**
- **Review guidance on REACH use-waivers.**
- **Determine to what extent industry are fulfilling their risk management measure obligations.**
- **Evaluate the effectiveness of current requirements in comparison to broader definitions of harms.**

5.3 Indeterminate Consensus

The final questions presented in this section formed part of the questionnaire phase of the Delphi but did not form part of the Phase 2 discussion group. It became clear that two types of polarisations had occurred. One was that there were opposing views as to whether the aspect raised in the question was an issue that needed to be addressed (section 5.3.2). The other was that there was agreement that the aspect in question needed to be addressed but that such a wide variety of ways to do so had been raised that it was difficult to discern specific policy options (5.3.1). With further refining research it should then be possible to gauge points of consensus for actions in these areas.

The points raised have been included here because this is still valuable data from the respondents, which further informs the debate around the uptake of NAMs for chemical safety assessments and they can be considered for further investigation.

5.3.1 Multiple Views

What are the greatest opportunities for NAMs to be used strategically in chemicals risk assessment? Can you provide examples?

With NAMs having the potential to challenge the current gold standard of animal testing, some respondents suggested types of NAMs which they saw as promising, most commonly referring to AOP and modes and mechanisms of action. These were qualified as needing to be quantified and requiring the key characteristics of adverse outcomes to be understood. Additionally, developing science and technology was mentioned, such as omics, high-throughput methods, and AI and machine learning (ML).

Existing adaptations to REACH were also raised, such as improving WoE, in vitro, qualitative or quantitative structure-activity relationship models (QSARs) and grouping and read across.

Respondents also considered how NAMs should be applied, such as: for addressing the backlog of chemicals such as through prioritisation; incorporating exposure information for a full risk assessment; and to focus on specific endpoints such as acute toxicity, acute toxicity in fish, and bioaccumulation. These responses indicate the wide utility of NAMs, and that their development may serve to be more focused to their contexts of use.

Others pointed to the existing successes of NAMs, such as the defined approach (DA) for skin sensitisation and the development of the in-vitro battery for developmental neurotoxicity (DNT IVB). These could be reviewed to understand what circumstances allowed these to be successfully progressed. Others again pointed to caution towards NAMs, such as understanding their precise domain of applicability.

An agenda for further investigation:

- **Identify the key characteristics of adverse outcomes and develop (quantitative) AOPs.**
- **Investigate areas of improvement or clarification needed in the guidance for existing REACH adaptations.**
- **Determine the applicability of NAM-types in relation to contexts of use.**
- **Analyse previous NAM acceptance to identify success criteria.**

Where do you see the earliest adoption of NAMs occurring? How can such incremental take-up be facilitated?

A wide range of responses were gathered for this question, indicating the differing views of respondents as to where the next lowest hanging fruit is. As some noted, NAMs are already available for use and could be seen as accepted, such as: QSARs; skin sensitisation DA; for cosmetics; DNT IVB; carcinogenicity; and AOPs. It was noted that the new requirements for endocrine disruption allowed for a mechanistic interpretation of that endpoint, and that NAMs are used for DNT and carcinogenicity whereas animal studies are rarely used, due to cost, time, and lack of sensitivity issues.

A range of needs were identified to facilitate take-up: guidance; reporting templates; knowledge sharing platforms; collaboration; training; demonstrations; capacity building; funding; acceptance pathways; case studies; and validation for regulatory confidence.

From these, it is difficult to discern whether or how any of these should be prioritised above others. However, since NAMs are already utilised, better understanding of why some advances have been successful in this utilisation is crucial. From this, other endpoints can be analysed as to their future potential for a transition to NAMs based on understanding the shared and differing characteristics of their socio-technical environments.

Areas of further enquiry:

- **More specifically define and prioritise aspects identified, to enable development in these areas and their effective deployment. For example, collaboration; demonstrations; capacity building; funding; acceptance pathways; and case studies.**

Are there other ways in which data from NAMs can be provided by independent studies, to reduce concerns of bias and promote familiarity with NAMs?

As with the first question (in section 5.1 'Broad Consensus', above), there was general agreement that having more data is useful. However, there were a large number of different responses as to what is needed.

To ensure such a flow of data, improved links and collaborative projects with academic institutions and the wider research community is needed. As with the industry data, open data sharing agreements/arrangements would need to be put in place. Moreover, this would need to be a joint effort both by the regulators and other communities that own the relevant data. Academic and research institutions can start with their own set of initiatives, such as facilitating open access to relevant studies and clear reporting, so that data can be used for regulatory purposes as well as being transparent about the strength and limitations of studies.

NAMs inventories were also proposed, such as could be maintained by an organisation with perceived independence, such as the JRC. It was suggested that such information could be linked with AOPs. Further options were suggested, such as: creating validation platforms (as with the Pepper platform for validating methods for identifying endocrine disruption);[7] inter-laboratory comparisons of results; an accreditation like Good Laboratory Practice (GLP) for model developers; and MS funding of studies. Additionally, it was queried whether all studies always needed to be from validated NAMs.

Areas of further research:

- **Identify effective means to further collaborate and improve links with academia and the wider research community.**
- **Analyse the effectiveness of various actions the research community could take to ensure regulatory relevance of studies and data availability and reporting.**
- **Consider the feasibility of the development of platforms and forums for comparing inter-laboratory results; the consequences of model-developer accreditations; means to improve the efficacy of MS validation funding.**

5.3.2 Opposing Views

Do we need a wider debate about the use of animal testing and the status of NAMs? How might these issues be communicated to the public, and be made accessible?

Some participants emphasised that there is no need for a wider debate as information about NAMs is already widely available and sufficient (EURL ECVAM yearly reports were signposted).[8] Respondents also questioned quite what the public would contribute. Some felt that NAMs are not yet developed for wider use, and therefore a more public debate is not yet a priority as it would not be suitable to have such premature pressure from civil society for a transition. Others felt that while centralised information was available, more information was needed at the MS level.

Others felt there exists a need for a debate about NAMs, with participants pointing out two important considerations. The first is regarding the need to have a scientific debate about NAMs, rather than a wider public debate. This is to explain both the limitations of NAMs and animal testing to allow for a balanced discussion about both forms of testing. Again, identifying the gaps that NAMs need to fill was identified. The second point is that if there is to be wide public debate about NAMs, this debate needs to be managed by communication experts who would be able to convey scientific and technical issues in a manner that a lay person can follow. Furthermore, this debate would need not focus solely on explaining the science but also provide information on safety levels offered by both animal and non-animal testing. We are aware from our empirical research on the barriers to the uptake of NAMs that the public pressure to transition away from animal testing for industrial chemicals is limited and countered by other public pressures for chemical safety in which new methods are greeted with scepticism.

Areas of further development:

- **This aspect would benefit from being redefined to separate the debate in the wider scientific community from that of the wider public domain. The scope of research should address what such engagement seeks to gain; and how it should be determined when a suitable time of engagement is, what form this should take, and at what governance level. This will characterise the opposing views on whether there is a need for a wider debate, and so better inform discussions on potential future actions.**

Is there a need for opportunities for regulators to dialogue with industry about the existing prescribed regulatory process? If so, can and should this be built into the process itself?

There was a clear divide among participants on this question. Those who believed that new opportunities for dialogue are not needed emphasised there are already sufficient opportunities for such dialogue. Illustrations include CARACAL, as the expert group of competent authorities advising the Commission and ECHA on the implementation of REACH and CLP,[9] as well as the work of the EPAA,[10] the range of workshops organised by the EU authorities and industry,[11] coupled with many informal meetings. Some participants emphasised that the perceptions of a lack of dialogue is just masking the wider problems of validation and policy.

Participants who argue in favour of greater opportunities for dialogue between regulators and industry raised thought-provoking considerations of both legal and more social complexities that would need to be addressed for this to happen. Some participants emphasised that a better dialogue would require legal changes of the procedures under REACH. This should be followed by soft law amendments, in the forms of new guidance that should encourage better consideration of NAMs. It was suggested that expert groups could be extended within ECHA (based on the endocrine disruption and PBT groups), which should have ground rules for participation. Yet, others argued that no legal changes are needed and instead it is a change of mindset of regulators that is needed, to be open about the science of NAMs and how to apply it within the existing legal and regulatory procedures

Areas of further research:

- **Identify means of improving knowledge of existing opportunities for dialogue, including characterising the scope of available engagement and inform of whether gaps exist.**
- **Investigate the forms and consequences of the further engagement being sought.**

Can we make better use of soft law guidance issued by regulators to offer clearer information about their interpretation of legislation, decision-making, and risk assessment criteria? If so, how might this be mobilised?

There were again stark differences in the opinions of respondents. Some felt that improving soft law guidance or passing new soft law instruments would provide more information on the interpretation of legislation, decision-making, and risk assessment criteria, which would be useful. A more comprehensive set of guidance was thought would improve understanding of what constitutes strong NAM evidence for regulatory purposes and so result in more prompt acceptance of evidence and improve evidence-based decision-making. Respondents thought support from the European Commission was needed for this and that ECHA should lead on these changes.

Other participants argued that amending hard law is required instead, as it is the hard law that provides regulatory certainty. Even the term ‘soft law’ was not liked by some respondents. While defined approaches allow NAM batteries to be validated, it was acknowledged that this OECD process is slow.

There were some isolated views that underlined there is no need for either amending hard or soft law but rather the priority should be to improve regulatory expertise and therefore confidence in interpreting, accepting, and using NAM data for decision-making.

Areas of further enquiry:

- **Evaluate the effectiveness of current soft law guidance to identify whether and where improvements are needed.**

6. ACTION PLAN

Discussion surrounding policy options to promote the better uptake of NAMs is timely. As a result of the European Citizens' Initiative (ECI): 'Save Cruelty Free Cosmetics - Commit to a Europe Without Animal Testing', which was submitted to the European Commission on 25 January 2023, the Commission published its Communication outlining the measures to address issues raised in the initiative. In responding to the 'ask' to 'Transform the EU Chemicals Regulation,' the Commission committed to develop a roadmap identifying milestones and specific actions that would lead to the gradual and safe replacement of animal testing. This work is driven by different EU Commission Directorates (GROW, ENV, JRC) in collaboration with relevant EU agencies (ECHA, EFSA, EMA), as well as the wider stakeholder community (industry, academia and non-government organisations).

This PrecisionTox report identifies areas where consensus among different stakeholders exists, to broad and moderate extents. Additionally, this report identified issues where agreement has not yet been reached, due to differing views as to the best way forward or of how the issue is individually framed by the experiences and priorities of participants. As indicated above, we used an element of judgement to categorise views as to where consensus has been generated, to enable the identification of action points and steps that will accelerate the uptake of NAMs. With regards to issues of broad consensus, we were able to outline concrete measures regarding the regulatory use of data; education and training strategies; and routes towards validation (Table 4A). With regards to the remaining areas of moderate and indeterminate consensus, instead of proposing concrete measures, we suggest further activity to refine the question at issue and so better determine the processes needed to enable greater acceptance of non-animal testing for regulatory purposes (Table 4A). Thematically these areas of moderate and intermediate consensus relate to meeting protective aims; enhancing the assessment of risk; the domain of application of NAMs; enabling the broader adoption of NAMs; the utility of the wider NAM community; engagement with the debate on NAM use; regulator-industry dialogue; and evaluating the role of soft law guidance. A significant area of division among participants related to the task of law and law reform. To some extent this is not surprising, as any law reform requires time and agreement among different actors. This is even more difficult to achieve in a multi-level governance structure, such as the EU. Nonetheless, calls for reform of EU chemicals legislation were frequently voiced and regarded as one of the significant barriers to the regulatory uptake of NAMs.

Table 4A: Action Plan from Consensus Building
Regulatory Use of Data
Create tools and guidance to help regulators better identify and use industry and academic data, including clarity of what is of regulatory use in terms of data and its generation and evaluation. This extends also to academic associations and publishing companies.
Develop incentives and risk mitigations to enable industry and academia to share their data.
Establish a repository of data that would be managed at the EU level.
Education and Training Strategies
Identify the leadership, funding, and development of structured and coordinated educational platforms or inventory of providers.
Identify the multiple audiences that would benefit from tailored forms and levels of further education and training, which should be provided in different languages across various governance levels (EU; Member State) and settings (formal education; staff development).
Deploy European Education Area to identify technologies such as NAMs as an area for collaboration; to strengthen links with academic institutions across the EU who have the potential to offer training; and to utilise Horizon to develop research-led teaching and training.
Utilise ASPIS both in terms of its educational offerings and as a model for the research-led educational approach.

Table 4A: Continued
Routes Towards Validation
Identify sources of human data and disease progression knowledge.
Establish alternative means for the EU acceptance of methods where human data is not available, such as the development of criteria for combining methods whose regulatory outcomes are consistent.
Determine the potential for comprehensively connecting tools, such as AOP frameworks with IVIVE and PBPK knowledge.
Create an accessible and comprehensive NAM inventory, which can be regularly updated and informs on relevance and reliability.
Areas of Refinement to Aid Consensus for Future Action Points
Meeting Protective Aims: • Review legislative requirements (priority: CLP) to understand where policy and interpretation changes can benefit the uptake of NAMs (especially regulating on mechanisms of action), thereby making it clear where hard law changes will then be needed. • Clearly define and draft guidance on what is expected of NAMs: is this to reproduce all aspects of an animal test? • Review of legislative endpoints to understand gaps in protection. • Undertake a cost-benefit analysis of NAMs and the potential of their application to thousands of chemicals.

Table 4A: Continued
Enhancing the Assessment of Risk: • Investigate how better to incorporate exposure information and manage risk, particularly under industrial chemical risk assessments, and the extent to which animal testing will be reduced as a result. • Consider the feasibility and usefulness of requiring full supply-chain use information, and the extension of requirements to lower tonnages. • Review guidance on REACH use-waivers. • Determine to what extent industry are fulfilling their risk management measure obligations. • Evaluate the effectiveness of current requirements in comparison to broader definitions of harms.
Domain of Application of NAMs: • Identify the key characteristics of adverse outcomes and develop (quantitative) AOPs. • Investigate areas of improvement or clarification needed in the guidance for existing REACH adaptations. • Determine the applicability of NAM-types in relation to contexts of use. • Analyse previous NAM acceptance to identify success criteria.
Enabling the Adoption of NAMs: • More specifically define and prioritise aspects identified, to enable development in these areas and their effective deployment. For example, collaboration; demonstrations; capacity building; funding; acceptance pathways; and case studies.

Table 4A: Continued
Utility of the Wider NAM Community: • Identify effective means to further collaborate and improve links with academia and the wider research community. • Analyse the effectiveness of various actions the research community could take to ensure regulatory relevance of studies and data availability and reporting. • Consider the feasibility of the development of platforms and forums for comparing inter-laboratory results; the consequences of model-developer accreditations; means to improve the efficacy of Member State validation funding.
Engagement with the Debate on NAM Use: • This aspect would benefit from being redefined to separate the debate in the wider scientific community from that of the wider public domain. The scope of research should address what such engagement seeks to gain; and how it should be determined when a suitable time of engagement is, what form this should take, and at what governance level. This will characterise the opposing views on whether there is a need for a wider debate, and so better inform discussions on potential future actions.
Regulator-Industry Dialogue: • Identify means of improving knowledge of existing opportunities for dialogue, including characterising the scope of available engagement and inform of whether gaps exist. • Investigate the forms and consequences of the further engagement being sought.
Evaluating the Role of Soft Law Guidance: • Evaluate the effectiveness of current soft law guidance to identify whether and where improvements are needed.

While principal responsibility of many of these actions reside with the leadership of policy makers, aiding the progression of several actions are within the domain of other stakeholder groups. These are particularly in relation to validation, including the identification of sources of human data and disease progression knowledge; proposing alternative means for the EU acceptance of methods where human data is not available, such as the development of criteria for combining methods whose regulatory outcomes are consistent; and determining the potential for comprehensively connecting tools, such as AOP frameworks with IVIVE and PBPK knowledge. Additionally, some areas of refinement that will aid the consensus of future action points would benefit from contributions from wider stakeholder groups, such as cost-benefit analyses of NAMs and the potential of the application of NAMs to thousands of chemicals; informing the feasibility and usefulness of requiring full supply-chain use information; identifying the key characteristics of adverse outcomes and developing (quantitative) AOPs; and investigating the forms and consequences of the further engagement that is being sought.

We conclude with Table 4B, which identifies actions of relevance to the activities of specific Work Packages within PrecisionTox, such that previously identified barriers to the uptake of NAMs can be avoided, overcome, or mitigated as deliverables are fulfilled, and new methodologies begin to contribute to safer and sustainable chemicals in Europe.

Table 4B: PrecisionTox Action Plan
Regulatory Use of Data
Work Package 6, for example, omics and grouping ('Group First, Regulate Better' (GFRB)) **Work Package 1.** Create tools and guidance to help regulators better identify and use industry and academic data, including clarity of what is of regulatory use in terms of data and its generation and evaluation.
Work Package 1 Develop incentives and risk mitigations to enable industry and academia to share their data.
Work Package 5 Establish a repository of data that would be available at the EU level.
Education and Training Strategies
Work Package 1 Identify the leadership, funding, and development of structured and coordinated educational platforms or inventory of providers.
Work Package 1 Identify the multiple audiences that would benefit from tailored forms and levels of further education and training, which should be provided in different languages across various governance levels (EU; Member State) and settings (formal education; staff development).

Table 4B: Continued
Work Package 1 Utilise ASPIS both in terms of its educational offerings and as a model for the research-led educational approach.
Routes Towards Validation
Work Package 1 Identify sources of human data and disease progression knowledge.
Work Package 6 Establish alternative means for the EU acceptance of methods where human data is not available, such as the development of criteria for combining methods whose regulatory outcomes are consistent.
Work Package 6 Determine the potential for comprehensively connecting tools, such as AOP frameworks with IVIVE and PBPK knowledge.
All Work Packages Consider route to validation, including feasibility in cost of use.

NOTES

1. See more about Delphi process at: https://www.cardiff.ac.uk/__data/assets/pdf_file/0010/1164961/how_to_conduct_a_delphistudy.pdf.

2. Interviewee I5, interviewed between January 2023 and May 2023.

3. NC3Rs, 'RIVER Recommendations' available at: <https://nc3rs.org.uk/our-portfolio/river-recommendations>.

4. NICEATM: NTP (National Toxicology Program) Interagency Center for the Evaluation of Alternative Toxicological Methods <https://ntp.niehs.nih.gov/whatwestudy/niceatm/3rs-meetings/past-meetings>.

5. EC's Joint Research Centre (JRC), 'JRC Summer School on Non-Animal Approaches in Science' available at: <https://joint-research-centre.ec.europa.eu/events/jrc-summer-school-non-animal-approaches-science-2023-05-23_en>.

6. BTS: British Toxicology Society <https://www.thebts.org/>; NC3Rs: National Centre for the Replacement, Refinement and Reduction of Animals in Research <https://nc3rs.org.uk/>.

7. Pepper: Public-Private Platform for the Validation of Methods for the Characterisation of Endocrine Disruptors <https://ed-pepper.eu/>.

8. EURL ECVAM: EU Reference Laboratory for alternatives to animal testing, <https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam_en>.

9. CARACAL: Competent Authorities for Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) and Classification, Labelling and Packaging (CLP), <https://ec.europa.eu/transparency/expert-groups-register/screen/expert-groups/consult?lang=en&do=groupDetail.groupDetail&groupID=2385>.

10. EPAA: European Partnership for Alternative Approaches to Animal Testing <https://single-market-economy.ec.europa.eu/sectors/chemicals/european-partnership-alternative-approaches-animal-testing_en>.

11. Such as the European Commission's workshops on the roadmap towards phasing out animal testing, <https://single-market-economy.ec.europa.eu/sectors/chemicals/reach/non-animal-testing_en>; and those organised by ECHA, <https://echa.europa.eu/events/2024>.

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