PRECISIONTOX

D6.1 REPORT ON SOCIO-TECHNICAL BARRIERS TO THE UPTAKE OF NAMS

2023

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Acronyms	
3Rs	Replace, reduce, or refine animal testing
AOP	Adverse Outcome Pathway
CLP	Regulation (EC) No 1272/2008 on the Classification, Labelling, and Packaging of substances and mixtures
DA	Defined Approach
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
FDA	Food and Drug Administration (United States)
GHS	Globally Harmonised System of classification and labelling of chemicals (United Nations)
GLP	Good Laboratory Practice
IATA	Integrated Approaches to Testing and Assessment
MAD	Mutual Acceptance of Data
NAM	New Approach Methodologies
NGO	Non-Governmental Organisation
OECD	Organisation for Economic Co-operation and Development

QSAR	Quantitative Structure-Activity Relationship model
REACH	Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation, and Restriction of Chemicals
SME	Small and Medium-sized Enterprises
TG	Test Guidelines
TSCA	Toxic Substances Control Act (United States)
UVCB	A chemical of unknown or variable composition; or a complex product of a chemical reaction; or a biological material other than a whole animal or plant
WoE	Weight of Evidence

EXECUTIVE SUMMARY

Over the past decade, considerable progress has been made in developing new approach methodologies (NAMs) for chemical risk assessment employing in vitro, in silico, and in chemico approaches, as well as the strategic use of alternative metabolic model organisms, to uncover the potential adverse effects of chemicals on human health and the environment. In general, these NAMs have been welcomed not least because of a desire, reflected in the wider ethical views of society, to curtail the use of animals for toxicity testing. Additional potential benefits include greater predictive precision, lower testing costs, and faster testing processes. Nonetheless, obstacles remain, for example, in the form of doubts as to the reproducible and predictive capacity of NAMs and the ability of regulatory structures to accommodate these diverse methods.

This report explores barriers, as perceived by stakeholders, to inhibit the take-up of NAMs for chemical safety assessment, including scientific, technological, regulatory, and social considerations. The PrecisionTox Working Group 6 (Regulatory Analysis & Application) produced this report. The report is informed by an empirical research study that generated qualitative data from semi-structured interviews with 32 stakeholders, including one to one and small group interviews of industry representatives, regulators, and policy makers from the European Union (EU) and other jurisdictions.

The barriers to uptake of NAMs identified in this study are not merely technical, but predominantly involve a range of social barriers, which have led to dependency on existing (and typically mammal-based) methods and apparent resistance to technological transition (Table 1). This focus on social and people-based factors distinguishes this study from the narrower scientific debate, which has tended to limit itself to the technological maturity of the next generation of chemical risk assessment methods. While scientific readiness is a critical component of the discussion, this report highlights where scientific considerations intersect — and sometimes collide or compete — with social and institutional factors.

Perceived barriers to uptake of NAMs include a broad range of regulatory issues including regulatory acceptance and culture, familiarity with and confidence in animal studies (though some interviewees highlighted the lack of validation of traditional animal testing methods), and the lack of trust between actors. Discussions

around the levels of regulatory confidence in understanding the data from NAMs, mentioned by regulators as well as industry representatives, identified various socio-technical aspects that impact acceptance, ranging from education and training to familiarity with methods and resource availability. These barriers are present at various levels and across the chemical landscape, though they may play out differently across jurisdictions depending, in part, on whether assessment is exposure or hazard based. Additionally, validation and standardisation, expertise and resources, and social perceptions were identified as issues.

Table 1: Barriers to the Uptake of NAMs

Theme	Sub-theme
Views of regulatory science and the legislative framework	**Regulatory culture:** • **Acceptance** • **Familiarity and confidence in animal studies** • **Lack of trust between actors**
Validation and standardisation	
Expertise and resources	
Regulatory objectives	• **Jurisdiction** • **Principles of exposure versus hazard that underpin the legal framework on industrial chemicals**
Social perceptions	
Scientific development	

EXECUTIVE SUMMARY

The research highlights the interconnectedness between different socio-technical barriers; for example, while legislation is identified as a technical barrier (being largely processed based), its interpretation and associated policy objectives exhibit social dimensions. This report provides a contextual understanding of the socio-technical barriers to the uptake of NAMs drawing on data from a diverse range of stakeholders. Though the majority of the conclusions are applicable to other jurisdictions, this report provides a strong steer on existing barriers in the EU context.

While this report makes some preliminary suggestions for policy directions, potential solutions in the realm of governance will be explored in a later, subsequent report.

Key barriers identified:

1. **Numerous vicious circles work against the uptake of NAMs:** Industry actors are reluctant to invest in producing and sharing NAMs data due to the perception that it will not be accepted by regulators, whereas regulators are reluctant to consider NAMs due to a perceived lack of data.
2. **Lack of consensus on scientific readiness:** Actors across industry, policy, and regulation hold a range of views on the present capability of NAMs to produce human-relevant toxicity data.
3. **The need to reconsider the governance framework that underpins NAMs:** The regulatory barriers, which include a range of issues such as regulatory culture, validation processes, and the interpretation of laws, needs to be holistically reassessed.
4. **Lack of familiarity, trust, and confidence:** Actors have less experience of and are less familiar with NAMs compared to animal tests. Industry is not considered to be a trusted source of information. A lack of clear policy direction and leadership will prove crucial in building individual and institutional confidence in NAMs.

1. INTRODUCTION

At first glance, a report on the problems associated with using methods other than animal tests to assess the safety of chemicals appears very niche. Yet, consider the wide use of chemicals, from making up the plastics in our everyday items and children's toys, to substances in manufacturing process and use in agriculture, and those in our cleaning products and fragrances. Chemicals are all around us, and the knowledge of the harms they can cause to people and the environment is very limited in many cases.

Over recent years, considerable progress has been made in developing new methods for use in chemical risk assessment employing in vitro, in silico, and in chemico approaches to uncover the potential adverse effects of chemicals on human health and the environment. In general, these new approach methodologies (NAMs) have been welcomed not least because of a desire, reflected in the wider ethical views of society, to curtail the use of animals for toxicity testing. Still, obstacles remain in the form of doubts as to the reproducible and predictive capacity of NAMs and the ability of regulatory structures to accommodate them. These two issues are inter-related.

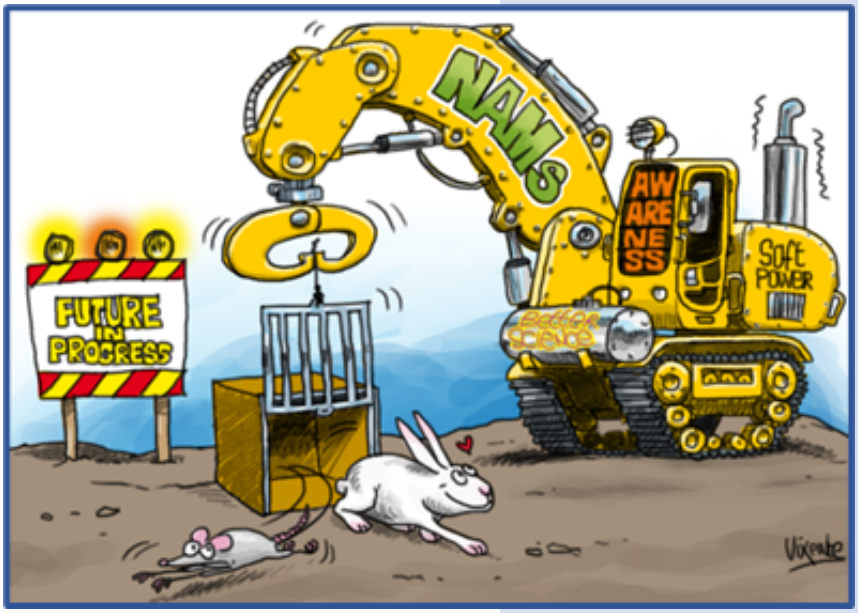
The incorporation of NAMs into the regulatory processes globally has been inhibited by technical uncertainty (including scientific methods and regulation) but there are also societal considerations which affect the appetite for NAMs. While in Europe cosmetics were singled out for a ban on animal testing, other substances such as industrial and agrochemicals have been shielded from those wider social pressures due to a lack of public awareness. This report provides the findings of research by the University of Birmingham in identifying and examining barriers that have been working against the greater use of NAMs in such chemical risk assessments, and these findings will inform proposals to overcome these issues.

The report demonstrates that many of the barriers are applicable to any jurisdiction, though we focus primarily on those applicable to the EU. Within the EU there are particular factors that reflect the different regulatory foci underpinning the chemicals risk assessment framework. In the EU single market of goods and services, this has a multi-level institutional structure in which member states confer significant powers to the EU institutions. Moreover, the inclusion of other stakeholders in the decision-making process is of great importance. These political structures form part of the social context, and, as is shown below, in general we find that many barriers are social rather than technical, as reflected in the governance structures that emerge, although both are intertwined. Note however, that there is a significant division of opinion with regards to scientific robustness of NAMs and their ability to become part of the regulatory process.

INTRODUCTION

This report not only relies on a review of scholarship on regulatory employment of NAMs, but it is underpinned by a qualitative empirical study undertaken with different stakeholders.

The report is divided into several sections. The second section outlines methods deployed to identify relevant barriers to NAMs. The third section provides a brief overview of the term NAMs and lists different methods encompassed by this term, followed by an explanation of 'socio-technical' terminology. The fourth section explores the barriers to NAMs identified from social, natural, and applied science scholarship and summarises findings of the qualitative research with three groups of stakeholders. Finally, the concluding section outlines the main policy solutions and recommendations to accelerate the uptake of NAMs.



2. METHOD

This report is underpinned by a desktop review of relevant literature coupled with data drawn from empirical research. The former method entailed the review of scholarship across a range of disciplines, including both natural and social sciences literature published in the last 18 years. This review informed the empirical research that was carried out between January and June 2023. The empirical research framework was reviewed and approved by the relevant Ethics Committee at the University of Birmingham. This report draws on interviews with 32 stakeholders involved in the risk assessment and management of chemicals. The participants represented three main groups broadly involved in the regulatory process, including industry, regulators, and policy makers. Although the PrecisionTox programme is primarily focused on chemical risk assessment in the EU, the research included interviews with regulators across different jurisdictions to provide a comprehensive review of perceived barriers to the uptake of NAMs. Multinational industry representatives were able to provide perspectives from different jurisdictions drawing upon their involvement with regulators across the world.

Interviews were carried out remotely using Zoom software, including one to one interviews and small group interviews, depending on interviewee preference. Each interview lasted between 40 and 60 minutes. The Zoom software also provided researchers with interview transcripts. The prospective interviewees were initially contacted by email to outline the research and provide a semi-structured interview guide and a consent form. The researchers adopted the format of a semi-structured interview to allow dialogue and provide data that went beyond the information obtained through the scholarship review that preceded the interviews. This approach to the interviews provided the opportunity to obtain rich insight and qualitative understanding of the regulatory process.

3. NAMS BACKGROUND

Chemical legislation in various forms requires the testing of substances to ascertain whether they have harmful effects, so that appropriate risk management measures may be applied. Traditionally toxicity testing has involved animals as a surrogate for humans. However, along with a desire to reduce the use of animals in testing, there have also been scientific and technical drivers that have accompanied the development of alternative methods. The umbrella term for such approaches that can provide information about chemicals is 'NAMs,' which can be an acronym for 'new approach methodologies,' 'novel approach methodologies,' or 'non animal methods.' Some of the key approaches of NAMs are briefly described in Table 2, though in practice the methods can be used in combination.

Despite the expectation that the implementation of the Regulation on the Registration, Evaluation, Authoristion, and restriction of Chemicals (REACH) would expand and deepen the fields of applied toxicology, currently the pace of regulatory uptake in chemical safety of NAMs such as those involving toxicogenomics, has been slow. This report explores why there has been this limited uptake in the use of NAMs.

Table 2: Key Approaches to NAMs	
NAM Approach	**Brief Summary**
In vitro	A broad term of any non-whole animal study encompassing tests using organs, tissues, cell cultures, cell lines and / or sub-cellular aspects such as mitochondria. Other microphysiological systems seek to replicate functionality as small-scale reproductions of aspects of human physiology, such as 'organ-on-chip' (OoC) and organoid methods.
In silico	Computational or 'non-testing' methods including machine learning and artificial intelligence, which can be used in planning and the analysis of other tests, or as prediction tools. This also includes quantitative structure-activity relationship (QSAR) models.
In chemico	Tools for taking physicochemical measurements of the reaction of a chemical on biology to understand the changes to, for example, covalent bonds and effects on electrons.
High throughput and high content technologies	Experimental measurement approaches that can rapidly test large numbers of samples for biological activity, associated with, for example, transcriptomics, metabolomics, and other 'omics' data.
3R-compliant model organisms	In addition to providing ecotoxicological data on the species used, such organisms are used where toxicity pathways are comparable to humans, such as invertebrates of fruit flies, nematodes, and zooplankton, and early life stages of other organisms.

4. SOCIO-TECHNICAL BARRIERS TO NAMS

This report considers the socio-technical barriers to the uptake of NAMs and uses this lens in recognition that many factors influence the acceptance of changes to ways of working in other domains. We all respond differently to the perceived risks of change and our views vary in terms of how costs and benefits are weighed. We may find changes disorientating and unwelcome, with our willingness to embrace a different process or approach to a task is heavily influenced by economics, politics, infrastructure, capacity, access, and habit. In terms of science, there may be unrealistic expectations in seeking points of closure or certainty when techniques are continually advancing. Risk assessments, meanwhile, may offer an enticing impression of control and in so doing reduce the appetite for the future refinement of methods. Both regulation and regulatory change demand resource, and regulators may seek to simplify processes, which can reduce the space for new approaches to fit within existing regulatory frameworks. While it may be necessary to make technical refinements to newly developed methods, it is also necessary to seek to fit these in social structures, including legally determined rules. This may not be easy. The concept of 'lock-in,' where socio-technical systems co-evolve to a dominant 'state of stability and self-perpetuation,' arises from multiple factors and their influence on each other, to the point that the adoption of alternatives is hampered, involving, as it does, a paradigm shift.

In other areas of technology transition the notion of a socio-technical domain is well recognised. In energy technology, the term 'technical' relates to hardware, and 'socio-' to misunderstanding and lack of awareness, and may also encompass economic and political barriers. Likewise, in the architecture, engineering and construction industry, socio-technical theory (STT) sees the socio- element as individuals or groups of stakeholders and how these social systems are structured, while the technical systems are the software, hardware, methods and tools needed to implement processes. In these sectors it is widely understood that by not considering socio-technical factors, the risk that systems will not contribute effectively will increase.

When it comes to NAMs, from the socio-technical divisions described above it can therefore be considered that social aspects relate to interactions among stakeholders and their awareness, (mis)understandings, opinions and informal working practices that surround the new methods. The technical domain includes the processes, procedures, use and application of results of these methods. There is no absolute or even clear dividing line between the social and the technical. Much of the technical advances are pursued in social settings: in discussions, debates, conferences, and peer review. The social and technical realms therefore coalesce to create barriers to NAMs, with each influencing the other to create uncertainty or ambiguity regarding the employment of NAMs, generating a lack of confidence in progressing the uptake of these alternative approaches.

Barriers to the regulatory uptake of NAMs have been explored and identified in earlier scholarship. These barriers have been compiled in Table 3 to indicate the initial assessment of their social and or technical dimension. While some barriers appear at the outset to be highly technical in nature, the discussion often elucidates a social dimension. Other barriers have been assigned as social barriers only, and their inclusion in this socio-technical analysis is critical because they form important landscape factors which might influence (or restrict) the development and implementation of NAMs as technical tools.

The grouping of barriers identified in the literature under these headings informed the main themes for the interviews. In the remainder of this section of the report, we explore each of these potential barriers in greater detail in combination with the findings of the empirical research conducted with the three groups of stakeholders, as explained earlier. Although there are some discrepancies in naming the barriers to the uptake of NAMs depending on the emphasis of the findings from the scholarship and the empirical research, there is close alignment between the two sets of data.

Table 3: Social and or Technical Barriers to NAMs		
Barrier	Social	Technical
Validation	X	X
Lack of standardisation	X	X
Scientific expertise	X	X
Information gaps	X	X
Regulatory framework	X	X
Lack of harmonised approach	X	X
Regulator resources	X	X
Bias, assumptions, lack transparency	X	X
Public involvement	X	
Lack of incentives	X	

Key to Quotes

Regulators

Industry

Policy

4.1 Observations About the Current Use of NAMs

We begin with some observations made by interviewees around the current level and means of use of NAMs. Industry interviewees reported they make use of NAMs for regulatory endpoints of local effects such as skin irritation and sensitisation, and that they welcome their inclusion in the United Nations' Globally Harmonised System of classification and labelling of chemicals (GHS) and the EU Regulation on the Classification, Labelling, and Packing of substances and mixtures (CLP). Non-EU regulators noted likewise they have seen greater use of read across, as well as modelling in submissions. Weight of evidence (WoE) is also seen (sometimes in combination with models), but to a lesser extent, and it is used more for a qualitative indication of risk rather than providing a quantitative assessment.

The limitations of animal tests in not being an exact proxy for humans was acknowledged by some industry and non-EU regulator interviewees, and consequently there is recognition that the role of NAMs is to improve safety assessments by helping to understand mechanistic toxicity and for tests to be relevant for humans. Industry stakeholders are keen to develop technologies to be accepted in regulatory frameworks and felt they are developing their understanding of mechanisms of action, and some had even gained experience in the process of adoption of NAMs at the level of the Organisation for Economic Co-operation and Development (OECD). EU regulators stated they are disappointed by the lack of replacement progress, particularly for systemic toxicity, and this was attributed to the difficulty in replicating the large amount of information for assessing the many hazard classes and sub-classes that animal toxicity tests provide. They contended that the mammalian tests provide a holistic picture of toxicity, and that much deliberation is focused on human relevance. Some regulators contested the view that animal tests are uncritically given precedence, stating that as this is directly relevant to classification and, as such, is legally binding.

"It's in the last five years that we're seeing more and more NAMs that people are talking about."

Some industry interviewees explained their use of NAMs in a tiered approach to testing as part of internal decision making, which starts with toxicology screening, then, for example, removing molecules identified as carcinogens or developmental toxicants. For this they also use internally developed alternative methods, before then applying the regulatory requirements to promising substances. The impression is that such an approach is utilised more with pesticides, pharmaceuticals, and biocides rather than industrial chemicals, due to the limited candidate molecules for the latter. The rigid endpoints in legislation are considered to result in a narrow and cautious view taken by regulators, while instead the wider data held by industry that informs their decision-making appears to give the latter greater confidence in these decisions. There was also a disconnect in the views on where NAMs are predominantly used, with some regulators reporting that data from NAMs are positioned more for human health than for ecotoxicological endpoints, whereas some industry interviewees considered there to be greater access to environmental models.

"There are different types of NAMs that we developed that we've been using and that's ultimately made it into REACH dossiers…we are thinking about the adaptations that we can apply…Not all of our dossiers have been evaluated so far…Where we had some methods…that kind of information has not been accepted…the outcome was that we were requested to conduct animal testing basically to fulfil our information requirements…The regulators are very open as well for us to bring in that data, but then rather in support of in vivo data."

Industry interviewees reported that while they use the adaptations of Annex XI such as WoE, grouping and read across, and exposure-based approaches, the information in some dossiers had not been accepted, and others were still to be evaluated. They are also concerned by regulators' requests to repeat animal testing where results were not as expected, thereby requiring further animal experimentation. Both industry and non-EU regulators noted that while regulators may state they welcome data from NAMs, this is when such data is in support of and complementary to in vivo, rather than in place of it. The perception of many non-EU regulators was that full replacement of

animal testing will not be achieved in the short term. However, this group appears willing to accept NAM studies and batteries of tests, in acknowledgement of the thousands of chemicals to be evaluated that need data generating for them, and in recognition of the time taken for traditional toxicity testing, along with the resource therefore needed.

"I think there is a willingness to embrace these new tools because there's a reality to the tens of thousands of chemicals that have to be evaluated... and the hundreds, if not thousands, of decisions that have to be made on pesticides...that we just don't have the physical resources to do things that will sit and wait for long periods of time as data are generated."

Some non-EU regulators undertook toxicity testing themselves, and reported using NAMs in their work, typically read across to avoid animal testing but are not yet largely using mode of action data. This is generally applied on a case-by-case basis in jurisdictions where chemicals had smaller markets, and this was acknowledged to be resource intensive (and still may result in lapsed statutory deadlines for reviews). Non-EU regulators also spoke of their involvement in collaborations on the development of NAMs, and participation in OECD activities and interacting with EU regulators such as the European Food Safety Authority (EFSA). Likewise, industry interviewees have a strong research interest in non-animal approaches and for working in partnership on this and have previously collaborated with likeminded regulators. Their main approach to encouraging wider acceptance of NAMs and toolboxes is through publications on use.

"It's just such a large issue that no one can really do it on their own... In general, we work with similar jurisdictions ... with respect to NAMs."

4.2 Views of Regulatory Science and the Legislative Framework

From the literature it was identified that the regulatory framework is a barrier to the uptake of NAMs. While the REACH regulation may express aspirations for innovation through the 3Rs (to replace, reduce, or refine animal testing), its annex requirements are based on specified apical adverse endpoints. Similarly, the current OECD Guidance Document on validation requires test methods to 'measure or predict the endpoint of interest.' There are therefore technical and legal barriers to overcome, and without an appropriate decision-making framework and guidance there has so far been limited practical acceptance by regulators. As only those methods that have been validated and approved by the OECD are expected to be accepted, there has been a reduced uptake by industry and consultants for regulatory dossiers as they perceive that those results from NAMs not passing this bar will not be recognised by regulators. From the regulatory standpoint, the social pressures for increased scrutiny and transparency requirements on modern science and technology adds to the pressure on decision makers to be accountable.

Stakeholders in our interviews also reported the design of the EU institutional and legal system as constituting an important barrier to consider.

"The biggest barrier is the legal one. Actually, the legal framework is so difficult to change that it is actually suppressing what the institutions feel they can do and should do. And then the whole regulatory machinery is kind of linked to the legal basis, and that also becomes highly inflexible. Number one is the law. It is like an immovable system."

Interviewees raised the challenge of having a legal framework that is overly restrictive and closes the space for NAMs and to that end discussed various ways of amending the existing legal framework, which naturally brought the discussion to complexities of the EU ordinary legislative procedure.

Added to the restrictive legislative framework as a technical barrier to NAMs, the regulatory culture is a closely related, albeit broad, social aspect. We have identified three subsets that make up this barrier from the literature and interviews: the willingness of regulators to accept and embed NAMs within regulatory process, their position towards animal testing more generally, and their relationship with other actors.

4.2.1 Regulatory Culture: Acceptance

Regulatory acceptance was widely reported as a major subset barrier within the broader theme of regulatory culture. Several challenges were identified with regards to regulatory acceptance. A major theme was the level of confidence that a regulator needs in order to accept data generated by NAMs. The interviewees reported that there needs to be a global acceptance of NAMs going forward which would then provide regulators with greater confidence. However, a significant number of interviewees, including some regulators across the world, pointed out that the decision on what constitutes an acceptable risk is ultimately a political decision which depends upon the level of risk appetite set by underlying political objectives. This threshold is undoubtedly underpinned by and dependent on science (therefore requiring dialogue), but its acceptance becomes a policy decision. With regards to the EU context, some interviewees felt that clearer political direction for NAMs is required from policy makers, rather than acceptance depending on the regulator. While political pressures may come from human and environmental health and safety concerns, or lobbyists with a focus on reducing animal testing, political judgments may be influenced by other social and technical factors, which in some cases may result in the reliance on traditional methods remaining, and different requirements across sectors and jurisdictions persisting.

"What is an acceptable risk is not a scientific decision. That's a social political decision and different countries and different organizations have very, very different levels of risk tolerance."

In reaching political decisions that might lead to a greater acceptance of NAMs, the interviewees pointed out that a crucial challenge was the level of confidence and understanding that a regulator requires from data presented to them. Industry, in particular, considered the main crux is the ability of the regulator to interpret the data, which is to some extent linked to the challenge of expertise that is also discussed later in this report. This lack of confidence in data creates long term uncertainty within the regulatory system. In discussing regulatory acceptance, the discussion with the interviewees exposed a correlation between the levels of acceptance and the levels of expertise and resources of a specific regulator.

"The main barrier is, I think, true understanding by the senior leadership in the regulatory world."

As mentioned, with interviewees considering EU chemical legislation to be too prescriptive in terms of the tests and requirements, while some conceded a harmonised system needs the implementation of requirements to be predictable and to provide the legal certainty sought, it was felt there is a balance to be struck with flexibility that allows the safe use of some hazardous substances. Here, some regulators themselves felt colleagues lacked flexibility and are 'hiding behind the legislation,' even in cases when this flexibility is permissive by law, which was raised as a particular challenge to the European Chemicals Agency (ECHA) in the EU. An illustration in the EU was the use of Annex XI, which allows for adaptations to be used, but still regulators are not demonstrating significant levels of acceptance of adaptations despite regular use within industry.

The regulator's view and settled practice also has an impact on the regulatory acceptance of NAMs. This was widely reported as an issue by all different stakeholders in the study. Regulators are by nature conservative and find it very challenging to move away from their established practices, which is to some extent linked to resources and expertise but also to a deeply engrained working cultures. With regards to willingness to embrace NAMs, interviewees pointed out to a stark difference between EFSA and ECHA which, some interviewees suggested, is causing confusion. Although such differences of approach may be justified as reflecting a variance in objectives of the legislation that governs the work of EFSA and ECHA, according to the interviewees, it still did not seem reasonable or consistent to the applicants. It was reported that it created confusion and unevenness with regards to labelling and

classification.

"What I see within ECHA is a culture which wants to ensure compliance but doesn't necessarily have the capacity or the expertise or the willingness to apply a science led approach. They're not in the lab using these methods."

Moreover, some policy makers reported that there are levels of inertia and conservatism with regulators, which also impede acceptance of new methods. It was also stated that this challenge is partly from the distance of regulators from laboratory practice. This leads to what was reported as a 'vicious circle' challenge for the industry. Due to the regulator's reluctance to accept NAMs, the industry is not willing to include NAMs in their applications due to fear of those new methods not being accepted. At the same time, industry makes a rational actor's decision not to invest to a great extent in NAMs while animal studies remain a safe option. This has economic knock-on effects where laboratories are doing less NAMs-based testing, with costs then remaining high.

"I do think that if enough companies believe that this is the direction it's going to go in, we will have the lab capability down the road. It's a demand issue... So labs aren't going to jump into it, or new labs aren't going to start because they're not going to start employing people and doing stuff unless they know there's a timeline that they can make a profit"

Linked to this question of confidence is the fear of future litigation or legal challenge coupled with the need to ensure good levels of social acceptance. As was also identified in the literature, if there are fears that tests and analyses on chemicals have not been conducted and assessed correctly, ultimately there may be concerns of legal challenge. The titanium dioxide case, *CWS Powder Coatings GmbH v European*

Commission, was used as a case in point that drove regulation towards a safe, if conservative approach, to decision-making.

"Confidence means that a decision that you make based on a hazard assessment isn't litigated ad nauseum. There's enough societal acceptance and therefore a regulator can say I can use this, and I'm not going to be bashed."

These responses reflect the literature in identifying a lack of clear organisational support for new approaches, from which it can be viewed that it is unclear who is the central promoter of the 3Rs. Having identified that experts, consultants, and laboratories are likely to have established links and contracts to provide existing traditional testing, and that this may indicate a conflict of interest and a scepticism of NAMs, the study corroborates that maintaining the status quo means opportunities to incentivise investment and implement change will remain limited.

4.2.2 Regulatory Culture: Familiarity and Confidence in Animal Studies

From the literature we also see that some NAMs do lack regulatory relevance, or approaches may be restricted to certain applications, or for a specific regulatory endpoint. However, the lack of a transition to NAMs is more commonly associated with scientific and regulatory culture being wedded to the view of traditional animal testing being the 'gold standard.' The above-mentioned lack of regulatory acceptance is therefore also linked to regulators' perceptions of animal studies, and a majority of interviewees spoke about the difficulties of shifting this 'gold standard' paradigm because of the discomfort it would cause regulators. To some extent this is to be expected as animal studies have been around for more than 50 years, and they are regarded as the norm. As such they are trusted by all stakeholders, including the public, who it was thought might fear a dilution of safety standards in the introduction of new methods and their capacity to predict harm. In effect, the social

history and shared experience of the testing processes plays a significant part in the regulatory acceptance of test methods.

"Have you ever really studied a 90-day rat study? You know the amount of data in one of those, all the haematology information, all the chemical chemistry information. Are you telling me you understand all that? You don't. You're just comfortable with the number that comes out at the end, so you can put it in the box. So, the fact that you're not comfortable with the new technology, absolutely, we should become more comfortable with it."

Some interviewees pointed out that regulators do not perceive NAMs as replacements to animal studies even in the long term, instead treating NAMs as an 'add on,' which was thought would impede their greater uptake. Some interviewees also pointed out that it is not helpful that some researchers in academia also share this 'gold standard' view and continue to use animal testing.

"The toxicology studies that are currently performed for pesticides were already being performed as our standard practice by the FDA in 1949... I find that quite shocking frankly, that we've not really moved on from the established science in the 1940s."

One of the major hurdles is that data gathered through NAMs are not comparable to animal studies. Some interviewees are concerned that the expectation is for NAMs to fully replicate data that animal studies provide to a regulator, despite animal testing requiring extrapolation (sometimes arbitrarily) for human relevance. It was pointed out by many interviewees that regulatory confidence here is not necessarily based on accurate data, but it is based on precedent, as animal studies have been around for decades, and confidence was built through their long-term deployment.

Therefore, as technology advances and safety are better scrutinised, it was said to place a burden on industry and create an uneven playing field for NAMs. NAMs, though, are not currently considered to offer data that studies on whole organisms can provide, and this is to some extent understandable as the majority of interviewees pointed out that NAMs are not ready for testing complex endpoints.

"A rat study isn't necessarily a one-to-one connection to people but they're willing to use it, because we have for so long."

Therefore, with lack of trust due to an excess of caution in the regulatory process, and a lack of familiarity with NAMs with some stakeholders involved not understanding NAMs or the relevance of data and how to use these, regulators are conscious of the fact that any error may have serious consequences on a national and even international scale.

"Regulatory staff such as myself, obsess about making a type 2 error...where you conclude that there is no effect when there actually is...and making a type 2 error at a national level has consequences that extend across the landscape...those mistakes come at a high price."

4.2.3 Regulatory Culture: Lack of Trust between Actors

One of the well-established insights into this culture barrier among interviewees revolved around the lack of trust between the regulators and the industry. This is partly due to the fact that their starting positions in the regulatory process are said to be different, in that industry uses data to show adversity, while regulator uses data to demonstrate safety. Thus, reaching an agreement between the two parties becomes

a challenge. Equally, there is a perception that industry is not a trusted source. This view of the industry is considered by some to be justified by examples of bad practice by some industry representatives. This includes submission of poor data, which fuels a mistrust that regulators may have in new methods. However, there is the suggestion that a very small proportion of companies have a large negative reputational impact on the wider industry.

"There are certainly companies that behave badly, but most companies, most people, and most people in industry don't want to see humans and the environment harmed. Mostly they don't, and the smarter companies are those that recognize that the most valuable thing that they have is their brand name. And if they do something stupid and destroy their brand name, that's the end of them and their company."

Interviewees considered that academic research on exposure in particular is lacking, and research from this sector would be important in providing an impartial view. Additionally, third parties running tests was identified as a means to avoid concerns of bias or mistrust in results.

The view that industry is not a trusted source is often further perpetuated by non-governmental organisations. Some interviewees emphasised that environmental organisations at times create a milieu whereby certain chemicals are polluting the environment or have adverse effects on health that ultimately causes upset among people, but in delving into toxicological studies it becomes apparent that some of those chemicals are not, for example, carcinogens or developmental toxicants. And, despite their commitment to 3Rs, it was also reported that some non-governmental organisations (NGOs) feel that replacement is occurring too quickly, and they are not ready for replacement but rather for refinement and reduction.

4.3 Validation and Standardisation

It is recognised that test methods should be reliable and relevant to be validated. Reliability is a scale of how reproducible test results are when a protocol is followed within (repeatable) and among (reproducible) laboratories over time. Relevance relates to whether and to what extent a test is useful for a defined purpose, such as meeting a regulatory goal. When applied to toxicity tests for chemicals, validation is impeded by the limited evidence of toxic effects in humans for all chemicals. Measuring test performance can therefore rarely be compared with a certain answer, and validation against current models (being subject to the same disadvantage) is not necessarily appropriate. Limitations come not just from the reliability of the initial test, but because human and environmental systems and interactions are complex, there is also a need to confidently relate an assay concentration to a likely, actual exposure. With many NAMs relying on models to extrapolate effects, the models may be limited by the chemicals and the algorithms that have been used in their building, such as when developing QSAR or in interpretation, as there are potentially multiple ways for an endpoint to occur in an organism. There does, though, appear to be the expectation of advancement, thereby requiring methods to be extensively deliberated on and researched. Thus, the social objective of advancing the science begins to create a barrier to its adoption. Additionally, the literature identifies a lack of or incomplete data-sharing, which limits the transparency and transferability of new approaches. There may be legitimate concerns over the potential for errors, such as with large data sets that are difficult to evaluate and methods may also be limited by the quality of their experimental data or the means of their statistical checks, which need evaluation to determine the confidence with which they may be applied.

Closely linked with validation is the approach of standardisation to harmonise regulated activities. Standards themselves may include documents of rules, guidelines, or characteristics that have been established by consensus and approved by a recognised body. Note that settling on an agreed appropriate standard and reaching a point of closure is itself a social achievement among a group or groups charged with this task. Through standardisation, the increased use of an approach might be expected, particularly in regulatory frameworks, by providing uniformity and recognition of delivering quality, safety, and reliability. Standards use precise, appropriate terminology, and set reporting requirements to improve communication between and understanding by stakeholders. They may describe and define the technical and biological aspects of an approach, the structures and functions of a device, and the materials to be used. Standardised reporting provides clarity as to

what data is to be provided, as with the OECD harmonised templates, and these may be in the form of single, integrated, modular frameworks, aiming to increase familiarity and reduce complexity. The interviewees agreed that standardised reporting frameworks are needed for new technologies, such as omics, and it was acknowledged that there are working groups charged with this.

Harmonisation can assist decision making by enabling the comparison of different substances using the same standard test or comparisons between similar approaches, and such indications of robustness leads to wider acceptance of an approach in demonstrating compliance with regulation and therefore supports the trading of products by opening access to markets. The OECD's principle of the mutual acceptance of data essentially ensures harmonisation through following their test guidelines. We see here then that these technical aspects enable consistency and help to demonstrate reliability as required for validation. However, the extent to which one demands harmonisation and accords advantage to accredited standards provides a strong social setting building on trust, which is very much the product of social processes.

From the interviewee responses, it was widely recognised that the information requirements for chemical safety testing are best (and usually) met by following the Test Guidelines (TG) of the OECD. Interviewees felt that regulators preferred OECD methods because of the scrutiny by expert groups and which inferred global acceptance, providing a level of assurance in their use. As these TGs have been based frequently on animal tests, this leads to a close association such that the information produced is expected to align with that from animal studies. It is also the general perception that EU regulators will not consider 'non-standard' studies. It was felt that robust and reproducible methods allow regulators to trust the data produced saving time-consuming checks on the method employed. It was therefore accepted that the use of non-standard or bespoke studies to evaluate thousands of chemicals would result in an excessive burden for regulators, whereas standardisation provides a pragmatic, predictable, and efficient approach. Additionally, regardless of regulatory expertise with NAMs, there was doubt as to whether regulators even have the authority to consider data from non-standard methods.

"You're dealing with 20 or 1,000 chemicals. You can't have bespoke solutions for each and every chemical... So, standardization is good, just for pragmatic reasons and just for efficiency. And of course, it's good for trade. So, lack of flexibility is a criticism, but also there are reasons for that."

Annex XI of REACH allows for adaptations to the standard information requirements, including the use of WoE. However, due to the issues in reaching consensus across numerous actors and jurisdictions of the OECD and EU, much guidance here consists mainly of principles. This then results in variations in implementation across endpoints, due to each actor giving differential weight to submitted data. While WoE was seen by some as a potential alternative to validation, it was acknowledged that the ideal was validated test methods. Others did not consider WoE to be a valid means of providing alternative information unless the interpretation of what is 'valid' is allowed to depart from TGs.

"There's no test method, guideline, that says this is how you do a weight of evidence assessment for a particular endpoint."

In the EU, the validation of tests is synonymous with the OECD system, although this is considered a slow process, taking years and a lot of resource for a method to be accepted, due to the need for consensus across members. This may be influenced by scientific discussions, personal views, as well as political motivations, demonstrating the socio-technical nature of this barrier and the resulting frustrations. The emphasis on the OECD highlights that the barrier posed by standardisation is closely associated with issues of global harmonisation. Particularly with the OECD mutual acceptance of data (MAD), despite the perception that this is intended to reduce trade barriers amongst OECD members around the world, any resulting standardisation does not extend, in reality, to the mutual acceptance of the resulting decisions. Given the sovereignty of individual jurisdictions to set the acceptable level of harm, this is not

necessarily something that will or should change. Nonetheless, different jurisdictions reaching different conclusions does raise issues for industry and access to markets. While the fixed Defined Approaches (DA), such as that for skin sensitisation, demonstrate a standardised approach within a legal framework, other approaches that still require flexibility and the application of expert judgement (such as Integrated Approaches to Testing and Assessment (IATA)) are therefore likely to struggle to be harmonised, with their use presumably to then remain that of adding to WoE.

"At the end it's a consensus process which involves a lot of stakeholders which are not only regulators, but also scientists. So, it's really requiring a lot of time and a lot of resources, and this is one of the reasons why people get frustrated."

Interviewees acknowledged the importance of confidence in methods, considering their use is to protect human health and the environment. However, some also reported to us their concern about how NAMs are validated. Validating performance in relation to existing animal studies is considered inappropriate and an area of hindrance, due to NAMs being developed for human relevance. Additionally, guidelines incorporating high doses and effects that are not representative of real-world exposures are also considered unsuitable. It was said more than once by interviewees that not all animal studies are validated, and nor would they pass that bar if it was attempted (particularly given the variability of results), with mention of research indicating some animal methods as poor predictors of human health impacts. It was felt that NAMs should be validated in accordance with whether they are fit for their actual purpose and whether they are protective. However, in lieu of using animal data, and with human data often being unavailable (as for skin irritation and sensitisation), it was not clear what information NAMs could be validated against. Clear criteria and guidance are thought to be lacking on validating NAMs in practice, and with many NAMs required to address harmful endpoints, it was noted that if each takes many years to validate under the current system, along with 'toolboxes' of NAMs, the time required is not considered practical. It was also thought that the current system did not reflect the different levels of certainty that could be acceptable for different purposes; for example, methods to be used for prioritising chemicals could be validated to a less rigorous standard than those used in quantitative

assessments. Others felt that any change to validation should still be within the OECD MAD (or similar) domain, to provide confidence for industry that other jurisdictions would accept the results obtained from NAMs.

"The question is, how can you validate these tests? What do you validate it against? … We don't often have the human data to validate them against."

Closely linked to validation is the expectation for standardisation and good practice (such as the OECD's Good Laboratory Practice (GLP)), to provide quality assurance. It was noted, though, that in vitro assays or in silico analysis can be conducted without the same level of oversight and ethical and regulatory burden as that required for animal studies, due to the licencing needed to conduct such tests. The benefit of standardisation as part of validation leads to trust and efficiency, notwithstanding the criticism of the current system as lacking flexibility. Additionally, some interviewees cautioned against too much reliance on standardisation alone, without appreciating the intentions of the specific scheme:

"GLP is a quality system…You can have a perfectly invalid study that is entirely GLP compliant. In fact, you can have scientifically meaningless studies that are GLP compliant, but at least it's a tracking system, and it's quality system."

The lack of funding, support, and incentives (such as academic merit) for validating methods was also identified as being a barrier. Resources in the NAM space was reported as being often directed to developing the methods, dissemination, and training. That validated methods are mainly those developed by industry (aided by their investors) indicates the lack of government funding for this activity, and the minimal involvement of small and medium-sized enterprises (SME) in this space.

4.4 Expertise and Resources

In seeking to emulate the complexities of human physiology and population variability, NAMs face an inevitable degree of complexity. The multi-faceted nature of their approaches is different to that of traditional toxicology procedures, and the need to rely on different forms of NAMs in combination could make coordination of their evaluation challenging. Some companies may undertake their own chemical studies, while others may rely on consultants and contract research organisations (CROs), and expertise and capability in delivering a service based on relaying information from studies using NAMs is required.

It is likely that a 'fusion' of data from approaches such as omics will be required to confidently identify adverse effects of toxicity, and therefore many such experts will need to collaborate to build consensus. Technical barriers here include the lack of knowledge across the scientific community in handling and interpreting new data sets (such as from omics), both in terms of the types of omics (transcriptomics, metabolomics, etc.) but also the steps within these, such as data cleaning, normalisation, contextualisation, statistical validation, data storage, and so on. Such approaches produce, and may depend upon, large datasets, and the programming and interfacing of computational tools for analysis requires still further expertise, although there remains limited experience here.

In addition to the scientific expertise required in conducting studies and analysing results, regulatory substance evaluations and risk assessments typically require judgement based on experience and knowledge to interpret results for or by decision-makers. Such decisions may therefore be influenced by scientific uncertainty outlined above, as well as by personal bias. The need for such judgement and interpretation may not easily accord with ideas of good laboratory practice and other harmonisation requirements. Moreover, regulatory acceptance of evidence from NAMs will depend upon the background and experience of the regulatory community, so that once again social factors begin to interact with the technical pursuit of accommodating new test methods.

The literature identifies that the lack of expertise may be exacerbated because there are seemingly few opportunities for practical 'learning by doing', and apparently limited transferability of technical expertise. However, such common understanding and experience gained in learning from others is important for applying judgement by building the required background (or tacit) knowledge, and therefore the value

from expertise can provide a socio barrier too.

The lack of expertise and resources were equally identified in interviews as being a barrier across regulators (applicable to all jurisdictions), EU member states, and small businesses. Lack of resources both in terms of staffing across disciplines and budgetary constraints were identified as a barrier among regulators, which affects their ability to act within statutory deadlines or to consider substances on a case-by-case basis in all jurisdictions.

"The simple reality is that there's too many chemicals, not enough time, and not enough toxicologists."

Levels of knowledge and skills vary among regulators across the world. A majority of interviewees pointed out that expertise in some disciplines generates technical and complex demands and there is a need for specific knowledge-sets sometimes lacking among regulators. A good illustration is expertise in transcriptomics and metabolomics. Interviewees also emphasised that although science moves quickly (e.g., computational approaches, bioinformatics), regulatory toxicology to some extent does not consider these new approaches and regulators are not comfortable with the new technology. It has been reported that regulators are out of touch, lacking practical expertise, and (as was identified from literature) do not have that 'hands on expertise,' which thus affects their understanding of NAMs. If this is coupled with limited staffing it becomes evident that some regulators cannot keep up with new scientific developments.

"Let me use toxicogenomics or metabolomics as examples. They just technically are really complicated and require quite a high amount of expertise. So, it is just a normal matter of fact that neither the Commission colleagues nor the Member State regulators are really expert in these technologies yet, and that certainly leads to a certain scepticism."

However, some interviewees mentioned that when it comes to knowledge and skills, uptake of NAMs effectively becomes a 'generational piece' whereby younger toxicologists have a better understanding of NAMs, unlike older cohorts. Concerningly though, upon joining the regulatory ranks, those young toxicologists are again becoming removed from the science on NAMs. This becomes even more challenging in countries with complex constitutional structures or regional organisations.

"Do regulators have the bandwidth of regulatory scientists to meet the demand from the number of applications submitted. You can't do new things if you've not got enough people in the agencies. What does their workload look like? You've not got the time to learn NAMs and retrain."

Limited knowledge in interpreting the data provided by NAMs was seen as another barrier. Although regulators should invest in research and training and be at the forefront of research, monetary constraints were identified as a major impediment to gathering new knowledge. Although EU member states were reported to be generally open to NAMs, there are differences with regards to resources and knowledge across jurisdictions when it comes to NAM. The interviewees reported that there is not enough familiarity and knowledge of the new methods in most member states. This is particularly the case with smaller member states which struggle with expertise in certain scientific fields. Certain member states are very open to NAMs, with Germany identified as one together with the UK pre-Brexit (though the UK was identified as continuing with this trend post-Brexit). This is not to say that there is not some level of opposition in several member states.

Finally, understanding capacity and capabilities of small companies was raised by several interviewees as a potential barrier. There is not a clear understanding what their capacities are and to what extent small companies are ready for NAMs. It was pointed out that small companies tend to use consultants, who by default will rely on animal studies as they know those studies will be accepted by regulators and this limits long-term capability of small businesses to deploy NAMs and acts as a disincentive.

"It's easier to pay a lump sum to some consultancy to get the work done for them. I mean, they don't want to invest in trying to develop themselves alternative methods or to implement them in house...for them it would be too costly."

4.5 Regulatory Objectives

Differences in approaches to chemical testing within regulation impacts both substances coming to market and the NAMs used to test them. Variations in regulatory requirements can increase the time it takes to bring a new product onto markets around the world, essentially limiting trade in those products. For industry and for the regulators themselves it becomes difficult or impossible to rely on data generated to support applications for market approval in their jurisdictions, impacting the efficient use of resources, duplicating effort, and increasing the amount of animal testing. It may lead to inconsistent implementation and data requirements across both sectors (such as industrial chemicals, cosmetics, and biocides) and jurisdictions, perhaps leading to WTO challenges. These disparate approaches to acceptable methods can discourage research, innovation, and growth in the face of conflicting requirements or unnecessary duplication. Programmes are in place to address such technical barriers to harmonisation. The OECD is a main actor in harmonisation across REACH through their TG programme, MAD, the development of transcriptomic and metabolomic reporting frameworks and templates, and the GHS.

Regulatory objectives are, though, implemented and experienced differently between jurisdictions, affecting access to markets both now and in the future. This is true in terms of NAMs generally, and additionally between agencies depending on the policy focus and legislative principles for the steps within risk assessment, whether that be a hazard or exposure focus, and we address these individually in the following sections.

4.5.1 Jurisdiction

Some industry interviewees explained that they work across jurisdictions and under many legislative frameworks, from REACH (which other jurisdictions reflect to differing degrees), to agrochemicals and food regulations, and from the Toxic Substances Control Act (TSCA) in the United States, to K-REACH in Korea. Some reported that in practice they conduct a general safety assessment, and later apply the details of specific legislation of jurisdictions around the world. As with the variable expertise of Member State competent authorities, some interviewees felt that some markets are not accepting of NAMs at all, while other countries are moving towards alternative testing methods, including their adoption in screening and prioritisation work. It was, though, cautioned that if one jurisdiction innovates towards NAMs, unless all markets also transition (and this will occur at the pace of the slowest) it is likely that animal testing will continue. This will leave businesses with decisions to make as to what tests they are willing and able to undertake to access markets.

"As soon as you have a global product, then you're gonna have to test it, or you have to come up with a regional variations."

There seemed a common approach of industry generating studies that regulators evaluate, however in some OECD jurisdictions the burden of proof is with the authorities, whereas in the EU the onus is on industry to make decisions and 'convince' the regulator. Additionally, the different roles and responsibilities in agencies within and across countries leads to perceived inconsistent messages and difficulty in determining what may be acceptable, with even different terms used as well as varying approaches to applying the requirements of GHS. From the interviews, the EU institutional framework was depicted as a multi-level and multi stakeholder system, rendering it more difficult to reach a wide consensus with regards to NAMs.

"REACH introduced the burden of proof on industry, and that changes everything; whereas in the EPA and Health Canada the burden of proof is still on the authorities, so they only have to convince themselves. They can use whatever they want, and they do it in a very autocratic fashion."

Different frameworks mean that, for example, ecotoxicological endpoints may be assessed at the regional level in non-EU jurisdictions, and some testing is also conducted by regulators themselves to understand toxicity. In the EU the lack of access to dialogue with some regulatory agencies was considered a barrier, meaning registrants did not have an iterative process to be able to discuss their use of NAMs before submission and evaluation. There is not a consistent approach across different EU agencies, and dialogue is also possible with non-EU regulators, therefore giving industry varying service experience depending on the agency. It was acknowledged that limiting dialogue contributed to assuaging concerns of industry influence and regulatory capture. Open dialogue was considered impractical considering the number of companies under REACH, even if it would provide the opportunity for industry and science to likewise understand the regulator's position.

"It still leads to particular problems, which is not because of us thinking in a different way, but because of the approaches which have been adopted since the beginning of the two agencies."

Typically, chemical legislation across jurisdictions requires the avoidance of animal testing, and policies have elsewhere embraced NAMs. Some non-EU jurisdictions are developing strategic plans to eliminate animal testing, and others are considering options to amend regulations to allow greater flexibility on how to meet the outcomes sought with updated guidance documents to offer greater clarity on the use of NAMs and to 'signal' the acceptability of resultant data. Despite this, some non-EU regulators noted that additional information is still required if such data was initially created to

meet the requirements of another jurisdiction. It was unclear how this would look if all jurisdictions transitioned such that no new data would be available from animal tests, as such data is still relied upon, even though animal tests are not expressly stated.

4.5.2 Principles of Exposure v Hazard that Underpin the Legal Framework on Industrial Chemicals

The modern toxicology of NAMs enables not only the consideration of the assays themselves, but also exposure scenarios and other information that helps construct a safety assessment. The interviewees considered the EU's focus on the hazard aspect of risk assessment to be a significant barrier to the uptake of NAMs. They judged this as being different to the experiences of jurisdictions that take an exposure-based approach to chemical regulation. Such jurisdictions include other OECD countries. It was reported to us that there is a greater acceptance of NAMs in countries taking such an exposure-based approach, with reduced animal testing also attributed to the ability to waive tests to allow a more effective application of the 3Rs. While potentially being more 'a far more difficult way to operate,' considerations of exposure and use were deemed by some to be more logical.

Interviewees noted that NAMs do tend to incorporate exposure information when they are developed, and they also provide upstream information on the events that lead to harmful effects. The regulatory framework, as discussed earlier, is considered rigid and not conducive to accepting such information from NAMs, and while issues pertain in determining doses in exposure-based systems, the ability to take a case-by-case approach was also considered a benefit when applying NAMs.

While the REACH annexes do list hazard-based endpoints, the requirements to meet these depend on tonnage bands, which are considered to be a surrogate for exposure. Although the EU could be considered as to some extent adopting an exposure-based approach on this basis, its application lacks the nuance of true exposure considerations. The widely perceived EU starting point of classification by hazard was linked by interviewees to the emphasis of the broad chemical and use domain of REACH allied to the closely associated CLP legislation and the horizontal system of chemical regulation. With EU legislative intentions being to enable joint submissions

of study data (with the application of exposure information later in the risk assessment), any change to a hazard-first approach would impact downstream regulations despite their different exposures, and despite the different uses by registrants even within REACH. Such information on substance use is currently considered to be lacking within REACH dossiers, and any amendment to the legislative framework would need to consider implications for the implementation of other legislation. While use is an inherent consideration for some regulations, the different approaches across regulations was considered to impact the acceptance of NAMs.

"I would rather tend to agree that ECHA is a little bit reluctant to use exposure-based waiving, but maybe that is again due to the fact that the legislation that REACH requires simply requests certain information, also independent on whether there's exposure or not. The exposure-based waiving of REACH has relatively limited possibilities."

Interviewees also identified that the differing hazard and risk approaches also resulted in variation to the implementation of the UN's Globally Harmonised System of Classification and Labelling Chemicals (GHS). It was perceived that risk-based jurisdictions use GHS to communicate hazard information down supply chains, rather than using this classification system to regulate chemicals. Instead, in the EU, 'decision-making criteria are based solely on the presence of a particular type of hazard,' such as carcinogenicity leading to the CMR requirements of REACH. While such dossiers do consider exposure later, the starting point is still the identification of the intrinsic hazard. Regulators acknowledged that the CLP regulation is restrictive in the EU, and this also increases the reliance on animal studies. With such close ties to CLP classification in the EU, it is considered that any new system will be expected to identify those substances that are of the highest concern, and which need to be regulated. In contrast, other jurisdictions do not have such policies to identify, for example, CMR substances, as being priorities, and instead consider harmful endpoints more broadly, for example, including neurotoxicity.

The EU's hazard-based approach was considered to limit the uptake of NAMs and led

to greater animal testing than exposure-based systems. The mechanistic information provided by NAMs is not considered a comfortable fit with REACH's endpoint prescriptive and test-driven framework, and the expectation for the broad application of a NAM is not realistic considering that NAMs tended to be more developed for more specific applications. While it was recognised that the legislation claimed animal testing should be a last resort, how this last resort is therefore defined and applied was considered to be unclear in the current application of the regulatory framework. Decision-making processes, exposure information, and impacts on legislative networks would all need to be addressed for a transition to a NAM-based system.

4.6 Social Perceptions

From scholarship, what we termed as public involvement was identified as a barrier to the uptake of NAMs because controversies and mistakes have led to erosion of trust in government and industry. A wider public awareness campaign about NAMs may be unlikely to succeed due to media soundbites not being compatible with the technical explanatory responses that have tended to accompany NAMs. Conversely public participation can add new perspectives, strengthen processes, and build acceptability, trust, and confidence in decisions. Groups have formed to lobby the government on glyphosate and neonicotinoids, petitions are circulated (such as the recent European Citizens Initiative (ECI) on animal testing in cosmetics, garnering nearly 1.5 million signatures), and the public have engaged in discussions on animal testing in COVID-19 vaccinations. So, harnessed appropriately, public involvement may induce movement towards uptake, and effective messages could be key to ensuring public interpretation of any change towards NAMs is not perceived negatively.

Wider societal perceptions and understanding of NAMs were reported as an important barrier to NAMs by a large majority of interviewees. As expected, a significant part of the discussion revolved around citizens and citizens' associations and their perceptions of NAMs. Some interviewees pointed out that an average person would not be familiar with NAMs and thus it is difficult to argue that their views could represent a barrier, though some of the EU policy makers reported occasional communications from citizens regarding NAMs. It was also reported that NAMs do not feature in primary and secondary education curriculum and young people are not aware of these new methods but solely aware of animal testing. However, it was said that citizens are often conservative and not open to change which is an important factor to consider. A small minority of interviewees did not believe that citizens' perceptions could be a barrier.

"Certainly, there are a lot of associations and NGOs that are really keyed into this, but I wouldn't say there's general understanding or dare I say it interest? But towards you know, ending animal testing, the general population, I don't think it's on their radar… I don't think they make the link that we're looking at animal tests."

Still, citizens are becoming increasingly aware and supportive of the ban on animal testing applicable to cosmetics. However, citizens believe that with regards to cosmetics non-animal testing, this is fully applicable and do not appreciate that there are still chemicals that are subject to animal testing even though they are used in cosmetics. It was also reported in the interviews that animal testing is widely used and the amount of animal testing in general is growing rather than reducing in the EU. For example, when it comes to reproductive toxicity, animal testing remains a requirement.

As was described above, the views of citizens' associations were identified as an important barrier to NAMs. NGOs have the potential to voice concerns in a more organised way and underpinned by science. Interviewees reported seeing opposing camps between NGOs supporting and advocating a wider ban on animal testing which would in time apply to other chemical regulation such as REACH and NGOs with strong concerns about levels of safety if NAMs become more widely used. These concerns are very real, and it was reported by interviewees that relevant EU policy departments are receiving correspondence from NGOs and to a smaller extent from individual citizens voicing their concerns about levels of safety if animal testing is reduced. This has a knock-on effect where the policy maker needs to reach a consensus on NAMs, and this may impact the longer-term decisions on NAMs. As articulated by interviewees, in this environment it ultimately becomes a political decision on what would be direction of travel for NAMs.

Although citizens featured as a main category whose views may have possible negative impact on the uptake of NAMs, interviewees emphasised the mindsets of other categories of stakeholders. Some industry representatives pointed out that changing the mindset is equally applicable to certain companies which do not want to focus on NAMs. In those companies, staff are not trained or expected to deploy

NAMs, and this requires a concerted effort for people to have a better understanding of NAMs followed by internal upskilling and allocation of funding to that end.

"Because why would we spend money generating data that we think is not going to be accepted?"

Social perceptions of regulators were discussed within the wider theme of social barriers. Some regulators and policy makers, both in the EU and those in wider jurisdictions, agreed that mindset of regulators to some extent does represent a barrier. It would be important to change how NAMs are perceived by focusing on new opportunities they can offer. Many interviewees pointed out that this mindset will change with incoming new generations of regulators who are more familiar with NAMs. Other interviewees spoke about thinking differently about health risks which will predominantly involve future discussions with risk managers. Finally, in addressing this issue there is a need to reach out to the broader scientific community beyond the EU, regulators in other jurisdictions and academia.

"Do we need to change the mindset or how we express science? It seems to be that we need to express science for those who are regulators but do not have scientific background."

4.7 Scientific Development

With the shift from in vivo observations to a mechanistic understanding of toxicological effects still developing, knowledge about some core toxicity mechanisms are also still being uncovered. Some endpoints and pathways are yet to be fully described, and thus linking specific molecular changes observed to such apical outcomes is beset by uncertainty. While mechanistic knowledge is increasing, the understanding of variables influencing toxicity is also incomplete, and might be lacking in knowledge of how substances are metabolised over time and how responses vary across a population. Consensus is also required on how to link in vitro

concentrations with in vivo exposures, and an understanding of the complex interactions between cells, tissues and organs is still developing. This means there are technical barriers from both the limited data such required as to develop new models, and that the range of models currently available is not comprehensive.

In the meantime, gaps in data may be addressed by applying judgment, and this may lead to differences in interpretation of data. While adverse outcome pathways (AOPs) have the potential to visualise how molecular observations impact human health and the environment, these, including, for example, the omics technologies to provide such data, are still developing, as are the IATA and DA within which NAMs can sit.

Chemical regulation depends upon science with a fair expectation that human health and environmental safety assessments will have a basis of sound science. This assists the authorities in delivering their protective mandate while producing regulatory decisions that are defensible. However, the type of science provided by NAMs and that which is being presented to regulators has changed from that imparted by animal tests. Instead, NAMs seek to elucidate factors to explain a harmful effect (through, for example, identifying mechanisms of action), and to also determine other endpoints.

"[NAMs] try to elucidate a little better how and why this particular chemical is exhibiting a hazardous effect... also trying to understand better what is the mechanism of action so that we can explain the toxicity in those terms"

The interviewees were split on whether the science behind NAMs themselves was a barrier to their uptake. Across the categories of interviewees, some felt science is ready and it is the regulatory context that is lacking, while others believe that science is not yet ready. The latter view could largely be attributed to the expectation of NAMs to be able to reliably address every endpoint specifically, in particular the complex endpoints. The difference, therefore, appeared to be in the role that science is expected to play in regulatory risk assessment and management, where those who felt the science is ready are not expecting it to provide exactness and knowledge of every mechanism of biology before it can be applied, but rather they believed science is already sufficient to determine whether a chemical presents a risk and that knowledge could prove adequate for regulatory application.

From those advocating that there did not need to be complete human biology replication, interviewees reported that while this is an interesting research area, it is not required for regulatory risk management. The concept of NAMs providing different information to that of animal tests therefore extended the type of application that NAMs allowed, such as for regulators to triage substances. This would not require NAMs to define specific hazard classifications for a substance, but rather allow them to be used to rapidly generate information that identifies irritation and acute effects to provide a direction towards which substances may cause some harm. There was some trepidation from other interviewees on the application of NAMs for prioritisation, as there remains the legal aspect of regulation which carries with it more caution and seeks more secure scientific grounds.

"First, that we need to understand what the method delivers, what is the domain of applicability of a new method. We certainly also need, to some extent, a mentality change... A new method we always compared with what we have. But maybe that is not really what we should do. We should rather see what we want to achieve, which is protection of human health and the environment."

Those interviewees who felt the science is not ready considered that the combination of NAMs to demonstrate meaningful results is lacking, along with knowledge of 'repair mechanisms and feedback loops,' as well as aspects such as absorption. It was apparent that there are many positives and negatives to the current state of play of NAMs; while NAMs are considered promising for mechanistic understanding, uncovering complexities such as multi-factorial disease and neuro development, epidemiology, and human relevance, it was considered that AOPs require continued development and to be assessed for their reliability. Some interviewees also felt the predictive element is missing from NAM submissions, with hypotheses needed on why, for example, biological fingerprints are relevant for predicting when a certain endpoint is absent. The substance applicability domain of NAMs was also considered to require development as it was considered that this tends to be defined against a narrow range of test chemicals, and accepted methods for polymers and chemicals with unknown or variable compositions (UVCBs) are lacking. Where NAMs are not available for complex endpoints, however, it was said that adaptations such as

grouping and read across are options to avoid animal testing. While NAMs have been accepted for endpoints such as irritation and sensitisation, and this is encouraging, NAMs are currently not available to cover the 'grand spectrum' that makes up, for example, mutagenicity or genotoxicity, and the same extent of human data is lacking for these.

How NAM development is organised was also identified as a barrier by some interviewees, with concerns of potential duplication of effort and a lack of research coordination of programs and assay development, which was said by interviewees to be akin to having ingredients all over the place. Interviewees considered the transition to NAMs to be slow, acknowledging that innovation to date has been where there is a 'relatively easy endpoint' with the ability to address all mechanisms of, for example, organism development, not considered possible using cell systems alone. The need for expert judgment was also considered an issue, with a lack of structured and objective assessments.

The term 'NAMs' was also considered misleading, as science is always progressing, so it was suggested that it may be more acceptable to consider alternatives to animal testing as an update to existing toxicological science, with improved accuracy and being more comprehensive, rather than something new and different. NAMs also suffered from the perception that their use is due to being 'easy and cheap' rather than also being an improvement by utilising science that was not previously available and making properties detectable. The language of science more generally was also considered problematic, in its reference to 'likelihoods' and 'probabilities' thereby creating the feeling of uncertainty for decision-makers. An interviewee considered this analogous to climate change, where the lack of categorical science leads to doubts, which is not considered desirable for regulators from a legal perspective. While it was acknowledged that there should be honesty around the limitations of science, transparency and care with the presentation and explanation of data could help overcome this, to build the confidence of regulators in the science, even if they don't fully understand every NAM. The relevance of NAM data in relation to regulations and to traditional toxicology data is also not considered to be well understood.

"I struggle to think of any other part of society where the law is forcing us to use technology from the fifties, ignoring where things have gone."

5. SUMMARY OF FINDINGS

From the empirical research undertaken, we offer some broad conclusions and key points about the socio-technical barriers to the uptake of NAMs to generate further discussion. Our findings show that this is not a simple case of NAMs not being put into use, but rather it is a nuanced debate about what NAMs have to offer, especially in relation to the regulation of chemical risk.

Our empirical research has uncovered nine main themes that can be used to describe the barriers to the uptake of NAMs. These are:

- Views of regulatory science and the legislative framework, encompassing regulatory culture, which includes acceptance; familiarity and confidence in animal studies; and the lack of trust between actors
- Regulatory objectives, comprising jurisdiction and the principles of exposure versus hazard that underpin the legal framework on industrial chemicals
- Validation and standardisation
- Expertise and resources
- Social perceptions
- Scientific development

The research highlights the interconnectedness between different socio-technical barriers; for example, while legislation is identified as a technical barrier (being largely processed based), its interpretation and associated policy objectives exhibit social dimensions. Figure 1 seeks to illustrate some of the main connections between the themes identified and previously described. This is not an exhaustive diagram, but instead serves to demonstrate the importance of taking a holistic approach when addressing these barriers.

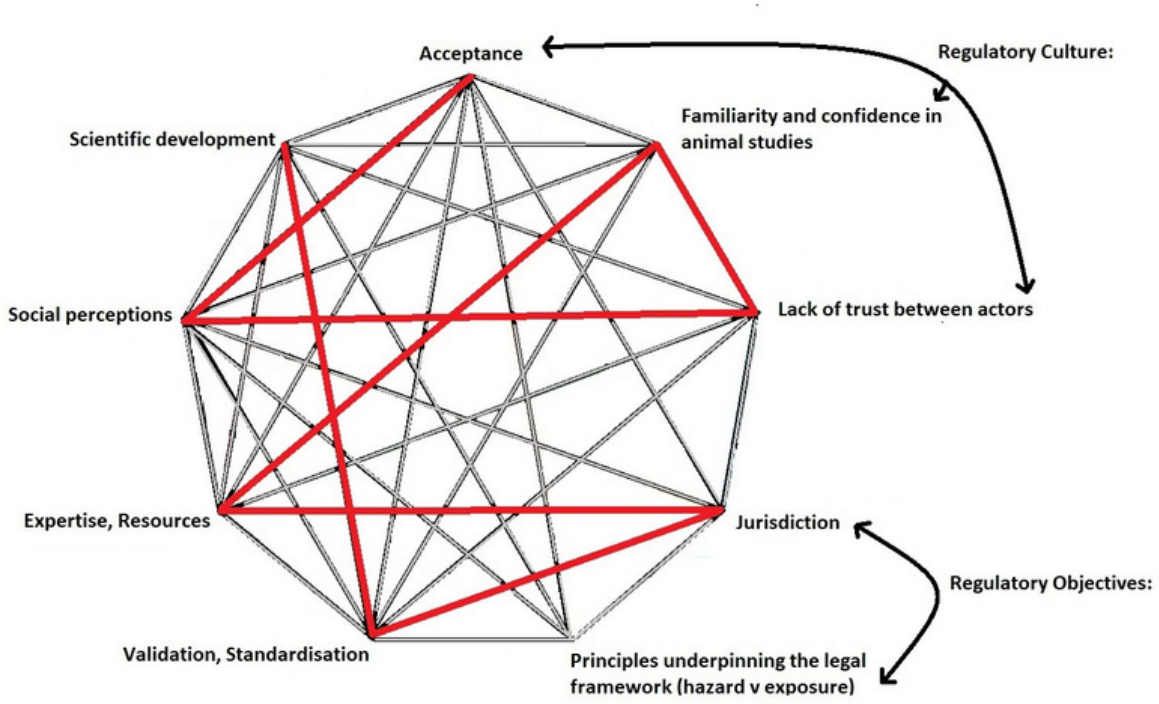


Figure 1: Inspired by the representation of 'repertoires' by Leonelli & Ankeny, the grey lines represent the (not exhaustive) connections between the barriers that were identified from the empirical study. The red lines depict an example narrative, described below.

From the example in Figure 1, we can describe that:

- Regulatory acceptance is affected by policy and political direction, which is influenced by social perceptions.
- These social perceptions are developed from NGO activities, which are, in some cases, associated with perpetuating the mistrust in industry and the narrative that NAMs lower safety standards.
- A lack of trust in industry, who provide data on their substances, can be the result of a lack of familiarity with the new methods that industry use, and so the familiarity (and therefore confidence) instead remains with animal testing.
- Building familiarity requires expertise and resources to develop understanding through, for example, 'learning by doing' with NAMs.
- Different decisions on resourcing and the development of expertise may be made by different jurisdictions, depending on their preferences and pressures.
- Jurisdictions also determine their own acceptance criteria for what makes a method 'valid' or acceptable, which in the case of OECD MAD will require consensus.
- Decision-making and consensus-building towards NAMs is aided by scientific development and its effective communication.

Being interconnected, the narrative can continue to unfold and the above serves only as an example.

From the empirical research undertaken, we offer some broad conclusions and key points about the socio-technical barriers to the uptake of NAMs to generate further discussion. Our findings show that this is not a simple case of NAMs not being put into use, but rather it is a nuanced debate about what NAMs have to offer, especially in relation to the regulation of chemical risk.

Policy recommendations based on these findings will be explored in a follow-up report. Here we indicate preliminary directions for discussion.

Among the findings are the following:

Regulatory acceptance is a key barrier. Despite statements from regulators expressing willingness to consider wider evidence and supporting 3Rs initiatives, regulatory acceptance was identified as a key barrier to uptake of NAMs. In this regard:

- There is a general acknowledgement that NAMs need to be underpinned by robust science, reliable (reproducible as a method), and regulatorily relevant. At the same time, it was accepted that what might be seen as constituting a sufficient level of confidence depends on a wider political appetite for risk or risk avoidance, which shapes regulatory practice.
- The regulator's view, culture, and settled practice also has an impact on the regulatory acceptance of NAMs. In this sense social barriers exist within regulatory structures. Inertia and conservatism are present among some regulators, driven by understandable concerns to avoid error and ensure safety.
- Regulatory acceptance is highly dependent on the experience and expertise of individual regulators, which is often missing due to the complexity of NAMs, the availability of qualified staff, and the type of (non-laboratory based) meta regulation typical in European regulatory frameworks.

Numerous vicious circles work against the uptake of NAMs. The lack of clarity, communication, and trust among actors drives several "vicious circles" with respect to the regulatory deployment of NAMs. Because industry cannot be confident that regulators will accept NAMs data, NAMs data which may be available are not included in dossiers submitted to regulatory agencies. This omission reduces the regulator's exposure to NAMs data, reinforcing their reluctance, while making it harder for industry to make a business case for investment in NAMs' development. Similarly, lack of regulatory clarity with respect to the interpretation of standards and requirements for NAMs data leaves registrants and the regulated sector without structure or guidance in directions for innovation. This lack of structured dialogue further widens gaps in regulators' knowledge of NAMs' capabilities.

Social barriers are significant. Many barriers are social (about the behaviours of actors in the system) rather than technical (the structures of and processes within the system), though different barriers explored in the report are closely interrelated, suggesting that these need to be considered holistically.

NAMs are already playing a role internally in industry. Industry is increasingly making use of NAMs for internal decision-making, despite the inability to utilise these data for regulatory approval.

NAMs are appearing in non-EU regulatory processes. In other jurisdictions with different chemical risk assessment processes, non-EU regulators undertook toxicity testing themselves, and reported using NAMs in their work, typically read-across to avoid animal testing, though largely not yet involving mode of action. Improvements may be achieved by reassessing the hazard versus exposure debate.

Campaigns against animal testing are perceived as competing with safety standards. Interviewees reported a stark lack of trust among NGOs and industry, with policy makers having to negotiate different lobby groups campaigning on chemical safety on one hand and animal testing on the other. These interests are perceived to be in opposition - i.e., eliminating animal testing is seen to lead to a lowering of safety standards.

There is little consensus on scientific readiness. Many different views were articulated as to whether the maturity of the science behind NAMs constituted a barrier to their uptake. Rifts were seen not only between industry and regulators but also among different regulators and policy makers as to whether the science is sufficiently robust to accommodate the regulatory uptake of NAMs. There was an accompanying debate about whether NAMs need to be predictive or protective, and what either decision would mean in practice.

There is a clear need to consider the value proposition of NAMs. The ethical, scientific, legal, and particularly the economic case for NAMs still needs to be made, to signal the imperatives and provide incentives to transition to NAMs. Additionally, greater political direction and steer from EU institutions is needed to build confidence.

Potential Policy Directions:

We offer the following potential policy directions, noting that this report only deals with barriers, and policy recommendations based on these findings will be explored in a forthcoming report.

- **NAMs implementation may begin with better leverage of adaptations.** There is a clear need to consider the value proposition of NAMs within different stages or components of the chemical safety testing process, as currently the full replacement of animal testing is not possible — suggesting a tiered approach to the introduction of NAMs into regulatory frameworks that could begin with grouping.

- **Soft law may hold greater potential for NAMs implementation than hard law.** Interviewees expressed a view that law may stifle development, being too prescriptive and too narrow in its interpretation. Under REACH's Annex XI adaptations, NAMs derived from in vitro and QSAR methods are specified, and grouping/read-across and weight of evidence allow some potential for use of NAMs. However, regulatory acceptance is considered as low, and greater change to soft law (guidance and procedures) might be required to reduce reliance on animal testing.

- **Exploring new modes of validation may advance NAMs acceptance**. There was a general agreement that validation processes are slow, taking time and considerable resources for a method to be accepted, due to the need for absolute consensus across expert panel members. The stakeholders recognised the need for global acceptance, but also raised possibilities of exploring alternative modes of validation. Notably, there are arguments against requiring NAMs to be validated against traditional animal testing methods, as these methods themselves have not been validated and may not be the most precise methods for assessing human health risk.

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