THE 2024 LUSH PRIZE SUPPORTING ANIMAL-FREE TESTING

A roadmap for modernising chemical safety testing in the UK

"Change often involves a pivotal event that builds on previous history and opens the door to a new era. Pivotal events in science include the discovery of penicillin, the elucidation of the DNA double helix, and the development of computers...

Toxicity testing is approaching such a scientific pivot point. It is poised to take advantage of the revolutions in biology and biotechnology. The envisioned change is expected to generate more robust data on the potential risks to humans posed by exposure to environmental agents and to expand capabilities to test chemicals more efficiently."

US National Research Council

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Ethical Consumer Research Association

for the Lush Prize

1. Introduction

Over the last ten years or so, there has been increasing concern from governments and civil society that our current approaches to chemical safety testing are not fit for purpose and that a better way forward is needed to improve protection for human health and the environment.

This is a complex and far reaching subject. Chemical safety testing helps us identify human health and environmental hazards and approves substances in industries including (but not limited to):

- food ingredients

- cosmetics and other consumer products

- pharmaceuticals and health

- agricultural chemicals

With the advent of new technologies like genetic modification and nanotechnology, new substances are emerging far faster than they can be reliably assessed using current test methods which remain largely animal-based.

In addition, there are risks that poor quality test methods are leading to the approval of dangerous chemicals, as well as risks that they may be preventing useful new products coming to market by falsely identifying them as toxic.

The current approach to safety testing is also expensive, inconsistent, and time consuming which acts as a brake on scientific and economic progress.

1.1 The benefits of a roadmap for the UK

Advances in molecular biology have led to the emergence of new technologies which have the potential to solve these problems. These include areas such as ‘toxicogenomics, bioinformatics and epigenetics’, as well as areas with more intuitive names like computational toxicology, ‘organs on chips’ and robotics.

These new approaches employ information derived from observation of effects on human cells, tissues and biological components. This avoids the problems of species differences, lack of predicitivity and poor reproducibility associated with current (animal-based) safety assessment methods[1].

The need for industry wide transition from a scientific paradigm reliant on animal research to one which is more fit for purpose, biologically relevant and animal free has led some governments to use the idea of a ‘roadmap’ to plan the journey and the stages needed to achieve the desired goal. It is highly likely that the UK as a whole would benefit from such a roadmap.

1 See e.g Gail A. Van Norman,: Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach? JACC: Basic to Translational Science, Volume 4, Issue 7, 2019, Pages 845-854,

In addition to creating better health outcomes for the population as a whole, there are economic opportunities to be had in this new paradigm which include the ability to participate in big growth areas like biotechnology. The general public are also keen to see alternatives to animal use in science on the grounds of cruelty and ethics.

1.2 This report

This short report is designed to answer the question: 'what might a roadmap for the UK look like?'

We have examined the approach taken with six pre-existing 'roadmaps' from Europe and USA. We have also looked briefly at one recent civil society report on the subject and at emerging plans for similar map across the EU. Text and background information has been reproduced for each of these reports in section 3 below.

In section 2 we ask the questions: are there common elements that most other roadmaps contain and what can we learn from them?

1.3 Recommendations

(a) A high quality roadmap for modernising chemical safety testing in the UK should require the following ten elements:

1. The establishment of a new institutional structure with a responsibility to implement the plan

2. The movement of funding and investment from animal research into new technologies

3. The active facilitation of interdisciplinary collaboration and networking

4. The development of new non-animal tests, test batteries and multidisciplinary non-animal approaches in key areas of need

5. The early engagement of regulators

6. Investment in skills, training and education in the new technologies

7. International collaboration and engagement to achieve consistency and harmonisation around new standards

8. Monitoring, evaluation and reporting against targets and including a final transition date of 2035

9. A work plan to tackle specific challenging toxicity endpoints

10. Systematic quality reviews of all current tests to provide evidence, prioritising those known to be redundant and duplicative for first phase out and achieve early stage success to set the course for the roadmap

(b) In 2015, a high level roadmap for advancing non-animal technologies in the UK was completed by the government agency Innovate UK. This is discussed in more detail in section 3.2 below.

Although its aim was to advance non animal technologies in drug discovery as well as safety testing, it couldprovide a useful foundation to any subsequent roadmap in this area. Also useful would be an honest retrospective review of the successes and failures of the 2015 plan to initiate and improve progress in future.

(c) In June 2023, the NGO Animal Free Research UK called for a “Human-Specific Technologies Act” modelled on the Climate Change Act of 2008.[2] They also recommended specific activities including ‘establishing a non-animal science innovation hub’, and ‘appointing a minister for Human-Specific Technologies’.

2 www.animalfreeresearchuk.org/how-human-specific-technologies-can-transform-lives/

2. Our analysis

2.1 The Table

The table below categorises the key points that other roadmaps and plans have contained. An 'x' shows that a particular reports contains that particular element. NATs is short for Non Animal Tests.

	2007: 20th Century Toxicology, NRC, USA	2015: Innovate UK	2016: NCad/TPI Netherlands	2017: FDA, USA	2018: ICCVAM, USA	2021: EPA, USA	2021: EU Parliament Resolution	2023: PETA, global
New institutional structure/ high level co-ordination	x	x	x	x			x	
Funding and investment for NATs	x	x	x		x		x	x
Interdisciplinary collaboration and networking	x	x	x	x	x	x		
Identification of gaps and development of new tests and test batteries	x			x		x	x	
Early engagement with regulators	x	x			x			
Skills, training and education		x	x	x		x	x	x
International collaboration and engagement		x	x		x		x	x
Monitoring, evaluation and reporting			x	x	x	x		
Plan work on specific toxicity endpoints					x	x		x
Enforce existing rules/ review and end poorly performing tests							x	x

2.2 A discussion on each of the elements

(a) New institutional structure/ high level co-ordination

Creating a roadmap is an achievement but equally it requires effective implementation to succeed.. The strategic advisory board recommended by Innovate UK back in 2015 is still to be established, meaning that the roadmap has struggled to have the subsequent impact that was hoped for.

Therefore, it is clear that having a new institution whose sole focus is to implement the plan is key. For example, the TPI in the Netherlands, now with a small budget of around £1m annually, is beginning to make progress. The NICEATM Centre in the USA, with its $6m annual budget, is another interesting potential model.[3]

(b) Funding and investment for NATs

The majority of roadmaps identified this as an issue. However, it should be noted that this could be achieved by *reallocation* of the very substantial funding that remains invested in animal research, towards NATs instead. The US and EU already have quite substantial programmes in this area and the UK must catch up.

(c) Interdisciplinary collaboration and networking

This element usually mentions the need for planned collaborations between government, associated agencies, industry, academia and regulators. It is likely that committees within the new institutional structure above could help to formalise this approach.

(d) Identification of gaps and development of new tests and test batteries

The idea that an optimised chemical safety strategy via the replacement of animal tests will come not from single 'test' procedures but instead from 'batteries' of tests combined from multidisciplinary approaches (e.g. advanced in vitro, in silico, big data analysis) to improve predicitivity and protection is now widely accepted. This approach requires planning and co-ordination, but the resources are available to achieve it.

(e) Early engagement with regulators

It is important that advances in new animal free technologies answer the questions that regulators are asking. Three of the plans identified this as key. Interestingly the 2007 US report appeared to caution against giving regulators too much control.

(f) Skills, training and education

Almost all the roadmaps mentioned this element. Lack of training in new methods has also been identified by the Lush Prize as a key barrier to progress. The Netherlands TPI and US programmes have already made some progress on the ground with this.

3 https://ntp.niehs.nih.gov/whatwestudy/niceatm

(g) International collaboration and engagement

Chemical safety has seen much international collaboration and standardisation over the years, and the OECD has been one key player. It remains clear that national governments make progress via international collaboration, demonstrated by some progress already happening in this area.[4]

(h) Monitoring, evaluation and reporting

On their own, these are obvious and essential elements of good management. The other implicit area here is targets to report against. Although not without controversy, without an overall target for the transition to have been completed, a roadmap can be easily sidelined.

As Cruelty Free Europe explains: “In other important areas of policy, the EU argues that unless ambitious and binding targets are set, industry and other stakeholders will not change. There are numerous examples: greenhouse gas emissions; vehicle emissions; targets for green energy; recycling; the representation of women in leadership positions and others. The logic is that targets focus the mind, incentivise and drive change.”[5]

At Lush Prize, we think that a final target of 2035 is achievable, via progress and transition phased in *from now until then*. The process would also incorporate full and frank consultation with the public, government, regulators and chemical industry stakeholders.

(i) Plan work on specific toxicity endpoints

There are some areas, like reproductive and developmental toxicology, which underline the urgent need to develop more biologically relevant methods, given decades of concern on how animal models fail to address these (and other) complex endpoints. Four of the ‘roadmaps’ review existing initiatives and seek to plan further work and investment specifically in these areas. Appendices in the PETA report provide considerable background detail here in accessible language.

(j) Enforce existing rules/ review and prioritise the end of poor (e.g redundant and duplicative) tests

Both of the civil society actors in this space have pointed out that many poor quality and unnecessary tests continue because existing rules to prevent them are not being properly enforced. In addition, a formal review of all tests also makes sense. There is no reason why this should not be part of a centrally co-ordinated roadmap projec with pragmatic action to start the process e.g. pilot studies in particular areas.

4 See e.g. The OECD adverse outcome pathway toolbox

5 Reducing and replacing animal experiments: Europe needs an action plan. Cruelty Free Europe 2023.

2.3 Obvervations on next steps for a UK roadmap

In addition to following the recommendations in Section 1.3 above, there are some obvious practical suggestions that are worth noting.

- Work on a UK roadmap does not need to start ‘from scratch’. As outlined, the Innovate UK report published in 2015 provides a comprehensive foundation to re-establish a UK roadmap to phase out animal research and transition to animal- free innovation

- A roadmap would maximise academic and industry wide opportunities to reaffirm the UK as a scientific leader via cutting edge new animal free research in both regulatory and academia. This can also be driven in part by recent engagement between the Animals in Science Committee and the Government on key recommendations to improve transition to NAMS (New Approach Methodologies) with specific reference to non-animal methods.

- Many UK based researchers are involved in these initiatives and are ready to provide their expertise and engage with regulators and policymakers

3. Pre-existing roadmaps

3.1 Toxicity Testing in the 21st Century: A Vision and a Strategy (2007)[6]

Nearly 20 years ago, the U.S. National Research Council was asked by the U.S. Environmental Protection Agency to review the state of the science and create a far-reaching vision for the future of toxicity testing. Their detailed and authoritative report, published in 2007, laid the foundations for all those who felt this subject should be taken seriously. It is, in many ways, the parent of all the subsequent reports here.

Although it did not call itself a roadmap, it identified key steps that would need to be taken along the way as well as broad assessments of the likely time frame. It explained that:

“A long-term, large-scale concerted effort is needed to bring the committee’s vision for toxicity-testing to fruition. A critical factor for success is the conduct of the transformative research to establish the scientific basis of new toxicity-testing tools and to understand the implications of test results and their application in risk assessments used in decision-making. The committee concludes that an appropriate institutional structure that fosters multidisciplinary intramural and extramural research is needed to achieve the vision.

“It felt that the new institutional structure would be needed to conduct and managing the research effort with the following considerations:

• The realization of the vision will entail considerable research over many years and require substantial funding— hundreds of millions of dollars.

• Much of the research will be interdisciplinary and consequently, to be most effective, should not be dispersed among discipline-specific laboratories.

• The research will need high-level coordination to tackle the challenges presented in the vision efficiently.

• The research should be informed by the needs of the regulatory agencies that would adapt and use the emerging testing procedures, but the research program should be insulated from the short-term orientation and varied mandates of the agencies.”

Although it did not have a target date by which the transformation should be completed, it imagined “that the new knowledge and technology generated from the proposed research program will be translated to noticeable changes in toxicity-testing practices within 10 years. Within 20 years, testing approaches will more closely reflect the proposed vision than current approaches. That projection assumes adequate and sustained funding. As in the Human Genome Project, progress is expected to be non-linear, with the pace increasing as technologic and scientific breakthroughs are applied to the effort.”

It explained that the research and development needed to implement the vision would progress in phases whose timelines would overlap.

6 https://nap.nationalacademies.org/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a

“Phase I would focus on elucidating toxicity pathways; developing a data-storage, -access, and -management system; developing standard protocols for research methods and reporting; and planning a strategy for human surveillance and biomonitoring to support the toxicity-pathway testing approach. “

Much work has been done in this area since this time. The language now used is of ‘adverse outcome pathways’ and the OECD plays a key role in cataloguing and sharing the data.[7]

“Phase II would involve development and validation of toxicity-pathway assays and identification of markers of exposure, effect, and susceptibility for use in surveillance and biomonitoring of human populations.”

A collaboration identified several new mechanistic assays to replace animals in skin sensitisation testing and won the Lush Prize Black Box award in 2016. Since then, further work has provided a ‘defined approach’ at OECD level for the use of these methods ·

More widely, the Adverse Outcome Pathway Knowledge Base (at the time of writing) now lists 497 AOPs incorporating 5829 Key Events in stages of development, peer review and approval. While many of these are still under construction and review, the scope of the knowledge base demonstrates the ever growing interest and recognition in the field.

“Phase III would evaluate assays by running them in parallel with traditional toxicity tests, on chemicals with large datasets, and on chemicals that would not otherwise be tested as a screening process. Parallel testing will allow identification of toxicities that might be missed if the new assays were used alone and will compel the development of assays to address these gaps. Surveillance and biomonitoring of human populations would also begin during Phase III.”

The US has been at the forefront of high throughput screening using robotics. The completed first phase of Tox21 involved testing of 2,800 compounds in more than 50 assays using the high-throughput robotic screening system now at NCATS. The resulting data are available in public databases, such as the National Library of Medicine’s PubChem, the EPA’s ToxCast, and NTP’s Chemical Effects in Biological Systems.[8]

Phase IV would involve assembling validated tests into panels for use in place of traditional (animal) toxicity tests. Validation will be a critical component of the research and development phases.”

The Document has been a landmark driver of later activities at the EPA and elsewhere in US institutions. See below.

7 www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

8 https://tox21.gov/overview/operational-model/

3.2 A non-animal technologies roadmap for the UK: Advancing predictive biology (2015)[9]

One of the first government-level responses to the 2007 NRC report appeared in the UK itself in 2015. A key driver was “Innovate UK” the country’s national innovation agency. Innovate UK had identified non-animal technologies as one of a series of emerging technologies with the potential to drive future UK economic growth.

“The UK has world-leading research in this area and companies, large and small, with the ability to take advantage of new commercial opportunities. The market potential is huge. The global market for cell based assays in drug discovery, safety, and toxicology will reach $21.6 billion by 2018. The estimated global market for induced pluripotent stem cells is expected to reach $2.9 billion in 2018, and the 3D cell culture market is expected to grow to about $2.2 billion in 2019.”

Innovate UK collaborated with the National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs), the Biotechnology and Biological Sciences Research Council (BBSRC), the Defence, Science and Technology Laboratory (DSTL), the Engineering and Physical Sciences Research Council (EPSRC) and the Medical Research Council (MRC) to develop the UK’s own strategy and vision for non-animal technologies for efficacy and safety in the UK and establish a roadmap.

Interestingly its vision extended beyond safety testing and into drug discovery and academic use too. Voicing pharmaceutical industry concerns, it wrote that “the lack of translation of data from animals to man has far-reaching implications, from wasted resources spent on the early development of compounds destined to fail in humans, to large financial losses due to late stage attrition.”

Using the language of ‘Non Animal Technologies’ (NATs) It produced a detailed map and timeline which saw regulatory use of NATs becoming standard by 2030. Although it appears to have become sidelined amidst the wider political turbulence of the intervening period, it should be a starting point to revive and re-establish the UK roadmap.

It had six interconnected strategic themes and related recommendations which included the following:

• Skills

Support capacity building in multidisciplinary science and technology development to ensure that the UK has the right skills base to drive NATs for company decision making and risk assessments.

9 https://www.ukri.org/publications/non-animal-technologies-in-the-uk-a-roadmap-strategy-and-vision/

• Collaboration and networks

Foster collaborations between industry, the SME sector and academia to improve understanding of cross-sector requirements and bottlenecks in the development and deployment of NATs.

Support collaborative working to ensure that the most promising technologies are identified, developed, validated and integrated into the product pipeline with minimum risk for those involved.

• Technology development

Maintain investment in underpinning basic research and business-led technology development in NATs.

• Commercialisation and uptake

Build capacity and confidence in NATs and accelerate the path to market by supporting the development of NATs with powerful predictive ability and bridging the gap between development, proof of concept and scale-up.

• Regulatory engagement

Ensure early engagement of regulators in the development and use of NATs to expedite a path to regulatory acceptance.

• International factors and landscape.

Analyse emerging international trends and activities to identify collaborators, avoid duplication and ensure that the UK is well positioned to influence global developments. Promote the UK NATs industry globally to maximise economic growth.

One of its other recommendations was to: “Establish a strategic advisory board, with academic and industrial members, to provide advice and to help drive forward the roadmap in the UK.” It is possible that the absence of implementation of this critical step played a key role in the lack of progress since that time.

There has been some more recent UK activity worth noting. In June 2023, the Animals in Science Committee(ASC) wrote a letter to ministers on the ‘Strategic Direction of Animals in Science’, which among several recommendations highlighted a “significant juncture between the use of animals in science and the development and uptake of alternatives”, also recommending that responsibility for animals in science be reallocated from the Home Office to the Department for Science, Innovation & Technology (DSIT). The Government’s subsequent reply was that this and other recommendations were being investigated.

3.3 Transition to non-animal research: on opportunities for the phasing out of animal procedures and the stimulation of innovation without laboratory animals. Opinion of the Netherlands National Committee for the protection of animals used for scientific purposes (NCad)(2016)[10]

On 8 April 2016, on the basis of an opinion issued by the Think Tank, the Minister for Agriculture, Martijn Van Dam, expressed in a letter to the NCad the aim that the Netherlands should be world leader in innovation without laboratory animals by 2025. In this letter, he asked the NCad for an opinion on how this could be achieved. The report from NCad recommended the following:

Clear transition objectives

1. In the field of ***regulatory safety research***, there are technical and strategic opportunities for completely phasing out animal procedures by 2025, whilst maintaining the existing level of protection. The NCad recommends for the Minister for Agriculture to adopt this clear policy objective and disseminate it on a national and international scale.

2. Within the field of ***fundamental scientific research***, the opportunities for a substantial reduction and phasing out of the use of animals vary from one area to another. The NCad recommends for the Minister for Agriculture to develop a ten-year vision for each area of fundamental scientific research in consultation with the public and the scientific community, with a view to reducing the use of laboratory animals, whilst maintaining the scientific objectives. This vision should inform the innovation strategy, which should systematically focus on the sharing of knowledge.

3. Within the fields of ***applied and translational research***, in which faster progress can be made, the NCad recommends for the Minister for Agriculture to encourage the exploitation and strengthening of these opportunities by focusing heavily on innovations without laboratory animals. By doing so, the Netherlands will be able to achieve its objective of becoming international leader in innovation without laboratory animals in the fields of applied and translational research by 2025.

4. By focusing on practices that do not involve laboratory animals and actively reflecting on the use of laboratory animals in education, the use of animals for ***education*** and training can be significantly reduced.

Transition strategy

The NCad offers the Minister for Agriculture the following recommendations:

5. Take the lead in calling for a new regulatory risk assessment procedure for substances at EU and international level, based on an intelligent and flexible step-by-step approach, without the use of or with minimum use of animal procedures.

10 www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research

6. Make the innovation policy of the Ministry of Economic Affairs more chain oriented and encourage multidisciplinary collaboration, so that promising innovations without laboratory animals can be better exploited and can progress more easily from development to application, potentially in a number of different areas of application.

7. Invest in the valorisation and acceptance of non-animal methods.

8. Ensure that better use is made of the results of research on human subjects.

9. Investigate risk acceptance in the field of regulatory research involving laboratory animals and invest in risk communication.

10. Ensure that monitoring and evaluation takes place and make knowledge concerning innovation without laboratory animals and 3R alternatives more available.

Since the report was published and number of initiatives have taken place including:

1. The Dutch Transition partner program to accelerate animal-free Innovation (TPI) was founded in 2018.

The TPI program consists of eleven partners: Health~Holland, NFU, RIVM, SGF, the Dutch Society for the Replacement of Animal Testing, VSNU, ZonMw and the national government – with the Ministry of Agriculture, Nature and Food Quality (LNV) as director and the Royal Netherlands Academy of Arts and Sciences and NCad as observers.[11]

Key elements that bind partners to TPI are its multidisciplinary network, knowledge sharing, the positive directed mission and the acknowledgement of each other's differences. A transition requires changes at various fields and levels, therefore innovation as well as collaboration between stakeholders (e.g. validation roadmap and knowledge agenda), involving early-career students and researchers (Young TPI), communication and adaptions in education are vital.[12]

2. In November 2020, the TPE was reviewed and some of the language changed. The eye-catching 2025 target was dropped. The focus moved to establishing animal-free methods and innovations. Instead of a phasing-out, is it now more of a change (transition). In the words of the German NGO Doctors Against Animal Experiments: "Critics of the adjusted plan see this as proof of failure – but that is not the case at all: from the very start, the NCad emphasized that the ambitious plan can only succeed if all efforts are aimed at promoting animal-free methods strongly also at international level and by governmental agencies. The targeted change still heads far beyond the usual 3Rs, i.e., simply reducing, improving, and replacing animal testing within the existing system. The original plan, and even the revised one, is still ground-breaking because it shows that a change towards non-animal methods is possible if, in the case of the Netherlands, there is a strong political will."[13]

11 www.animalfreeinnovationtpi.nl/documents/reports/2020/11/11/review-of-tpi-2018--2020

12 Erica van Oort, Monique Janssens, Judith van Luijk and Eelco Ronteltap(2023) Accelerating animal free-innovations: Milestones and lessons learned in the Dutch transition program. WC12 Abstract.

13 www.aerzte-gegen-tierversuche.de/en/specific-infos/international/global-approaches-to-achieve-the-transition-to-non-animal-research

3. One of the recommendations was to create target images for basic/fundamental research. Target images describe clear transition objectives for a specific research domain aimed at reducing the use of laboratory animals with equal or better research quality and define the prerequisites that must be met to achieve the targets.

The typical horizon for a target image is 5 to 10 years. Currently, four target images are in different stages of realization. The target image for the Neurosciences was published in 2021, and the one for Education and Training at the end of 2022. The target images for cardiovascular research and immunology are expected to be published in the second half of 2023. See also abstract NAMs: target image immunology.[14]

4. A professorship “Evidence-Based Transition to Animal-free Innovations” at Utrecht University, was established in spring 2022. In contrast to the usual 3R efforts, its aim is to specifically drive the paradigm shift from animal experiments to human-based methods on a scientific basis (7).

The launch of the TPI has also resulted in nine ‘Helpathon’ events to date, including the first held in the UK in October 2022, hosted by Animal Free Research. More detail can be found on the TPI Helpathon website.

14 Jan-Bas Prins and Leane van Weereld (2023) Target images and their role in facilitating the transition towards non-animal science. WC12 Abstract.

3.4 The US FDA's Predictive Toxicology Roadmap (2017)[15]

In 2017, the U.S. Food and Drug Administration (FDA) Commissioner tasked the Agency's Toxicology Working Group with developing a roadmap for integrating predictive toxicology methods into safety and risk assessments. Directly referencing the influence of the 2007 NRC report, the roadmap came up with the following six recommendations:

1. Organizing Committee

FDA has formed a senior-level Toxicology Working Group to (1) foster enhanced communication among FDA product centers and researchers and (2) leverage FDA resources to advance the integration of emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments. Specific activities will help identify areas where research is needed and may reduce duplication of efforts inside and outside FDA.

2. Training

Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators. To this end, FDA's Toxicology Working Group has established an Agency-wide education calendar of events and a Toxicology Seminar Series to introduce concepts of new toxicology methodologies and updates in toxicology-related topics.

3. Continued Communication

FDA will continue to reaffirm its commitment to and support for incorporating data from newly qualified toxicology methods into regulatory submissions and that it encourages discussions with stakeholders as part of the regulatory submission process. FDA product centers will encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process and to engage in frequent communication with the Agency. Such interactions are essential to ultimately ensuring that new toxicology methods can be used in regulatory risk assessments.

4. Collaborations

FDA will continue its long practice of fostering collaborations across sectors and disciplines nationally and internationally. An example is the DARPA/FDA/NCATS Partnership that was formed to develop in vitro microphysiological systems, also known as organs on a chip. FDA considers these types of partnerships pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.

15 www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap

5. Research

FDA's research programs will identify data gaps and support intramural and extramural research to ensure that the most promising technologies are identified, developed, validated, and integrated into the product pipeline.

6. Oversight

The Toxicology Working Group, with representation from each FDA center, will track the progress of these recommendations and report to the Chief Scientist annually. Its key goals are to ensure continued communication and collaboration among the different FDA centers and with the Agency's stakeholders. The Working Group will help foster collaborations within the Agency, nationally, and internationally and will be pivotal to maintaining momentum for the roadmap goals. The Working Group will also ensure transparency, fostering opportunities to share ideas and knowledge, showcase technologies, and highlight collaborations on developing and testing new methods.

The report also begins to identify some of the data gaps it refers to earlier: "Certain areas of toxicology prediction remain challenging and could benefit from greater predictivity. In addition, often a better understanding of mechanisms can be useful when considering the possible human relevance of toxicological findings."

It also brings an interesting perspective to the issue of validation in a discussion under 'Context of Use.'

"Critical to FDA's ability to reach sound regulatory decisions and to retain the public's trust are high- quality data; a thorough, unbiased, and transparent scientific review process; and confidence in the tools used to demonstrate safety and assess risk. FDA must be able to evaluate the applicability, limitations, relevance, reliability, reproducibility, and sensitivity of a test or series of tests (performance standards) to confirm that the test or series of tests has been appropriately *validated or qualified*. Current formal approaches to validation involve lengthy and expensive processes that may not be necessary for all uses of a particular test.

Rather than validation, an approach we frequently take for biological (and toxicological) models and assays is *qualification*. Within the stated *context of use*, qualification is a conclusion that the results of an assessment using the model or assay can be relied on to have a specific interpretation and application in product development and regulatory decision-making.

The *context of use* refers to a clearly articulated description delineating the manner and purpose of use for the tool (when and how it will be used). Adequately specifying the context of use is often a difficult first step towards qualification and regulatory acceptance of new methodologies. Qualification also identifies the boundaries of the available data that adequately justify the use of the tool. Models and assays should be suited for a purpose and, in that context, they will have different applicability, assumptions, and limitations.

Once a new model or assay is considered qualified by FDA for a specific context of use, industry and other stakeholders can use it for the qualified purpose during product development, and FDA reviewers can be confident in applying it without needing to re-review the underlying supporting data. “

3.5 *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States: ICCVAM (2018)*

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was formally established in 2000 by the ICCVAM Authorization Act (ICCVAM Authorization Act 2000) as a permanent committee of the National Institute of Environmental Health Sciences (NIEHS).

Its agency members include the following US government departments:

- **Consumer Product Safety Commission**
- **Department of Agriculture (USDA)**
- **Department of Defense (DoD)**
- **Department of Energy**
- **Department of the Interior (DOI)**
- **Department of Transportation**
- **Environmental Protection Agency (EPA)**
- **Food and Drug Administration (FDA)**
- **National Cancer Institute**
- **National Institute for Occupational Safety and Health**
- **National Institute of Environmental Health Sciences (NIEHS)**
- **National Institute of Standards and Technology**
- **National Institutes of Health (NIH)**
- **National Library of Medicine (NLM)**
- **Occupational Safety and Health Administration (Department of Labor)**

As such, its roadmap is different to the others in that its audience is, to some degree, these agencies as well as other stakeholders like industry groups.

As the report says: “During its first 15 years, ICCVAM’s evaluations of new methods followed a linear, stepwise validation model that proved to be lengthy, inefficient, and resource-intensive. This validation paradigm can no longer be solely relied on to meet the needs of federal agencies. Moreover, it is not compatible with many modern approaches to toxicity testing, which place less emphasis on replacement of in vivo tests with a single alternative method and more emphasis on NAMs [Non-Animal Methods or sometimes New Approach Methodologies] that incorporate batteries of assays, in silico approaches, and computational models. It is important to understand and address the shortcomings of the historical approach as we move forward with a new paradigm for establishing confidence in NAMs.”

The report identified three strategic goals steps in its roadmap and these are listed below, edited for space.

1) Connect end users with the developers of NAMs.

The successful implementation of NAMs will depend on research and development efforts developed cooperatively by industry partners and federal agencies. Currently, technologies too often emerge in search of a problem to solve. To increase the likelihood of NAMs being successfully developed and implemented, regulatory agencies and the regulated industries who will ultimately be using new technologies should engage early with test-method developers and stay engaged throughout the development of the technologies.

This will involve:

Identifying anticipated testing requirements;

Encouraging the establishment of grant review criteria tailored to the development of alternative methods;

Developing mechanisms to improve communication between end users and researchers.

2) Foster the use of efficient, flexible, and robust practices to establish confidence in new methods.

Stakeholders and federal agencies should work together to establish confidence in NAMs using flexible, robust, and integrated approaches spanning from early product development to the ultimate intended use. This will involve:

• Clearly delineating testing requirements and context of use.

• Promoting the use of new approaches for establishing confidence.

Utilizing public-private partnerships to promote cross-sector communication and cooperation.

3) Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries.

This will involve:

• Providing clear language regarding the acceptance of NAMs.

• Collaborating with international partners to facilitate global harmonization and regulatory acceptance.

•Exploring processes to incentivize and promote the use of NAMs.

•Identifying appropriate metrics for prioritizing activities, monitoring progress, and measuring success.

Since the ICCVAM roadmap was published, teams involved have reported that: “Key to the success of the roadmap has been implementation plans paired with specific toxicity endpoints, and communication with regulatory decision makers and end-users to understand stakeholder needs when designing and evaluating new methods. Efforts to replace the “six-pack” of acute toxicity tests and development of computational resources were particularly highlighted.[16]

16 Progress towards reducing use of animals in chemical testing and adoption of new methods to evaluate the safety of chemicals and medical products in the United States. Nicole Kleinstreuer (2023) WC12 Abstract.

3.6 EPA New Approach Methods Work Plan (2021)[17]

In 2018, the U.S. Environmental Protection Agency (EPA) published its Strategic Plan to Promote the Development and Implementation of Alternative Test Methods, as directed by The Toxic Substances Control Act (TSCA), following landmark amendments^ by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

EPA first published a list of NAMs in June 2018 and committed to updating the list at least once a year. The list has since been updated twice more in December 2019 and February 2021.

As also defined in the Strategic Plan, the EPA's the U.S. EPA's Office of Research and Development (ORD) and the Office of Chemical Safety and Pollution Prevention (OCSPP) were tasked with developing a work plan for reducing the use of vertebrate animals. The original EPA NAMs Work Plan was released in June 2020 and laid out the Agency's five objectives and strategies.

The objectives were:

(1) evaluate regulatory flexibility for accommodating the use of NAMs;

"An initial review of the major environmental statutes reveals that these statutes do not prevent EPA from considering information from NAMs when carrying out its responsibilities. Most of the statutes and regulations surveyed include statements such as the necessity of upholding scientific standards and using "the best available science," which may include NAMs".

(2) develop [animal use] baselines and metrics for assessing progress [towards NAMs];

(3) establish scientific confidence in NAMs and demonstrate application to regulatory decisions;

(4) develop NAMs that fill critical information gaps; and

(5) engage and communicate with stakeholders to incorporate their knowledge and address concerns.

There is already a website where EPA releases NAMs informational materials and updates (https://www.epa.gov/nam). This online resource provides a mechanism for EPA to distribute NAM information including the baselines and metrics on how the effort is progressing; a portal to access informational materials such as fact sheets, conference reports, webinars; and a mechanism for stakeholders to provide feedback.

In the 2020 Report, the Agency committed to regularly reviewing the work plan and acknowledged that the work plan would evolve as EPA's knowledge and experience grows, and as outside experts offer their perspectives and contributions. In the updated work plan, the main objectives and strategies were left unmodified. The primary changes in the updated 2021 work plan included:

- Expansion of the species covered in the work plan to include all vertebrate animals to be consistent with TSCA [Toxic Substances Control Act]
- Modified deliverables that provide revised timelines through 2024 that reflect the expansion of covered species and incorporate feedback received over the preceding years.
- Updated scope of the U.S. National Academies of Sciences, Engineering, and Medicine

17 www.epa.gov/chemical-research/new-approach-methods-work-plan

- study to include a review of validation and scientific confidence frameworks for NAMs in addition to evaluating the variability and relevance of existing mammalian toxicity tests.
- Two new case studies for building confidence and demonstrating application of NAMs.
- A pilot study to develop NAMs training courses and materials for a broad range of stakeholders.

The section under ‘establish scientific confidence’ included the following paragraph with an undertaking to”Characterize scientific quality and relevance of traditional toxicitytests.”

“Section 4(h)(2) of TSCA notes the need for information of “equivalent or better” scientific quality and relevance to vertebrate animal test-based results. This requirement implies that the scientific quality and relevance of the existing toxicity tests should be considered to understand the strengths and limitations of the existing models, as well as NAMs under development. The amount and type of analyses needed will depend on the NAM being developed, the adverse outcome of interest, and information available. For example, the inherent variability in traditional toxicity tests may limit the predictivity that could be achieved in any comparison. Furthermore, differences between laboratory animals and humans can impact the ability of these models to predict human health effects. As such, it may not always be appropriate to compare NAMs to traditional toxicity tests. EPA will need to focus on the mechanistic and/or biological relevance of the NAM for the hazard being assessed and potential uncertainties both with respect to and independent of the existing toxicity testing model. Although existing studies have evaluated important components associated with characterizing scientific quality and relevance, such as variability and human concordance, no authoritative study has been developed that can inform expectations for NAMs. The expectations will be incorporated into the scientific confidence framework in the subsequent deliverable.”

Several animal protection stakeholders were involved in sustained efforts to secure the TSCA amendments and were awarded the Lush Prize for Lobbying in 2017.

At the time of writing, the EPA is seeking stakeholder input on its work plan for discussion in forthcoming events in 2024.

3.7 The Research Modernisation Deal: A strategy for ending animal experiments. PETA (2023)[18]

In 2023, the NGO People for the Ethical Treatment of Animals (PETA) released a comprehensive report containing recommendations for 'modernizing U.S biomedical research' and, at the same time a slightly modified one for UK audiences. Although the report focusses its arguments on the problems animal use is creating for drug discovery, it also addresses regulatory [toxicity] testing more widely.

Both reports contain the following six recommendations:

1. Immediately eliminate animal use in areas for which animals have already shown to be poor and unreliable predictors for humans and have impeded progress.

2. Conduct critical scientific reviews to identify the areas in which the use of animals has failed to advance human health and should therefore be ended.

3. Implement transparent, robust prospective and retrospective evaluations for all projects using animals and allow for a public commenting period.

4. Work with organisations and agencies globally to harmonise and promote international acceptance of non-animal testing methods for regulatory testing requirements.

5. Increase funds for non-animal studies and decrease funds for animal studies.

6. Educate and train researchers and regulators on the benefits of and how to use non-animal testing approaches.

The reports contain substantial appendices which, as well as making specific recommendations for human relevant approaches under disease headings like cancer and Alzheimers disease, provides detailed advice for the following toxicity assessment areas:

Ecotoxicity

Aquatic Toxicity

Avian Toxicity

Endocrine Disruption

Eye Irritation/Corrosion

Genotoxicity and Carcinogenicity

Genotoxicity

Carcinogenicity

Phototoxicity

Pyrogenicity

18 www.peta.org.uk/features/research-modernisation-deal/

Reproductive and Developmental Toxicity

Skin Irritation/Corrosion

Skin Sensitisation

Systemic Toxicity

Acute Systemic Toxicity

Repeat-Dose Systemic Toxicity

Oral Route

Dermal Route

Inhalation Route

Tobacco and E-Cigarette Testing

In the same year, PETA UK began to build a formal call “for a government-led roadmap – with an ambitious time frame, clear milestones, and achievable goals – to reduce experiments on animals, with the objective of phasing out their use entirely.” [19]

19 www.politics.co.uk/comment/2023/09/24/peta-the-uks-political-parties-must-embrace-21st-century-science-without-animals/

3.8 A roadmap to phase out animal testing in the EU

(a) The European Citizens' Initiative (ECI)

In August 2021, concern that the cosmetics testing ban in Europe was not being enforced, led to a large public campaign involving both NGOs and companies called the "Save Cruelty Free Cosmetics European Citizens' Initiative (ECI)." The campaign's petition was eventually signed by more than 1.2 million people, thereby requiring a set of formal responses from the European Commission.

The petition had three requests:

1. Uphold the ban on all testing on animals for cosmetics ingredients for any purpose at any time.

2. Ensure human health and the environment are protected by managing chemicals without the addition of new animal testing requirements.

3 Commit to a legislative proposal, plotting a roadmap to phase out all animal testing before the end of the current legislative term.

(b) The Parliament's resolution

On September 16th 2021 The European Parliament adopted a **Resolution calling on the European Commission to establish an EU-wide Action Plan for the active phase-out of the use of animals in experiments.** The resolution:

- Calls on the Commission to improve coordination to achieve the goal set out in Directive 2010/63/EU by establishing a high-level inter-service taskforce, involving all key Directorates-General and agencies, to work with EU member states and other relevant stakeholders to draw up an EU-wide action plan, with the aim of driving an active phase-out of animal testing.

- Stresses that a clear and ambitious timeline and list of milestones should be set out to incentivise progress.

- Underlines that the action plan should include ambitious and achievable objectives and timelines to be set under the overarching reduction and replacement goal in order to incentivise change, with concrete and coordinated actions accompanied by indicators.

- Stresses that the plan should include, inter alia, proposals for better implementation and enforcement of existing initiatives, including a well-functioning system of controls.

- Highlights the need for increased and targeted funding under Horizon Europe for advanced non-animal models.

- Calls on the Commission, the Council and the member states to make sufficient medium- to long-term funding available to ensure the fast development, validation and introduction of alternative testing methods to replace animal testing methods, particularly for key toxicological endpoints.

- Calls on the Commission to set reduction goals in consultation with relevant agencies, in particular ECHA and EFSA, through a more proactive implementation of the current regulations on the safety of chemicals and other products, and to support the reduction goals by using a fully

connected and interoperable EU chemical safety database.

• Recalls that Article 13 of REACH requires that the test method requirements be updated as soon as non-animal methods become available.

• Urges the Commission to work together with member states to prioritise actions to educate, train and retrain scientists, researchers and technicians in using advanced non-animal models and in sharing best practices, and to raise awareness of validated non-animal

models among those involved in evaluating project proposals and attributing funding.

• Highlights the need to work within international structures to speed up validation and acceptance of alternative methods, ensure knowledge transfer and provide financial support to non- EU countries, where scientists may be unaware of alternative methods and

where testing facilities may lack the necessary research infrastructure.[20]

(c) The Commission's response

The Commission issued a detailed response to the three requests in the Petition in July 2023. Campaigners were disappointed by its response to the first two, but on the third it wrote this:

"The Commission will immediately launch the work to develop a roadmap that will outline milestones and specific actions, to be implemented in the short to longer term, to reduce animal testing and that would be pre-requisites for a transition towards an animal-free regulatory system under relevant pieces of chemical legislation (e.g. REACH, Biocidal Product Regulation, Plant Protection Products Regulation and human and veterinary medicines).

Core of the roadmap will be to analyse and to describe the necessary steps to replace animal testing in pieces of legislation that currently require animal testing for chemical safety assessments. The roadmap will outline the path to expand and accelerate the development, validation and implementation of non-animal methods as well as means to facilitate their uptake across legislations. The Commission intends to discuss with Member States and stakeholders elements of the roadmap at a workshop in the second half of 2023 and to present the progress made at a second workshop in the second half of 2024.

It is intended to finalise the work on the roadmap in the first quarter of the term of the next Commission. When drawing up the roadmap, the Commission will work closely with its agencies, the Member States and relevant stakeholders from NGOs, industry and research. The roadmap's development will be supported by assessments that were carried out by the Joint Research Centre, EFSA's work on non-animal approaches, the EFSA roadmap and the expertise of ECHA, EFSA and EMA."[21]

20 Resolution summarised in "Reducing and replacing animal experiments: Europe needs an action plan. Cruelty Free Europe 2023". The original text is here: www.europarl.europa.eu/doceo/document/TA-9-2021-0387_EN.html

21 https://single-market-economy.ec.europa.eu/publications/communication-commission-european-citizens-initiative-eci-save-cruelty-free-cosmetics-commit-europe_en

The workshop referred to in the Commission response to be held ‘in the second half of 2023’ was hosted by the Directorate-General for Internal Market, Industry and Entrepreneurship (DG-GROW) on the 11th-12th December 20231. As described above, the Commission announced its intention for its roadmap to be finalised in the first quarter of the mandate of the next Commission. During introductory presentations at the workshop this was described as “end of 2025/beginning 2026”.

Stakeholder responses outlined how work should start now to be ready for the roadmap deadline, rather than waiting until after the roadmap is finalised.

Appendix 1 Other "roadmaps" not considered in this review

Alliance for Human Relevant Science

Launched in 2017, the Alliance for Human Relevant Science is a UK collaboration of scientific organisations, contract research organisations (CROs), NGOs and individuals. In 2020, the Alliance published the White Paper "Accelerating The Growth Of Human Relevant Life Sciences in the United Kingdom."

The alliance vision is that, in order to achieve this, strategic funding of animal-free methods, implementation of multidisciplinary infrastructures and collaborations, methodological training for (prospective) scientists, and regulatory changes are needed.

The focus of the Alliance and the White Paper is drug discovery and preclinical toxicity testing rather than regulatory testing for chemicals, meaning that it was not considered here, though key recommendations are similar. The White Paper also includes a comprehensive review of roadmaps, including some in this paper

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State of the Discovery Nation 2018

A report *'State of the Discovery Nation 2018',* by the Medicines Discovery Catapult and the BioIndustry Association, provided insights into the productivity of the UK's drug discovery community and the challenges and opportunities it faces.[22] Its focus on drug discovery also meant that it was not considered here.

Specific non-animal roadmaps for toxicology endpoints or specific technologies

(a) Organ-on-chip in development: Towards a roadmap for organs-on-chip: Massimo Mastrangeli, Sylvie Millet, The ORCHID partners, Janny van den Eijnden-van Raaij[23]

(b) Roadmap for Development of Alternative (Non-Animal) Methods for Systemic Toxicity Testing: Transatlantic Think Tank for Toxicology (T4)[24]

22 https://mspl.co.uk/news/mdc-state-of-the-discovery-nation-2018-report/

23 https://www.altex.org/index.php/altex/article/view/1339

24 https://www.altex.org/index.php/altex/article/view/455

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