National Centre for the Replacement Refinement & Reduction of Animals in Research

NC3Rs submission to POST: Technology alternatives to animals in life sciences research

Purpose and background

1. The NC3Rs is the UK's national centre for the 3Rs. We work nationally and internationally with the research community to replace, reduce and refine the use of animals in research and testing. Our response to the POSTnote consultation outlines the latest developments in replacement technologies, summarises key barriers to their adoption and describes how the NC3Rs is addressing these, highlighting opportunities for future UK leadership.

2. We refer to *replacement technologies* (also referred to in the POSTnote as 'technology alternatives to animals') as approaches that replace the use of animals in research and testing, with the term new approach methodologies (more commonly known as NAMs) used specifically for describing approaches to replace animals in the safety testing of new medicines and chemicals.

Who we are

3. The NC3Rs is an independent scientific organisation established by the government in 2004. We receive core funding from the MRC and BBSRC as well as support for specific funding calls, posts and programmes from other public, charitable and commercial organisations. We lead work across academia, industry and the public sector (including with research funders and government/regulatory agencies) to accelerate the development, adoption and regulatory acceptance of 3Rs approaches. We have extensive collaborations with the pharmaceutical, biotechnology, chemical and consumer products industries. Our work has multiple impacts – it minimises the use of animals, improves animal welfare, delivers robust and predictive models, tools and technologies for a range of research purposes, supports economic growth, addresses issues relating to research quality and integrity, and ultimately helps the UK's ambition to lead globally in the life sciences.

4. Replacing the use of animals is at the heart of the NC3Rs mission. We focus on replacing studies that involve large numbers of animals, high levels of animal suffering or are poorly predictive in terms of their translatability or reproducibility (and therefore waste animals). We have a strong track record in this area delivering outputs that range from research models and technologies to guidance and information resources, that combined have contributed to the use of hundreds of thousands of animals being replaced. We achieve our impacts through funding research and innovation, strategic partnerships with key national and international organisations, cross-sector collaborations and bespoke programmes that focus on areas such as toxicology and regulatory sciences to develop best practice recommendations that inform policy change across both regulatory and research contexts.

Why is replacement important?

5. Advancing replacement technologies is not only a scientific necessity but a strategic opportunity for the UK to lead globally in innovative research. For decades animals have played an important role in answering scientific questions related to human health and environmental protection. However, they are often costly and time-consuming to use and can present scientific limitations such as poor relevance to human biology. We have shown that replacement technologies offer the opportunity to address this by providing models that better recapitulate human physiology and disease than existing animal models, facilitating their use for various purposes including for disease modelling, the identification of therapeutic targets and safety and toxicity testing – this is illustrated in a report we have recently published which highlights the NC3Rs investment in human-based *in vitro* models to replace the use of animals, with over **£60M** committed to date.

6. Replacement technologies also present an opportunity for economic growth. Through the NC3Rs CRACK IT innovation programme we have funded 46 SMEs focused on human-based *in vitro* models, with four being established as a direct result of NC3Rs investment. For example, we supported the development of retinal organoids by the Newcastle-based SME Newcells Biotech to replace the use of rodents and rabbits in ocular disease research and toxicity testing. New cells Biotech now produces thousands of retinal organoids a month for screening therapies on behalf of more than 100 biotech customers globally. The organoids are also shipped around the world for customers to study retinal diseases and generate efficacy and safety data prior to first-in-human studies. The retinal platform accounts for a significant proportion of Newcells Biotech's total revenue, driving the growth of the company and enabling access to significant venture capital investment.

7. It is important to note that not all *in vitro* and *in silico* models are relevant to endeavours to replace the use of animals. Much of the funding for discovery research using *in vitro* or *in silico* models is focused on addressing biomedical and biological research questions and not on finding alternatives to animal studies – indeed in many cases they will be deployed for purposes in which animals would never have been used in the first place. That said, the increased emphasis by major funders in the UK on *in vitro* and *in silico* models will help to increase the complexity of the models (and therefore in the longer term their potential to replace animal use) and encourage scientists to shift their research priorities in order to use them.

Which technologies show the most promise as alternatives to animal testing in life sciences research?

8. Replacement technologies include a broad range of *in vitro* cell-based models (e.g. 2D cell cultures, organoids and organ-on-a-chip devices), human tissue approaches and *in silico* tools such as artificial intelligence (AI) and computational modelling. They offer opportunities across the biosciences sector, from basic research to drug and chemical screening, disease modelling, and regulatory safety assessment. Their suitability depends on the specific scientific question being asked – whether understanding normal biology, investigating disease mechanisms, predicting drug safety or efficacy, or assuring environmental safety. In areas such as chemical safety assessment, regulators already accept

some replacement approaches, removing the need for previously required animal studies. More broadly, these technologies are reshaping how human biology is studied, enabling the use of more predictive models. Key technologies and approaches include:

- **Simple *in vitro* models** (e.g. 2D single cell type models): Although these models do not fully capture the complexity of human physiology, they offer cost-effective, reproducible and scalable platforms for testing and screening. Their utility is particularly evident in applications such as chemical and compound screening, where they are already widely used in translational research. We have committed a total of **£20.1M** for the development, characterisation and adoption of simple *in vitro* models to replace animal use. Technologies we have funded include cell-based assays to replace animals in the testing of Botulinum B neurotoxin products and in measuring the toxicity of tetanus-based products for vaccine quality control.

- **Complex *in vitro* models** (e.g. organoids, 3D tissue cultures and organ-on-a-chip devices): Developing more complex 3D models that recapitulate the architecture of tissue and organ systems is a rapidly accelerating field. A major advantage is that the cells are maintained within a 3D matrix which more closely resembles a physiological environment than 2D models. This enhanced physiological relevance is critical for increasing their replacement potential, enabling use for studying disease mechanisms, identifying new treatments and conducting safety assessments. Complex *in vitro* models include *ex vivo* tissue (e.g. recovered during human surgeries), organoids (cell cultures that can self-assemble and replicate many aspects of organ physiology) and organ-on-a-chip devices that mimic the structure and function of human organs by combining living cells with microfluidics to enable the modelling of organ-level responses. We have invested **£51.6M** in the development of complex *in vitro* models to replace animal use. These include 3D epithelioid models that replicate human epithelial tissue, replacing the use of mice in some cancer research; tissue regeneration and gene editing studies; and organ-on-a-chip technologies such as the first *in vitro* human growth plate model which enables the study of cartilage development and musculoskeletal disease mechanisms, replacing traditional *in vivo* approaches that involve significant animal suffering.

- ***In silico* models and AI**: Computational approaches, including machine learning and quantitative systems toxicology, are increasingly used for early screening of drugs or chemicals, and integrating large datasets. They include mechanistic models based on known biological pathways, data-driven models that use AI or machine learning to find patterns in large biological datasets, or virtual patient populations which simulate variability between individuals to predict drug efficacy or toxicity. The potential for these models to replace animals is high – from building virtual models of animal species to *in silico* models of human organs and using AI in drug design to improve development. We have invested **£11.5M** in computational biology approaches, including for the development of a virtual dog to ultimately replace dog use in the testing of new medicines and human-based *in silico* models for evaluating cardiac drug safety and efficacy in industry, regulatory and clinical settings.

What are the main challenges/barriers to using these alternative technologies?

9. The use of replacement technologies in academia and industry is limited by a combination of scientific, regulatory, societal and economic challenges that we have summarised below. For new approach methodologies, these were detailed in a paper we published in 2024 in collaboration with industry and regulatory experts, and further explored in the context of medicines development at a workshop we recently co-hosted with the MHRA and ABPI.

Scientific and technological challenges

10. Replacement technologies face several scientific hurdles that limit their adoption. One of the primary barriers is the maturity of the technologies in that they do not yet fully replicate the complexity of whole organisms, particularly when assessing systemic or chronic effects. While many can offer valuable mechanistic insights, their predictive capacity for long-term or multi-organ responses currently remains limited.

11. A further challenge lies in validation – the process by which a method or model is assessed to determine whether it is scientifically reliable and suitable for its intended use, such as predicting human responses or ensuring medicine or chemical safety. Replacement technologies are often subject to more stringent validation requirements than traditional animal tests, which can delay their acceptance and use for regulatory purposes. It is essential that there are robust, fit-for-purpose validation and standardisation processes in place to build confidence in their reliability and appropriateness. Without consistent and reproducible performance standards and benchmarks, uptake of replacement technologies (and specifically new approach methodologies) will remain constrained. Following the exit from the EU, the UK lost direct access to formal validation processes via ECVAM[1], the EU's validation body for alternative methods. The UK would benefit from the establishment of a national validation centre, as well as ensuring that there is active representation in relevant international forums.

Regulatory challenges

12. Regulatory acceptance of new approach methodologies for safety assessment purposes has been slow and inconsistent across geographical jurisdictions. A lack of global harmonisation in regulatory frameworks and limited guidance on how data derived from replacement technologies can be integrated into regulatory submissions creates uncertainty for method developers and industry users and can discourage innovation and investment in alternative approaches.

13. Single alternative methods are unlikely to fully replace an animal test on a one-to-one basis. Instead, combinations of *in vitro* and *in silico* approaches are increasingly used to support early decision-making in drug development and chemical safety assessment, with some examples of combination approaches (e.g. for assessing skin sensitisation) now being accepted by regulators instead of data from animals. These integrated strategies can offer more predictive insights and reduce reliance on animal studies, particularly in the early stages of research and development, but can be challenging to implement

[1] EU Reference Laboratory for alternatives to animal testing.

because they require expert judgement and training, with consideration on a case-by-case basis. A shortage of platforms for data sharing hinders collaboration and limits the accumulation of the evidence needed to support regulatory acceptance of new approach methodologies, with industry stakeholders highlighting concerns about access to shared data and the challenges of contributing proprietary information.

14. While much of the focus tends to be on barriers to the acceptance of alternative technologies in regulations that require animal use (e.g. for product safety purposes) there are also factors that affect the use of replacement technologies in the regulations that are intended to protect the use of animals. In the UK, animal procedures that cause pain, suffering, distress or lasting harm are regulated by the Animals (Scientific Procedures) Act 1986 – the Act requires the use of scientifically-satisfactory replacement alternatives wherever possible instead of protected animals. In 2022, we commissioned the Rawle report to assess how effectively the 3Rs, including replacement technologies, are embedded in the oversight and review processes for academic research – from the funder to the institutional ethics committee to the Home Office regulator. The report highlighted significant gaps in the consideration of replacement opportunities with actions for all stakeholders required to address these.

Behavioural and cultural challenges

15. Resistance to change is a common barrier to the development and use of replacement technologies. There is often a lack of awareness among researchers, including regulators, industry and academic scientists, about the utility, capabilities and limitations of replacement technologies, and how the data derived from them can be used in practice. This knowledge gap can lead to hesitancy in adopting new technologies. In academic research disciplines in particular, familiarity with historically established 'gold standard' animal models, combined with the perceived barriers to accessing funding or publishing findings can discourage the use of replacement technologies even when they offer superior scientific value to animal models. The RSPCA published a useful report in 2024 on the barriers to the use of replacement technologies which included a qualitative study on the sociocultural factors impacting acceptance and uptake.

Economic and infrastructure challenges

16. Fragmented infrastructure and short-term funding cycles present barriers to the development, validation and use of replacement technologies. Many initiatives lack the sustained investment needed to support long-term research and ensure that promising methods are fully characterised and validated for integration into research and regulatory practices. Without appropriate infrastructure, replacement technologies often remain confined to individual research groups, limiting their broader uptake and impact on animal use.

Addressing the challenges to replacement technologies

17. The NC3Rs work involves a number of inter-connected approaches to address the scientific, regulatory, behavioural, cultural, economic and infrastructure challenges/barriers to replacement technologies. These include:

- Providing funding to support the development of scientifically robust replacement technologies and their characterisation to assess their reliability, reproducibility and translation for use across academic, industry and regulatory settings.

- Tackling the lag between the development and subsequent use of replacement technologies with dedicated funding to enable researchers to trial them in their own labs, helping to de-risk the process and build the confidence needed to transition to alternatives to animal research.

- Supporting the scale-up, assessment of market potential and commercialisation of alternative technologies into products and services that are readily accessible to replace the use of animals. We primarily deliver this through the NC3Rs CRACK IT Challenges programme but also have collaborative arrangements in place with the BBSRC for example to fund business interaction vouchers and to enable participation in the ICURe programme with £650k being committed for these in 2025.

- Funding infrastructure and skills development to build capacity and capability. For example, in 2024 we were allocated additional funding from DSIT to enable 11 awards, totalling £3.95M to be made. The awards included support for establishing core facilities to supply organoids and for specialist equipment to be purchased to allow the wider use of organ-on-a-chip technologies. Alongside this, we have funded first-class training and skills development in replacement technologies, making 53 PhD studentship awards since 2020.

- Collaborating with regulators and industry scientists nationally and internationally, acting as an honest broker for sharing data and case studies to develop consensus recommendations and regulatory guidance. For example, our work to remove the requirement for single-dose acute oral toxicity studies – tests that involve severe animal suffering that were historically used as part medicines development – resulted in changes in international guidance, with the MHRA no longer seeing these tests routinely included in clinical trial applications. We have also led a global audit of WHO guidance documents for the quality, safety and efficacy of vaccines and biologics, collaborating with regulators and manufacturers worldwide to identify opportunities to remove obsolete animal tests from manufacturing and quality control requirements.

- Working with academic and charitable research funders so that the use of replacement technologies is included in their policies and assessed as part of their grant review processes.

- Partnering with major research funders to run joint calls to increase the funding available for replacement approaches and raise the visibility of alternatives as a desirable scientific goal – see for example the joint call with the BBSRC on next generation non-animal technologies in 2022.

- Developing the RIVER (Reporting *In Vitro* Experiments Responsibly) recommendations to improve the reliability and methodological rigour of *in vitro* studies in order to firstly help build confidence in the utility of *in vitro* studies and secondly avoid animals being wasted to provide cells and tissues for poor quality *in vitro* experiments or used in studies based on unreliable findings from *in vitro* research.

- Facilitating open science and the rapid dissemination of replacement technologies via the *NC3Rs Gateway*, a publishing platform in collaboration with F1000Research which enables researchers funded by the NC3Rs to share their detailed methodologies in order to build confidence and awareness of the alternative technologies that are available. There are currently 47 papers on the gateway – 64% are on replacement technologies – these have been viewed in total 91,148 times and downloaded 13,930 times to date.

- Fostering collaboration, knowledge sharing and capacity building through specialist Networks, workshops and the establishment of the NC3Rs Regulatory Science Forum. The latter was launched in 2024, specifically to support dialogue and joint working between industry scientists and regulators to identify priority areas for replacement technologies and clarify data requirements for the use of new approach methodologies.

- Publishing policy documents including, for example, the UK Chemicals Regulation Vision launched in 2024 in collaboration with the British Toxicology Society on the steps required to modernise chemical safety assessments to reduce reliance on animal testing; and the 2022 Rawle report on the inclusion of the 3Rs in the review and approval processes for academic research using animals. For the latter we are working to improve consideration of replacement technologies, primarily through supporting specific roles and functions that are required of all establishments licensed under the Animals (Scientific Procedures) Act 1986 in the UK. Alongside this, we are delivering a commission from the Animals in Science Policy Unit to improve the exposition of the 3Rs in Project licence applications.

- Addressing knowledge/information gaps with a range of resources and online and in-person events which reach thousands of researchers worldwide each year. Examples from 2025 include a joint event with the British Toxicology Society on the use of AI in safety assessment and a webinar series on replacement technologies with Togeth3R – a consortium of eight European 3Rs centres.

What do you think about government policy in this area?

18. The UK is widely recognised as having a world leading role in the 3Rs. Maintaining this position is essential for scientific and economic growth reasons and for addressing societal concerns about the use of laboratory animals. The UK is well placed to do this with its strong life sciences base, the national expertise provided by the NC3Rs and a regulatory regime that mandates the development and use of 3Rs approaches. However, there have been significant changes in the last five years with a global shift in attitudes and support for the use of replacement technologies by major organisations in the EU and North America. The UK risks being left behind without sustained investment in replacement alternatives, including in the associated infrastructure to support equitable access and in the skills development required to maximise the use of these technologies. There is also a need for regulatory reform to accelerate the use of alternative approaches and underpinning this a clear pathway for validation and regulatory acceptance is required. There are substantial opportunities for collaboration internationally and it is essential that the UK is represented on relevant fora with a unified voice. The latter is dependent on joined-up thinking across Government departments (including the Home Office, DSIT, Defra and DHSC)

and associated agencies and advisory bodies. The recent work to define departmental responsibilities as they relate to animal research and the use of alternatives is an important step that we welcome. This together with the forthcoming Government strategy on animal alternatives and its delivery in practice should ensure that the UK has the ambition needed in this area.

19. It is important to note that while there are exciting and realistic opportunities to replace the use of animals, there are still significant scientific and technological barriers to be addressed which mean that animal use will be required for many years to come. It is essential that the messaging around the maturity of replacement technologies (and indeed the limitations of animal models) is accurate from both 'sides' on what is often a polarised debate between those 'for' and 'against' animal research. The UK should ensure that it remains at the forefront of high standards in the conduct of animal research and that those involved have the necessary support in place to enable them to do this.

If you could get policymakers to understand one thing about this area of research, what would it be?

20. Coordinated, long-term investment in research, validation, infrastructure and skills development is essential to realise the full potential of replacement technologies in academia and industry and for regulatory testing purposes. Their successful integration and translation depends on global harmonisation and improved regulatory clarity – the UK has an opportunity to play a greater role in international efforts to align regulatory frameworks and data requirements. The widespread use of replacement technologies in academic research will not happen without supportive practices and policies. The latter includes ensuring that funding, peer-review and journal editorial criteria improve scientific confidence and foster cultural acceptance of replacement technologies, challenging the often default reliance on *in vivo* models.

Further reading

1. Peer-reviewed publication: Sewell *et al.* (2024). Article outlining key barriers to NAMs adoption and recommendations for overcoming them.

2. NC3Rs Network: NAMs. A hub connecting researchers, regulators and industry to share models and best practices.

3. Workshop report: Incorporating new approach methodologies in the development of new medicines. Joint MHRA/ABPI/NC3Rs workshop exploring regulatory integration of new approach methodologies.

4. Policy paper: UK Chemicals Regulation Vision. Strategic recommendations for modernising UK chemicals regulation using new approach methodologies.

5. Briefing paper: Improving translation and minimising animal use with human-relevant *in vitro* preclinical models. Overview of how advanced *in vitro* models can reduce animal use and improve research outcomes.

6. NC3Rs Gateway. An open-access publishing platform in collaboration with F1000Research for 3Rs research, supporting transparency, reproducibility, and rapid dissemination of new findings.

7. Rawle report. Review of the regulatory approvals processes for animal research in the UK.

8. RSPCA report: Supporting replacement in academia (2024). Review of the barriers around the acceptance and uptake of non-animal methods in science in UK academia.