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Review

New approach methodologies (NAMs): identifying and overcoming hurdles to accelerated adoption

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New approach methodologies (NAMs) can deliver improved chemical safety assessment through the provision of more protective and/or relevant models that have a reduced reliance on animals. Despite the widely acknowledged benefits offered by NAMs, there continue to be barriers that prevent or limit their application for decision-making in chemical safety assessment. These include barriers related to real and perceived scientific, technical, legislative and economic issues, as well as cultural and societal obstacles that may relate to inertia, familiarity, and comfort with established methods, and *perceptions* around regulatory expectations and acceptance. This article focuses on chemical safety science, exposure, hazard, and risk assessment, and explores the nature of these barriers and how they can be overcome to drive the wider exploitation and acceptance of NAMs. Short-, mid- and longer-term goals are outlined that embrace the opportunities provided by NAMs to deliver improved protection of human health and environmental security as part of a new paradigm that incorporates exposure science and a culture that promotes the use of protective toxicological risk assessments.

Key words: chemical safety assessment; exposure science; new approach methodologies (NAMs); risk assessment; 3Rs.

Introduction

New approach methodologies (NAMs) can be defined as any *in vitro*, *in chemico* or computational (*in silico*) method that when used alone, or in concert with others, enables improved chemical safety assessment through more protective and/or relevant models and as a result, contributes to the replacement of animals. While animals are still currently heavily relied on or required by law in some sectors for conducting safety assessments, the 3Rs (replacement, reduction, and refinement of animals in research) are being increasingly welcomed by the scientific community, and not only for ethical reasons. Embracing NAMs, in addition to addressing important animal welfare concerns, has the potential to deliver significant scientific advances and/or in some cases provide economic benefits. These include the provision of more relevant methodologies and the use of tools that represent more species-relevant biology, such as those using cells or tissues from more appropriate species (for example humans or relevant environmental species) to model pertinent biological pathways and elucidate important mechanisms of action, which when complemented with modelling and systems biology approaches could be used to reflect the *in vivo* complexities.

A NAM-based approach for systemic toxicity using advances in our understanding of biology and subsequent rapid development in tools was first proposed in 2007 by the US National Academy of Science: *Toxicity Testing in the 21st Century*.[1] The vision did not aim to replace animal toxicity tests as such, but to approach toxicological safety assessment in a new way, through consideration of exposure and mechanistic information, using a range of *in vitro* and computational models. Since the publication of that report, significant scientific progress has been made in harnessing NAMs to move towards a new testing paradigm based firmly on relevant biology. The term Next Generation Risk Assessment (NGRA) has subsequently emerged, defined as an exposure-led, hypothesis-driven approach to risk assessment that integrates *in silico*, *in chemico* and *in vitro* approaches, where NGRA is the overall objective, and NAMs are the tools used to achieve it.[2] A fundamental premise of NAMs-based NGRA is that safety assessments should be *protective* for those exposed to the chemical, but not necessarily predictive of the specific adverse effects that may be seen at irrelevantly high doses. However, it should be noted that such a protective (or risk-based) approach may not suit current hazard-based regulations, or those related to classification and labelling such as the EU CLP Regulation No. 1272/2008[3] or the UN Globally Harmonised System (GHS),[4] where regulatory paradigms rely on the ability to identify and characterise many different types of toxicological hazard using internationally harmonised guideline

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methods for each (for example, the chemical is an observed mutagen, target organ toxicant, a skin sensitiser, a carcinogen or is toxic to the reproductive system or foetus). The method associated with each hazard endpoint usually has an Organisation for Economic Co-operation and Development (OECD), or equivalent, guideline to assure laboratories are correctly identifying hazards in the same way globally and most of these guidelines currently rely on animal data. Transition to a more *risk-based* approach that embraces NAMs and places less emphasis solely on hazard identification will require a robust context-specific exposure assessment. This will necessitate greater investment into exposure sciences, also highlighted as part of the US Strategy in their publication "*A Vision for Exposure Science in the 21st Century*".[5] In recent years, there has been a significant acceleration in the development of new technical approaches that have the potential to contribute to NAMs-based safety assessments. These collectively encompass a broad spectrum of technical and regulatory readiness, including: (i) computational, modelling and machine learning tools, (ii) read-across and grouping approaches, (iii) high-throughput and high-content data sources including multiple omics-based test systems, (iv) *ex vivo* and *in vitro* assays of varying complexity from 2D cultures to tissues and microphysiological organ-on-a-chip systems, (v) *in vitro* stress and bioactivity assay panels, and (vi) human *in vitro* to *in vivo* extrapolation approaches.

Although the development of new approaches and technologies has been rapid, the key challenge is how to keep pace with and increase confidence in these novel methods to translate this new science into practical use, particularly within a regulatory context for decision-making to ensure safety. Initially, in some use cases, NAMs may be employed alongside traditional methods to address specific questions, or as part of a health protective NGRA for a given exposure scenario, rather than to predict or replicate changes that might occur in the whole organism. However, despite the widely acknowledged benefits offered by NAMs, there continue to be barriers that prevent or limit their application for decision-making. These include barriers related to *perceived* scientific and technical issues, as well as those driven by concerns that data derived from studies using NAMs will not find acceptance by regulatory agencies, sponsors, or the wider scientific community and a lack of experience or understanding of NAMs.

This article focuses on chemical safety science, exposure, hazard, and risk assessment, and explores the nature of the barriers that may be preventing the more widespread adoption of NAMs among the safety science communities and examines how these barriers can be overcome to drive their wider exploitation and acceptance.

Technical and scientific barriers

Over the past 20 years, significant progress has been made in the adoption of NAMs for assessing the safety of chemicals. Successful use of NAMs has already been achieved for some specific local defined toxicity endpoints driven by chemical reactivity or physicochemical properties (for example, for skin corrosion/irritation, serious eye damage/eye irritation and skin sensitisation and skin absorption). For some of these toxicity assessments, the development of Defined Approaches (DAs) - specific combinations of data sources (e.g. *in silico*, *in chemico*, and/or *in vitro* data) with fixed data interpretation procedures, has facilitated the use of *in vitro* methods or NAMs-based approaches within a regulatory context. DAs for serious eye damage and eye irritation, and for skin sensitisation, have been outlined within their own OECD test guidelines (TGs) (for example, OECD TG 467,[6] 497[7]) and are now widely used and referred to in many regulations worldwide. Here, the historical animal tests addressed very specific chemically induced adverse health effects seen in humans (corrosion, irritation or skin sensitisation) and the data from the animal tests were subsequently used to determine whether the NAMs approaches were fit-for-purpose[8–11]). Where human data on these effects were also available (for example, for skin sensitization[7]) it showed that the combination of human-based *in vitro* approaches had a similar performance to the traditionally used Local Lymph Node Assay (LLNA) performed in mice, but a combination of the three *in vitro* approaches outperformed the LLNA in terms of specificity. These data allowed the individual assays to be validated for the purposes of hazard identification. In another example, a multiple NAM testing strategy was performed for the crop protection products Captan and Folpet[12] for a total of 18 *in vitro* studies, including eye and skin irritation and skin sensitisation assays compliant with OECD TGs, as well as the GARD®skin skin sensitisation and rat EpiAirway™ acute airway toxicity assays for which there are currently no formal guideline tests available. The NAM package appropriately identified Captan and Folpet as contact irritants, demonstrating that a suitable risk assessment could be performed with available NAM tests, broadly in line with risk assessments conducted using existing mammalian test data.

Benchmarking of NAMs against animal data

It is important to emphasise that NAMs do not aim to recapitulate the animal test without the animal, but to provide more relevant information on a chemical to allow exposure-based safety assessment. The aim is to improve the overall approach to safety assessment rather than to find direct replacements for the animal test, and it is important to note that the successes described in the above examples relied upon the use of combinations of *in vitro* tests to develop NAM-based strategies to allow safety decisions to be made. A one-to-one approach would not be scientifically achievable other than for very specific or acute adverse health effects, for example skin sensitisation, where individual NAMs have been validated for the purpose of hazard identification, and where NAM-based approaches for measurement of potency and risk assessment are being developed. This particularly applies to the identification of more complex toxicities resulting from systemic exposure (such as carcinogenicity, developmental and reproductive toxicity) or chronic/repeat dose effects subject to multiple mechanisms.

It is important to highlight that NAMs may never be wholly representative of every aspect of organism level adverse response, irrespective of the cell type choice and the complexity of integrated NAMs. Similarly, NAMs are unlikely to mimic every aspect of human-relevant acute or chronic exposure, even in a complex physiologically-based model. Essentially, NAMs are a human-focused and different way to assess human hazard and risk and are likely to be conceptually different from the tradition of assessing toxicity in whole animals as a basis for human safety.

Furthermore, it should also be considered whether it is appropriate to benchmark NAMs against methods in animals. It has been well documented that rodents, which are commonly used as a test species in many sectors as part of safety assessment, have a poor true positive human toxicity predictivity rate of only 40%–65%[13–19]), yet they are frequently viewed as the "gold standard" and a relevant performance standard to be met by NAMs to ensure similar or higher levels of protection. For local toxicity, the validation of non-animal methods has traditionally been reliant on correlation to the results in animal studies and used together with uncertainty factors to make a safety decision. However, for

complex endpoints and systemic toxicity, it is clear that another way is needed, and whilst NAM-based points of departure are being used alongside physiologically based kinetic estimates of systemic exposures more widely and proposed for more inclusion in regulatory decision-making (for example, Health Canada[20]), there is still much work to be done to demonstrate the robustness of a decision-making process that does not include the use of experimental animals as surrogates for other species. For risk-based approaches, this will include necessary advances in exposure science to ensure robust exposure assessments can be made, as well as confidence building for assessments of *ab initio* chemicals where there is no prior information on which to build a testing strategy. Whilst it might be useful to understand *how* results of animal and non-animal methods compare with one another, it is important to appreciate that the animal models are not necessarily superior and have their own limitations.[21]

Relevance of NAMs

An important potential benefit of NAMs is greater accuracy and relevance achieved by using cells or tissues of the species for which the safety assessment is being made, rather than using animals as surrogates and extrapolating the results to another species or population. Despite this, there are some concerns that to gain a complete picture of how systems interact, suitable (whole) animal models are still required, particularly for more complex endpoints. However, while a benefit of animal studies may be that they can facilitate detection of unexpected toxicity, when unanticipated responses occur it can be difficult to determine their relevance for humans without mechanistic understanding, as the animal models themselves do not always provide relevant mechanistic information. However, such information *can* be elucidated through NAMs, and it may also be possible to address aspects of organ and tissue complexity and/or the dynamics of an intact organism by integrating multiple types of NAM data computationally, such as integrating biokinetics (physiologically based kinetics; PBK) with results from bioactivity assays to mimic dynamics in a whole animal or as part of an adverse outcome pathway (AOP).[22,23] As is true for animal models, it will not be possible for a single NAM to predict all possible hazards at once, or for a combination of NAMs to cover the whole toxicological space. This is not the ambition of the new approach. Linking NAMs to key events or key event relationships within AOPs can help understand the relevance of the data being generated, through a biologically relevant mechanism/mode of action that has been linked to the cause of an ultimate adverse outcome.[24] However, since it is unrealistic to create AOP networks that can cover all possible adverse effects, it may be more appropriate to use AOPs in combination with other models and artificial intelligence (AI) approaches to create virtual human systems for example, to test the effects of chemicals together with some information on mechanisms. The potential value of AI within toxicology, including its use to extract, integrate and apply relevant information from results generated from NAMs, including AOPs, has been explored in recent publications.[25,26] These sorts of approaches could help ensure the NAMs and resulting data are valid to use for decision-making within a *given context*.

Despite rapid advances in biotechnology, systems biology and predictive methods, there are still significant limitations in our understanding of how chemicals interact with the body and the molecular pathways that can lead to adverse health effects at defined exposure doses, particularly for repeated dose/systemic exposures. Further work is needed to understand the areas where NGRA may indeed be protective for human safety versus areas where additional tools, approaches and knowledge may be needed. There is ongoing debate around the successful application of NAMs and the need for these to be fit-for-purpose; protective but not necessarily predictive of the toxicity that may be seen at irrelevantly high doses or unrealistic exposure scenarios.[27] With this in mind, in addition to exposure considerations such as the dose, frequency, duration and route, there are other factors that potentially impact on the generation of adverse health effects, including for instance development stage and age, diurnal rhythms, co-exposures and comorbidities that need to be taken in to account when making safety decisions. It is highly likely that when thinking about more complex aspects of systemic toxicity additional tools and approaches will be needed in an NGRA toolbox.[28]

Personal, cultural and societal barriers

In some instances, the move away from safety assessments based on well-established animal methods to safety assessments based on NAMs will not only require significant technical and/or practical changes but may also represent significant cultural or societal change; a mindset shift. Despite the widely recognised potential advantages of NAMs from a scientific perspective, a change from the *status quo* can prove uncomfortable: non-technical hurdles include inertia, familiarity, and comfort with established methods, perceptions around what will be expected and accepted by regulatory authorities, uncertainty about how new approaches can be used and applied, as well as concerns around loss of data continuity (i.e. the ability to directly compare new results with previously generated data).

Comfort with established methods

Reliance upon, and comfort with, established methods is not a trivial issue. In biomedical research and safety assessment there is a long history of experimental animal use[29] where strong competence and familiarity in the conduct and interpretation of methods has developed over many years. These have accumulated a wealth of historical data, knowledge, and experience against which results can be compared and interpreted. A reluctance to move away from methods that have provided the bedrock of a successful research laboratory or safety assessment facility is understandable as it has underpinned and gained public confidence in regulatory and ministerial decision-making for decades. Alongside this, there may be apprehension around generating new types of data that could potentially confound previous results. Therefore, a change to NAMs from animal methods should be facilitated through the demonstration of the clear financial, productivity and/or scientific benefits, including more accurate and relevant data, and/or improved protection. Accompanying regulatory imperatives/policy changes that address societal pressures/-expectations, particularly towards supporting economic growth, innovation, and reduced animal use are also required.

Regulatory acceptance of NAM data

Although there is a welcome and increasing appetite by many regulatory authorities to embrace the advantages offered by NAMs, confidence in the reliability of NAMs for safety assessments within a regulatory context is growing very slowly. Positive initiatives from regulatory agencies include the US EPA, Health Canada, UK Food Standards Agency, the European Commission, European Food Safety Authority (EFSA), the European Medicines Agency and European Chemicals Agency (ECHA), who have all held recent NAMs workshops and/or incorporated NAMs in to their current

and future workplans or roadmaps.[30–33] NAMs-based risk assessments have also been integrated into international guidelines for safety assessments of cosmetic ingredients,[34] where legislative bans on animal testing are in place for cosmetics in some regions. These include a new section on NAMs in the Scientific Committee on Consumer Safety (SCCS) 12th Notes of Guidance,[35] which covers the use of PBK approaches. There are also well-documented examples of NAMs used in individual risk assessments both within the consumer goods industry (e.g. coumarin[36]; phenoxyethanol[37]; benzophenone-4[38]) and within other sectors (e.g. chlorothalonil,[39] Captan and Folpet[12,40]).

However, there are inconsistencies and ambiguities around the acceptance of NAMs across geographies and sectors. The conservatism seen in some regions may reflect risk aversion from the registering company due to a *perceived* regulatory expectation for animal data and uncertainty around the regulatory acceptability of NAMs. This creates a "chicken and egg" conundrum where, because NAM approaches are not submitted, regulatory agencies do not have the opportunity to review and become familiar with-/build confidence in new approaches, and without the precedent and encouragement to apply a new approach registrants may not conduct or submit them, and so opportunities to use NAMs are not taken up. Similarly, a lack of regulatory demand may also reduce or influence contract research organisation (CRO) and/or industry investment to develop and supply new approaches. Although a certain level of conservatism is needed in terms of assuring consumer and public confidence, it is important to explore how sufficient protection can also be achieved through other new methods that are based on the latest technological advances, rather than stagnate and rely on methods established decades ago based on the scientific thinking at the time. This especially applies when NAMs can cover endpoints and elucidate mechanisms that have been traditionally difficult to model in animals, such as developmental neurotoxicity, as well as to provide safety assessments for emerging/future substances where traditional approaches may not work or be practical. This could be due to the physico-chemical properties of the substance (for example, nanomaterials and polymers) or where there is a need for higher-throughput approaches, for example, for UVCBs (unknown or variable composition, complex reaction products and biological materials). Indeed, work published by global regulatory agencies has demonstrated that safety decisions based on points of departure derived from NAM toolboxes are largely more conservative than those derived from traditional animal toxicology studies.[41] Whilst this conservatism ensures protection from a human health perspective, particularly where data are ambiguous, there are legitimate concerns that an overly protective approach could have a negative impact in terms of costly and unnecessary restrictions or protective measures that may be put in place. Here, a tiered and/or iterative approach, as set out in the SEURAT-1 ab initio risk assessment workflow[42] and the ICCR principles on the use of NAMs[34] may help overcome such concerns, such that, at least initially, lower tier NAMs approaches are more conservative than using traditional animal data, but with the option to move to more complex tools in further tiers of the risk assessment where results in the lower tier do not demonstrate safety.

To overcome the more cultural and societal hurdles, particularly regarding the perceived regulatory expectations to move towards wider adoption of NAMs, there needs to be a better understanding of the potential benefits of NAMs (scientific, business and societal), and incentives to drive their development and encourage use. Showcasing examples of regulatory acceptance will help build confidence and stimulate investment in this area.

Regulatory and legal barriers

The regulatory barriers to the acceptance of NAMs are numerous. They include current legislative constraints, risk aversion and conservatism/perceived expectations, as well as available resource, including knowledge and experience in handling and interpreting new datasets from unfamiliar cell- or omics-based assays or computational technologies, and the resource required to train staff and maintain expertise. The success of using NAMs to assure safety of a pharmaceutical or a chemical relies on the safety paradigm moving to a more risk-based approach and considering exposure first in a chemical assessment alongside how the chemical is to be used. This is something that is already part of the safety assessments in sectors such as cosmetics, but in many areas current regulatory regimes and technical guidance are not set up in a way that allows incorporation of exposure considerations and these new types of data. Another important point here is that we do not have clarity on the current levels of health protection being offered by current regulations/laws so the target performance for new methods is unclear. Therefore, to progress and fully embrace NAM approaches, there is a need for policy change, regulatory reform and infrastructure change, including appropriate training of government and industrial technical staff and legislative changes where *in vivo* tests are currently required by law.

Guidelines and the law

One of the biggest barriers to the uptake of NAMs is legislative constraints, particularly where the law demands a classification based on hazard. Current hazard-based systems, including classification regulations, globally harmonised standards of classification and systems such as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) are traditionally based on identification of hazards in animal studies, despite opportunities outlined in REACH that animals should only be used "as a last resort". Historically there has been an expectation that NAMs and NGRA approaches replicate these studies but, as discussed in section 2.1, it is not the intent that these new approaches replace the existing toxicological animal testing paradigm, especially on a one-to-one basis. Whilst flexibility already exists within the REACH regulation to use alternative approaches, this needs to be exploited to ensure opportunities for NAMs are taken up. However, for CLP/GHS where the data have traditionally been used to assign classes based on animal tests, a rethink is needed to consider the role of NAMs as part of CLP and hazard identification. The 2023 European Partnership for Alternatives Approaches to Animal Testing (EPAA) Designathon has posed this challenge, to look at opportunities for NAMs to inform the development of a potential future classification system for human systemic toxicity.[43]

For certain chemicals under REACH, the data generated have to be suitable for hazard classification for CLP, and ideally be quantitative in nature so that a risk assessment can be performed comparing the high dose to real levels of exposure. However, in EU REACH and UK REACH, the current law does not necessarily need to be changed to accommodate the use of NAMs in regulatory decision-making—there is already the option to incorporate NAMs via dialogue between the technical civil service and the scientific community (for example, as part of adaptions through REACH Annex XI[44]). However, despite the legislation allowing flexibility—animals to be used "as a last resort" and alternative approaches being allowed if "scientifically acceptable"—ambiguity remains, and there are differences in interpretation as to what is acceptable, in terms of legal defensibility, and

a tendency to take a conservative approach. The EU and UK Cosmetics Regulations can similarly accommodate NAMs when deemed scientifically appropriate in making a safety case for a cosmetic ingredient, and again, this is a discussion between the regulators, industry submitting the dossier and the scientific advisory committee reviewing it.

While the cosmetics sector has led the way due to legislative bans in Europe around the use of animals, the agrochemicals and biocides sectors are not as flexible and animal-based data requirements are still set in law, particularly for complex endpoints such as repeated dose toxicity, reproductive toxicity, and carcinogenicity. For these endpoints there are requirements for studies where animals are dosed at relatively high systemic exposures, much higher than would realistically be experienced by a consumer, worker, or member of the public. These high doses are driven with the aim of identifying hazards in the animal to make a regulatory classification, irrespective of the expected exposure and therefore risk.

For pharmaceuticals, there is significant flexibility with regard to data requirements, especially since the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) Guidelines (www.ich.org) provided by the International Council for Harmonisation are *guidelines* rather than rules and can be interpreted and implemented by sponsors and regulatory authorities based on sound science.[45] For each individual drug project, sponsors can put forward a sound scientific plan that might not contain all studies mentioned in the relevant ICH guideline but nonetheless addresses human risk-benefit. Within this, the use of NAMs is encouraged wherever possible as outlined in the FDA Modernization Act 2.0[46] with a thorough assessment of gaps and challenges,[47] and in the European Medicines Agency (EMA) workplan.[30]

Validation

Although in law some sectors require the conduct of "validated" tests (for example, formally adopted as an OECD or ICH guideline), the majority of NAMs are not validated at an international level, and it is not clear how validation can be achieved, nor what would be considered acceptable. This lack of "official validation" may be hindering the regulatory acceptance of NAMs in many jurisdictions. Whilst there is flexibility both within REACH and the FDA Modernization Act to use non-standard/non-animal approaches, "suitable" alternatives are required and there is ambiguity over what is accepted, especially for non-OECD TG studies. For example, in REACH Annex XI, which sets out general rules for the adaption of standard testing approaches, only read-across, QSAR and *in vitro* alternatives that have some degree of formal validation and meet the European Centre for the Validation of Alternative Methods (ECVAM) pre-validation criteria are mentioned. The topic of "validation" is an ongoing area of research and debate[24] and, as a concept, may not be as crucial as ensuring reproducibility in assay outcomes between laboratories, and the relevance of the data being generated to a biologically relevant mechanism/mode of action that has been linked to the cause of an ultimate adverse outcome, as part of an AOP.[24] Interestingly, while formal validation seems to be a requirement for the acceptance of NAMs, most traditional *in vivo* tests have not been validated formally, with test guidelines instead using the perceived best custom and practice. This topic is considered under the 2005 OECD Guidance document No. 34 on the validation and international acceptance of new or updated test methods for hazard assessment addresses which is currently under revision.[48]

Common barriers: Economic

Investment in NAMs can be associated with significant financial cost and uncertainties, especially concerning the potential loss in return in investment if a safety decision cannot be reached from use of NAM-based data alone, and/or is not accepted by regulators. Uncertainty around regulatory acceptance has consequences for industry and especially small companies which cannot take the risk of investing significant amounts of money and time in developing and/or applying NAMs if these will be rejected by the regulators in certain sectors and jurisdictions because of legal requirements. Although most current CROs do already have significant *in vitro* testing services, many do not offer the type of complex NAM toolbox testing envisaged for use in NGRA. In time, bespoke CROs offering expertise in NAM-based approaches may evolve, but this will require significant buy-in and investment. A viable business case for CROs is needed – a switch away from animal studies towards NAM-based approaches will in the short-term reduce the return-on-investment in CRO assets currently dedicated to the existing animal testing. Therefore, to encourage or support investment in NAMs, there needs to be a viable economic transition plan to ensure current CROs can be financially sustainable. From a company/sponsor perspective, the perceived business risks and uncertainties associated with NAMs may result in companies continuing to use animal studies as the more financially certain approach, even if a NAM approach might be available. These create disincentives, and commercial barriers to investment need to be considered to enable the transition. However, it should be noted that there is already a legal requirement to use non-animal approaches, irrespective of economic impacts, if there are suitable alternatives and animals should only be used "as a last resort" (for example, Article 25 of REACH[44]), though ambiguities around "suitability" and acceptance create uncertainty around the implementation of this requirement.

Initially, it is likely that for NAMs to be used in regulatory decision-making for some sectors, dual data-packages will be required, where the new types of data will be compared with the more classical types of data and risk assessments performed to see if the outcomes lead to the same types of decision-making. Of course, this approach would not apply to industries where animal studies are no longer permitted (for example, cosmetics), but in some instances there may be historical animal data available that could be used to determine if the same decisions/conclusions are made using NAMs alone. The nature of the old and new types of risk assessments are likely to be different in detail but fundamentally will compare effects with real-life exposure. However, this will require extensive investment in training and resource, from both regulators and industry to support the generation of dual data-packages and the subsequent assessments, and it will be important to publish the resulting evidence to show how protective safety decisions can be made using NAM information. It is most likely that the first examples of regulatory acceptance of NAMs will be their use in risk assessment for scenarios where there are low levels of chemical exposure, such as food contaminants, or in regulations which already allow the use of NGRA. Showcasing examples of how NAMs can be used as part of a NGRA will help build confidence and support wider uptake and use of NAMs in the future.

The way forward

The barriers to uptake and adoption of NAMs are numerous and lie not only within the status of the science, but also across the cultural, societal, and regulatory landscapes. The barriers need

to be addressed in concert to ensure that advances in science are paralleled by advances in skills, education and training, and regulation for the full benefits and opportunities to be realised.

There is a collective onus for the acceptance of NAMs, with responsibility shared between national and regional regulators and government scientists in discussion with industrial and academic scientists to reach agreement on safety cases. Where there is a lack of confidence, real or perceived, in the degree of protection offered by NAMs, then targeted discussion and generation of new evidence should be encouraged, supported and published.

Progress can only be made if there is international effort and investment to develop and implement guidance on a realistic stepwise implementation of NAMs in the short- and medium-term, with recommendations for future work in the long-term. Given the new initiative by the United Nations Environment Assembly in Resolution 5/8[49] to establish a new science panel for chemicals, waste, and pollution prevention by 2025 and the EU Chemicals Strategy for Sustainability,[50] it is imperative that any capacity building activities incorporated into that global programme to support chemicals policy considers the future landscape of how testing paradigms and NGRA will change toxicological risk assessment.[31] Current experience in applying NAMs to regulatory risk assessment in the international regulatory community has been low, but this is improving and there are already several regulatory statements/commitments and roadmaps in development (see section 3.2). There needs to be a greater onus on scientists to share knowledge and best practice about NAMs and their use in safety decision-making in the development of global chemicals policy. The development and publication of case-studies outlining what works (and what does not) and for which decision context, ideally in partnership between industry, academia, and regulators, will play a vital role in building confidence in understanding how the many *in vitro* and computational elements involved in NGRA can be used together to result in safety decisions. These will require an appropriate level of funding to support their development and publication.

Identification of the strengths and weaknesses of current NAM-based approaches should guide the future development of new tools/approaches to complement the discussion about what the current non-animal tools may miss, a conversation which is equally relevant to the current animal tools in toxicology. For example, how metabolism of the target species can be addressed in NGRA, a topic that is often of concern when some NAMs used in an NGRA toolbox may not themselves have metabolic capability.

Successful use of NAMs has already been achieved in some instances. However, the challenges in some areas are substantial and timelines will vary considerably, particularly since the use of NAMs in safety assessments for complex toxicological effects requires not only robust experimental and computational NAM approaches, but also a change in mindset for how these techniques are used in safety assessment.

The successful adoption of NAMs as part of safety assessment will not be through one-to-one replacement of animal methods by *in vitro* or computational approaches. Creative methods are called for that reconfigure future approaches to hazard and risk assessment. Current guidelines followed on from and, therefore, are based around a battery of animal tests and until regulatory technical guidance changes significantly it will be difficult to fully implement NAMs, save on a case-by-case basis in the short-term. This largely requires a conversation between industry and government scientists, to agree on new technical guidance. Ultimately, changes to the law, as well as better enforcement of opportunities within existing requirements, are needed to mandate the use/consideration of NAMs in the first instance; changing the existing requirements that animals be used "as a last resort", to one where it is the use of the animal that needs to be justified, rather than the use of the NAM.

Further research investments will advance the science, but also help to support the *application* of NAMs for decision-making, including putting parallel NAMs dossiers together and highlighting where the fundamental gaps are for further development/investment. Training and retention of expertise will also be crucial to ensure knowledge advances with the technology and the ability to re-position the questions and decisions made in a regulatory capacity so that they can incorporate new approaches to risk assessment as required, keeping pace with, and exploiting the latest scientific developments.

It is envisaged that broadly, there are short-, mid- and longer-term goals that can be reached by capitalising on the opportunities for NAMs to improve protection of human and environmental health.

Current opportunities:

- There are defined instances where NAMs are clearly reliable and protective, for example NAMs used for skin and eye irritation, skin sensitisation and genotoxicity and where there is scope for implementation, these should be required and accepted by regulatory authorities in place of the previous traditional animal methods.
- Where animal data are still deemed necessary, NAMs should be submitted and considered in parallel, with scientific feedback given if the approaches taken are, or are not, considered to be scientifically robust. This will require significant buy-in and investment to support the extra resources required for dual data packages, both in generating and interpreting/assessing the data.
- Cases of regulatory acceptance, including demonstration of improved safety provided by NAMs should be collated to build an evidence base to showcase scenarios where NAMs are accepted. Examples should be published in the peer-reviewed scientific literature to allow others to critically appraise the approaches taken and then build on them, allowing lessons learned and experiences to be shared more widely between different sectors and regulations. These cases should be incorporated into dedicated resources and training available to all stakeholders, covering laboratory-based expertise, data interpretation and regulatory decision-making.

In the medium-term:

- Significant research investment will improve scientific knowledge and increase biological coverage. The scope and potential of NAMs will be increased by developing AOPs, with an emphasis on quantitative AOPs to incorporate exposure thresholds, so that safe doses can be predicted from assays based on earlier (*in vitro*) key events in the pathway.
- Other tools will help quantitatively understand a chemical's mechanism of action, such as *in vitro* high throughput transcriptomics (HTTr) and high throughput phenotypic profiling (HTTP) methods that can provide information on concentration thresholds for changes in gene expression or cell morphology to characterise a chemical's biological activity.[33]
- Expansion of knowledge/chemical space through wider public access to private data will widen the scope for NAM

implementation, to improve the reliability of QSAR (quantitative structure–activity relationship) and computational toxicology tools and predictions, for example.

- Improvement in the consideration of uncertainty and a better understanding of knowledge/data gaps will help quantify uncertainty in NAM-based safety decision, and an improved understanding of the inherent biological variability also present in *in vivo* experiments will lead to wider acceptance of NAMs.[19]
- Investment will accelerate the development, standardisation and application of a wide range of bioactivity assays capable of investigating an adequate number of stress responses associated with adverse effects. The development and application of improved PBK models to translate *in vitro* NAM points of departure to *in vivo* points of departure, will enhance extrapolation and applicability.
- A focus on the application of machine learning approaches to computational tools in relation to toxicity models, and increased investment and emphasis on the capability of organs-on-chips to address complex endpoints, and opportunities for exposure-based waiving and exposure-driven testing will enable a move towards a more risk-based approach.

In the longer-term:

- Risk assessment is improved through contemporary articulation of the required evidence and transparency in decision-making to assure product safety based on learnings from historical decisions made using animal data.
- Decisions will be based on NAMs in a NGRA framework leading to improved health protection.
- Considerable investment in science and education, as well as significant investment in cross-stakeholder engagement will lead to the creation and acceptance of such a new paradigm. This will be resource intensive in the short-term, but this transition will save time, resources and animals in the long run as well as provide protection for humans or the relevant environmental species.

Conclusions

In recent decades, there have been significant scientific advances in the use of NAMs for safety decision making,[41] yet there are currently only a limited number of examples of where NAMs have been used to provide safety data either as a stand-alone or to replace animal studies. Whilst many technical and scientific barriers have already been overcome, there is still a need for further scientific progress, as well as cultural, societal, and regulatory issues to resolve. Current barriers to uptake may be more to do with culture than they are attributable to the quality and relevance of the NAMs; more and more development of better and better NAMs will not change this.

For NAMs and NGRAs to be widely adopted in regulatory frameworks, a change in thinking is required. New paradigms for their use and evaluation of their relevance for decision-making in specific contexts of use is required, and perhaps in the first instance will involve inclusion in parallel with traditional animal tests as part of confidence building to work towards acceptance and validation. However, it must also be borne in mind that animal tests can be poorly predictive of human outcomes and that they also suffer from lack of reproducibility. Therefore, NAM approaches should not aim to replicate the animal, but instead assure decisions made based on NAMs are protective, rather than predictive of effects in humans or the ecological populations.

NAM-based approaches should, in the future, be the default starting position for safety decision-making, with justification for an animal test needed, being that it is truly a "last resort" if NAM-based approaches have proved unable to support robust safety decision-making.

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