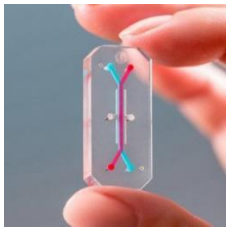
Could we achieve a phase-out of animal experiments in the UK?

Report of an RSPCA online debate



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On 1 July 2021, the RSPCA held an online debate on the feasibility of phasing-out animal experiments in the UK. European Union (EU) Directive 2010/63/EU, which regulates animal use, includes a Recital stating that the Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals as soon as it is scientifically possible to do so. Commonly referred to by the European Commission as the 'phase-out strategy', this ambition has been widely accepted by the scientific community and regulators alike, in recognition of the scientific, economic and ethical benefits of replacement with Non-Animal Technologies (NATs) – but the UK currently has no such explicit goal in place.

The discussion was chaired by Emma Slawinski, RSPCA Director of Advocacy and Policy, and the panel comprised Dr Penny Hawkins, Head of the RSPCA Animals in Science Department; Professor Sir Chris Evans, Excalibur Healthcare Services; Professor Martin Knight, Queen Mary University of London and Emulate Organs-on-Chips Centre; Dr Julia Fentem, Unilever Vice President, Safety and Environmental Assurance Centre; Professor Andrew Jackson, Newcastle University; and Professor Dominic Wells, Royal Society of Biology. The audience included members from the National Centre for the 3Rs, Laboratory Animal Science Association, Animal Free Research UK, Institute of Animal Technology, Animals in Science Committee, British Toxicology Society, British Pharmacological Society and Fund for the Replacement of Animals in Medical Experiments. Attendance at the event does not necessarily indicate support for any of the statements or conclusions within this document.

This report sets out the main points from the discussion. It summarises statements made by the panellists, each of whom had differing perspectives and backgrounds.

The debate was framed around three driving questions:

- Which research fields are most promising with respect to replacement?
- What are the key ongoing obstacles to replacing animal use with Non-Animal Technologies, and how might these be overcome?
- What would a feasible 'phase-out' plan look like for the UK?

Summary of key points

Regulatory testing shows particular promise for replacement. Major obstacles relate to mindset and ambition, rather than science or the availability of NATs. Much **medical research** is already done *in vitro*, but more models of different organs and diseases are needed. Some areas of **fundamental research** present challenges to replacement. Recent developments in NATs, such as organs-on-chips and organoids, are exciting, but there are still **not enough NATs** to replace all animal experiments.

The primary driver for a UK phase-out would be a clear statement, and commitment, from the Government.

Also needed are:

- More funding to develop and validate NATs
- A phase-in of NATs to match the phase-out of animal use
- Government follow up to the 2015 Innovate UK NAT Roadmap
- Learning from phase-out initiatives and strategies in other countries
- Immediate enforcement of a legal principle that animal testing is a last resort for chemicals regulatory testing
- An immediate end to the use of animal testing for consumer products (such as cosmetics, toiletries and novel foods)
- Mentoring for the regulatory community by early career scientists, with challenges to regulatory requirements for outdated animal tests in which it is unclear how they protect human health and the environment
- Better training for life scientists in searching for NATs, using new techniques and – for those working in regulatory toxicology – challenging regulatory requirements for animal tests

"The RSPCA is right to lead the charge for the Government, leading funders and investors in the UK to speed up the move to the use of Non-Animal Technologies in science. Make it a priority and it can happen, but it needs bold and ambitious leadership which this government could deliver."

Professor Sir Chris Evans

Which research fields are most promising with respect to replacement?

Animal experiments are done for many different purposes, including human and veterinary medical research, risk assessments of chemicals, such as pesticides, and fundamental (or 'basic biology') research. Broadly speaking, the potential for replacing the use of animals varies between these different fields.

Regulatory testing, or the risk assessment of chemicals that may be hazardous to human health, other animals or the environment (including medicines, pesticides, agricultural and industrial chemicals and pollutants), shows particular promise.

For example, Unilever has spent over 15 years building knowledge, capability and confidence in NATs, and now believes that product safety can be effectively assessed without animal tests. This is having a positive effect in practice; the EU Scientific Committee on Consumer Safety, which advises the European Commission on health and safety risks of non-food consumer products, has recently incorporated NATs in its Guidance Notes. The forthcoming UK REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation, which will establish procedures for collecting and assessing information on the properties and hazards of substances, could be an opportunity to avoid the use of hundreds of thousands of animals, by using a combination of NATs to protect human health and the environment from adverse effects of chemical exposures (note: REACH is originally an EU regulation; the UK is defining its own version as a consequence of leaving the EU).

Much **medical research** is already done *in vitro* (using cultured cells or tissues outside a living organism); for example, studies to see how drugs act on different tissues and to select promising candidate drugs. Advanced *in vitro* models are increasingly available, such as organs-on-chips, which are sophisticated, three-dimensional, human-based models that can be used to predict the safety and efficacy of new therapeutics. For example, the lung-on-a-chip was part of the test battery to develop COVID therapeutics, successfully predicting long-term performance. Other advanced models include organoids, which are small, three-dimensional tissue cultures which can replicate specific organs, or aspects of an organ. Advanced models like these have the advantage of using human cells and tissues, which can make results more translatable, although more work is needed to ensure diversity of the human source material regarding gender, age and ethnicity.

NATs therefore have the potential to lead not only to reductions in animal numbers, but also to better science and therapeutics. The current drug pipeline includes *in silico* (computer modelling) and *in vitro* methods, animal 'models' and tests, and human clinical trials, with significant attrition at every stage. NATs could reduce this attrition rate by enabling more effective screening out of harmful or ineffective candidate drugs and facilitating more translatable tests that are based on human cells.

What are the key ongoing obstacles to replacing animal use with Non-Animal Technologies, and how might these be overcome?

The current lack of availability of NATs is the primary obstacle across many research fields. Recent developments are exciting, but ongoing needs include a greater diversity of human cells, models of different organs and diseases, and ways of modelling interactions between different organs.

There should also be more incentives for scientists, regulators and companies to recognise the benefits of NATs, making animal tests a last resort.

In **safety science and regulatory testing**, there is a significant gap between the available science and the requirements of regulatory authorities. Major obstacles in this case relate to mindset, ambition and belief, rather than science and the availability of NATs. There is often poor understanding of available new technologies, and how to apply these when making decisions about chemical and product safety. This makes toxicologists more likely to default to 'traditional' animal tests.

There is also a lack of investment in building new safety science and regulatory capabilities. This could be overcome by increasing the number of contract research laboratories that are skilled in using NATs and interpreting the data these generate. The US has already initiated this transformational change, investing in a centre for computational toxicology at Research Triangle Park and is currently the world leader.

Fundamental research, which is done to investigate how human and animal bodies work while healthy or diseased, is more complex and challenging. For example, gene regulation cannot currently be studied *in vitro*, because an individual gene can be activated at different times and in different organs within the body. In gene therapy trials using viral vectors (modified viruses that 'deliver' genetic material into cells), only one dose can ever be given to the human patient because they will develop immunity to the vector. Animal studies are done first to make sure that the dose will benefit the patient.

A complete, functioning organism is also needed for much brain research, especially if this is looking at links between brain and behaviour. A lot can be done using humans, for example using scanning technology and brain tissue from surgery. The BrainGate programme involves helping people with paralysis by developing Brain-Computer Interface technologies to afford them some independence, and these implants can also include a 'scientific payload' to enable researchers to gather data at the same time. Brain organoids can be used in some studies, but they cannot capture the effects of experience during brain development. Some have also expressed concerns that a highly developed brain organoid may develop a level of consciousness and could experience 'suffering'.

Unfortunately, in many cases **science is currently the limiting factor** for replacement in fundamental and medical research, because sufficient NATS have not yet been developed and validated. The vision should be to develop medicines from bench to bedside without touching an animal, but the timeframe, cost, and regulatory overhaul will be significant. This is worth achieving, not only for ethical and animal welfare reasons, but also because it is logical to use human cells and tissues to develop drugs for humans - ultimately leading to truly personalised medicines. A successful example of an initiative to help build capabilities is the NC3Rs CRACK IT Challenge programme, which funds collaborations between industry, academics and Small and Medium-sized Enterprises (SMEs) to solve business and scientific challenges that will deliver the replacement, reduction or refinement of animal use.

The will to replace animals is present amongst the scientific community (and there is a legal requirement to use alternatives wherever 'practicable'), but the time frame is unpredictable, and individual scientists can leave it to others to pursue. The rapid development of COVID vaccines has shown what can be achieved when priority is given and minds are focussed towards a scientific problem, and efforts were made to avoid animal use within the process, but animal experiments were still a part of this and a battery of technologies is still needed in medical research.

Although the value of many animal 'models' has been questioned, others have, and do, lead to medical progress. It is essential to review what an animal experiment is aiming to achieve and which other scientific tools are available, or could be repurposed, to fulfil the objectives. Using animals is not an 'easy option' for scientists, as licences are required from the Government (via the Animals in Science Regulation Unit), but more information also needs to be shared about NATs and alternative approaches. For example, it is difficult to publish a scientific paper that solely describes a new model.

In all fields, **NATs will need to be effective** at predicting mechanisms of action and assessing risk, otherwise a public health incident could set the field back significantly. It is important to recognise that the current levels of attrition in the drug development process are due to a number of factors, including the relatively small numbers of animals and humans used in pre-clinical and clinical trials. When drugs are marketed and prescribed, they are used by much larger numbers of patients, making it more likely that lower-probability adverse effects will be observed. Despite this, it is possible that limited predictability in NATs could be perceived as exposing the public to avoidable risk.

A strategy for the replacement of animal research with NATS could be developed now. It could not (and should not) be an instant 'ban', but a clear process that takes us towards the ultimate objective. The

existence of, and support for, such a strategy, would itself provide a clear incentive for investment of time and resources in developing new NATs.

What would a feasible 'phase-out' plan look like for the UK?

The RSPCA is currently considering what a realistic and constructive UK phase-out plan would look like, which was a key reason for holding the debate. We recognise that multiple stakeholders will have roles to play, including the Government, regulators, funding bodies, industry, Animal Welfare and Ethical Review Bodies (AWERBs) and individual scientists.

The primary driver for a UK phase-out would be a clear statement, and commitment, from the Government.

The European Commission Policy Coordinator has discussed approaches to implementing the EU's goal of full replacement. These include analysing and prioritising efforts; ensuring that resources are available, including education and training in replacing animals; and using research funding programmes to develop scientifically sound research tools bridging between different disciplines.

An equivalent approach in the UK would require a clear ambition, strategic roadmaps and action plans in key areas likely to be most successful, with investment in building capability and driving the application of NATs. Large-scale academia-industry-clinician-regulator partnerships would be needed, such as those initiated by the NC3Rs CRACK IT programme.

A phase-out strategy will require stretching, yet realistic, milestones that will not lead to unintended, negative consequences for animal welfare. For example, arbitrarily reducing animal numbers could lead to greater severity for individuals or poor experimental design, wasting animals' lives.

The general public would also need to accept that medicines can be safe if they are not tested using animals. Given that three quarters of people consistently agree there should be more research into humane alternatives, public support for a considered phase-out would likely be high.

The list below (which is not exhaustive) sets out some actions that were identified as components of a phase-out strategy:

- **More funding to develop and validate NATs.** Academics find it difficult to secure funding and there needs to be a change in mindset to better support *in vitro* technologies. Whilst there are replacement (or 3Rs)-specific funding bodies such as the NC3Rs, AFRUK and FRAME, other funders should also decide to prioritise the development and validation of NATs, to facilitate the scientific breakthroughs that are needed. For example, UK Research and Innovation (UKRI) could build the development of NATs into its funding strategy, potentially through further support for the NC3Rs. This has been the model in the US, where grant giving bodies have been investing in NATs such as organoids and organs-on-chips, enabling new companies to be established with an academic research base, which are now collaborating with the pharmaceutical industry. As a consequence, the US Food and Drug Administration has relaxed its requirements for animal tests in some areas and is encouraging the use of NATs.
- **A phase-in of NATs to match the phase-out of animal use.** This should focus on the most 'urgently needed' models, with the greatest likelihood of success; the brain may be a step too far at present. In the future, it may be possible to model the brain by integrating NATs with machine learning, combining organs-on-chips with *in silico* modelling.

- **Government follow up to the Innovate UK NAT Roadmap.** Innovate UK (an agency which is part of UKRI) published a Non-Animal Technologies Roadmap for the UK in 2015, with the participation of funding bodies including the Medical Research Council, Biotechnology and Biological Sciences Research Council and NC3Rs. However, although the NC3Rs has a major 3Rs research and innovation programme which has awarded over £100 million in funding since 2004, the Government has not provided adequate leadership or support for the Roadmap. This should be revisited, updated (ideally led by the NC3Rs) with the scientific progress that has been made over the last six years, and used to focus a refreshed strategic plan on critical 'game changers'.
- **Learning from initiatives in other countries**, such as the Netherlands Transition Programme to stimulate innovation and set up interdisciplinary networks regarding NATs and the US Environmental Protection Agency (EPA) ambition to reduce its requests for, and funding of, mammal studies by 30% by 2025, and to eliminate all mammal study requests and funding by 2035.
- **Immediate enforcement of the legal principle of animal testing as a last resort for chemicals regulatory testing.** The UK could be more ambitious than the US EPA, by including a challenging milestone to end testing chemicals on animals for regulatory purposes by 2025. It is highly questionable to extrapolate data from animal tests to human health and protection when the variability in animal risk assessments is poorly understood. Achieving this will require commitment and investment, but it should be achievable.
- **An immediate end to the use of animal testing for consumer products** (e.g. cosmetics, toiletries, novel foods), on the basis that using animals for testing ingredients used in consumer products is neither scientifically necessary, nor ethically justified.
- **Mentoring for the regulatory community** (globally, as well as in the UK) by early career toxicologists, to achieve radical change by facilitating more creative use of available NATs. This would be coupled with challenges to regulatory requirements for data from outdated animal tests that cannot be justified because it is unclear how they protect human health and the environment.
- **Better training for life scientists** in searching for NATs, using new techniques and (where relevant) navigating regulatory frameworks.

A serious UK vision and strategy to phase out animal use, incorporating all of the above elements and more, would require political will and commitment from Government departments, industry, academia, research funders and individual scientists, as well as adequate funding and resources.

In the interests of animal welfare, better science, economics, and addressing legitimate public concerns about animal use, the RSPCA believes that it is time to create that vision.

The RSPCA is opposed to scientific procedures that cause animals pain, suffering, distress or lasting harm, and our ultimate goal is the replacement of animal experiments with humane alternatives such as Non-Animal Technologies. The Society's Animals in Science Department works to help ensure animals are replaced wherever possible, animal numbers and suffering are reduced, and welfare improved, for as long as animal use continues. For further information, please see rspca.org.uk/animalsinscience