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Governments have announced plans to reduce the number of animals, such as mice, used in experimental procedures.

CAN WE REALLY GET RID OF ANIMAL TESTING IN RESEARCH?

Advances in organ and computer models are raising the prospect that some animal experiments could be eliminated. But there are still huge hurdles to overcome. **By Diana Kwon**

Last November, the UK government announced a bold plan to phase out animal testing in some areas of research. Animal tests for skin irritation are scheduled for elimination this year, and some studies on dogs should be slashed by 2030. The long-term vision is "a world where the use of animals in science is eliminated in all but exceptional circumstances", the government policy reads.

Other nations are making similar moves. Last April, the US Food and Drug Administration (FDA) announced plans to make animal studies the "exception rather than the norm" in drug safety and toxicity testing in 3–5 years. The same month, the US National Institutes of Health (NIH) revealed an initiative to reduce the use of animals in research that it funds. This year, the European Commission plans to publish a road map to end animal testing in chemical safety assessments.

Ethical and animal-welfare concerns have long fuelled efforts to curb animal use in research — and now rapid advances in alternative scientific methods are accelerating the shift. These 'new approach methodologies' (NAMs) include devices known as organs-on-chips, 3D tissue cultures called organoids and computational models, such as artificial-intelligence systems. The number of biomedical publications using only NAMs grew from around 25,000 to 100,000 between 2006 and 2022, according to an analysis of studies on seven diseases by Animal Free Research UK, an organization that promotes the replacement of animal experiments[1] (see 'Alternatives on the up'). And China is investing heavily in this area: in 2024, it launched the Human Organ Physiopathology Emulation System, an infrastructure project dedicated to developing NAMs, backed with an investment of 2,640 million yuan (US$382 million).

Proponents say that NAMs can be better than animals at mimicking human biology and predicting whether new drugs are safe and effective. Organs-on-chips and organoids are often created with human cells, and computational models can be designed using human data. The shift towards alternative models is "long overdue", says Donald Ingber, a bioengineer at the Wyss Institute for Biologically Inspired

Engineering in Boston, Massachusetts, and a co-founder of Emulate, a biotechnology company in Boston focused on organs-on-chips.

But NAMs are a long way from ousting all animal procedures in research, scientists say. Some biological systems are too complex and unpredictable to study without animals. And many of the alternative methods have yet to be validated — to show that they represent the system they are modelling accurately and reproducibly enough to satisfy drug and chemical regulators. "Not all of these [alternative] models are ready for prime time," Ingber says.

On the decline

Efforts to replace, reduce and refine the use of animals in research (known as the 3Rs) have been ramping up for decades; in some places, use of animals is already falling. Data from the United Kingdom show that the number of scientific procedures on animals fell from 4.14 million in 2015 to 2.64 million in 2024. The total number of animals used in research and testing in the European Union and Norway dropped by 5% between 2018 and 2022. (The number used in the United States is hard to pin down because the law does not require reporting on rats, mice and fish.)

In the United Kingdom, around 76% of experimental animal procedures are for basic and applied research: understanding organisms, modelling disease and developing new therapies. Another 22% are part of regulatory procedures — mostly testing the toxicity and safety of new medicines and other chemicals before they can be used. Some 67% of all procedures involve mice or rats (see go.nature.com/3mzfkgw).

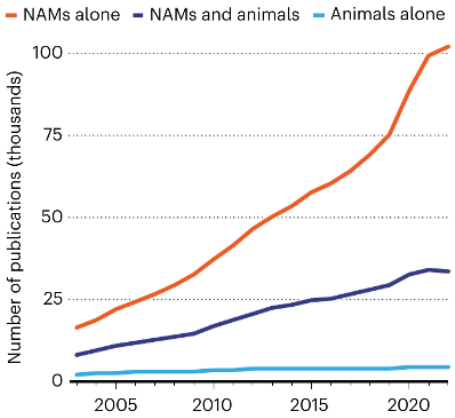
But these and other animals have limitations, especially when it comes to understanding and intervening in human diseases. Medicines that work in animal models during preclinical testing often prove ineffective in humans. This is one major reason that around 86% of investigational drugs fail in clinical trials[2], and why many researchers are focused on developing alternatives.

Take sepsis, for instance, a severe reaction to infection. Researchers have developed more than 100 therapies for sepsis that looked promising in rodent models but that were ineffective in clinical trials[3]. That's partly because of differences in human and rodent immune systems and the difficulty of mimicking a complex condition that varies from one person to the next in inbred mice that are genetically similar and raised in uniform conditions.

Increasingly, researchers see NAMs as a way to help. Joseph Wu, a cardiologist and researcher at Stanford University, California, and his team have been developing an approach that they dubbed "clinical trials in a dish". This involves generating induced pluripotent stem cells (iPSCs) from a range of people with a medical condition, using these to grow cells or organoids and then testing whether potential drugs improve how the 'diseased' models function.

ALTERNATIVES ON THE UP

In research on seven diseases, the number of publications reporting the use of new approach methodologies (NAMs), which do not use animals, has grown since 2003.



SOURCE: REF. 1

In one 2020 study[4], Wu and his team grew iPSCs and then endothelial cells — which line blood vessels — from members of a family carrying a mutated gene that can cause a common form of heart failure. Using these cells, the researchers were able to screen possible drugs and pinpoint one that helped to improve cardiovascular function in two members of the family with the mutation, and that might be used more widely. Integrating this method into a drug-development pipeline, says Wu, could help to reveal whether a drug works before animal testing, reduce the number of animals used and increase the success of clinical trials.

Studies suggest that some NAMs are as good as, or better than, animal tests. Emulate has developed an organ-on-a-chip system called Liver-Chip, a USB-stick-sized device in which human liver cells are grown in tiny fluid-filled channels and used to test whether potential drugs might cause liver damage. A 2022 study[5] by the firm suggested that the chips could correctly identify compounds known to have caused liver injury with 87% accuracy, without falsely flagging harmless compounds as toxic. The chips also detected 12 of 15 liver-harming drugs that were previously, using animal models, deemed safe enough to proceed to clinical trials.

"There is much more openness to considering these alternative approaches."

In 2024, Liver-Chip was accepted in the FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot programme, which supports the advancement of tools for drug development. If approved, pharmaceutical firms could use the chip to test for toxicity in place of animal models and submit the data as part of a drug-approval application.

Such chips are highly specialized, however. Edward Kelly, a toxicologist at the University of Washington in Seattle, and his colleagues developed a kidney chip that can reproduce aspects of acute kidney injury in humans[6] and that is being considered for the ISTAND programme. But the device includes only one of the kidney's more than two dozen cell types, he says. "It's a reductionist approach, which allows us to study those cells in greater detail. But understanding what happens in the whole human kidney still requires animal studies," he says.

Organoid options

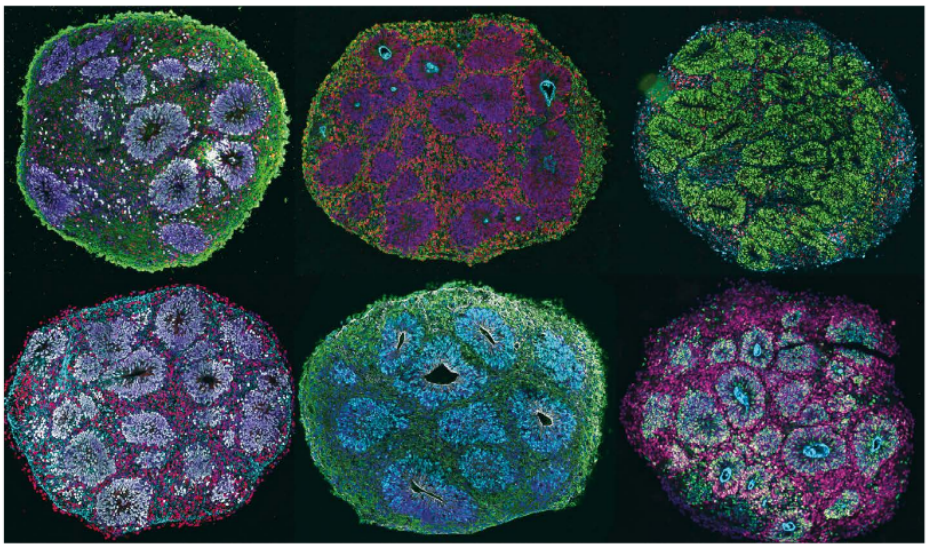
Another popular alternative to animal testing is organoids — 3D living systems that capture many of the features of real tissues or organs.

Over the past decade or so, researchers have created a wide array of organoids that can model human diseases, including cancers and genetic disorders such as cystic fibrosis — and used those to screen for possible drugs and test for toxicity. In a 2021 study[7], researchers generated human liver organoids using iPSCs. They used these to create a toxicity screening tool that detected substances that curbed the organoids' bile transport and mitochondrial function. The assay was highly accurate when tested on 238 marketed drugs.

And a third alternative is computational models, in which researchers test how a drug behaves *in silico*. In 2021, a team developed a tool for testing whether a compound causes skin sensitization — an allergic reaction in people. This is a standard part of safety testing for chemicals in industrial and household products and medicines, and conventionally requires animal tests. The team built a virtual test using data on around 430 chemicals from previous human, mouse and laboratory studies, and showed that it could accurately identify chemicals with a 1% chance of causing a skin reaction[8]. The tool was accepted as an approach for skin-allergy testing last year by the Organization for Economic Co-operation and Development, which sets internationally recognized guidelines for safety testing chemicals.

Researchers hope that AI can help too. Several regulatory agencies, including the FDA and the European Medicines Agency (EMA), are working on integrating AI tools into their chemical or drug safety-assessment pipelines.

In 2023, researchers at the FDA's National Center for Toxicological Research in Jefferson, Arkansas, and their colleagues used clinical data on more than 8,000 rats treated with 138 compounds to build a generative AI model called AnimalGAN. In a simulated experiment involving 100,000 virtual rats, the team showed that the model could correctly rank the liver toxicity of three drugs with similar



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Human brain models and other organoids could reduce the use of animals in research.

chemical structures[9]. This approach is now part of a broader programme at the agency to advance the use of AI tools in toxicology.

The pharmaceutical industry is increasingly investing in NAMs. Marianne Manchester, global head of pharmaceutical sciences at the multinational drug company Roche in Basel, Switzerland, says that the firm has a growing number of studies using NAMs to test drug candidates in areas such as oncology and immunology. In 2023, the company launched the Institute of Human Biology, which is developing human model systems, including organoids, to speed up drug development. Animal data are still mandatory for most new drug applications for marketing approval in the United States and Europe, but the company has waivers to use NAMs data for 12 submissions to regulatory authorities, including the FDA and EMA, Manchester says. "There is much more openness to considering these alternative approaches."

Staged approach

The 2025 announcements from the UK and US governments contained various commitments to accelerate the development and uptake of NAMs. The UK government strategy — in line with some other policy and trade groups — defined three 'baskets' of animal tests, and targets for their replacement.

The first encompasses tests that can be quickly phased out because good replacements exist, such as the skin-irritation tests due to be dropped this year in favour of computational, cell or chemical tests.

The second includes procedures that will take longer to replace. NAMs in this group include 'pharmacokinetic' studies that analyse how the body moves and metabolizes a drug. The government says that it will cut such tests in dogs and non-human primates by at least 35% by 2030. The third basket, methods for which no good alternative methods exist, contains just one example: use of fish to test endocrine disrupting substances as part of environmental testing. (In this case, the goal is to develop alternative methods by 2035.)

As part of its April announcement, the FDA published a road map to reduce, refine and replace animals in drug testing. The programme will focus, at first, on doing this for testing of monoclonal antibodies because, the road map says, animal studies are expensive and poor at predicting human responses to these drugs. The NIH, meanwhile, announced last July that it would no longer issue funding opportunities "focused exclusively on animal models of human disease" as part of a wider programme to encourage studies with NAMs.

One of the biggest obstacles to the use of NAMs in drug and chemical testing is validation. Researchers must typically submit data showing that a model system is accurate and reproducible to national and international validation bodies — such as the EU Reference Laboratory for alternatives to animal testing or the Interagency Coordinating Committee on the Validation of Alternative Methods in the United States. These help other agencies to decide whether data from a model is sufficient for future regulatory applications.

But this process can be costly and labour intensive, says Natalie Burden, head of NAMs strategy at the National Centre for the Replacement, Refinement & Reduction of Animals in Research in London. And the validation studies needed can differ from one method to the next.

The new UK and US strategies all put an emphasis on accelerating validation so that data from more alternative methods will be accepted by regulators. The UK government said that it would establish a Centre for the Validation of Alternative Methods that will connect labs, policymakers and regulators in pursuit of this goal. Last September, the NIH announced a Validation and Qualification Network to speed up regulatory approval of NAMs, and said it was investing $87 million in a centre to develop standardized organoid models.

The increasing adoption of NAMs makes rigorous validation essential, says Kent Lloyd, a geneticist and director of the NAMs Testing Center at the University of California, Davis. "Unless we hold NAMs to the same level of rigour and transparency that we expect of animal models, there will be harm done," he says.

Accelerating uptake

Many researchers have welcomed the latest push to speed the uptake of animal alternatives, saying that these techniques have not been adopted at a quick enough pace. "For years, it's always been thought that animals should be the default," says Valerie Speirs, a cancer biologist at the University of Aberdeen, UK. Speirs, Wu and other scientists have expressed frustration at the slow pace of change and argued that peer reviewers and funders still favour papers or grant applications that include animal experiments.

But scientists also have concerns. Some of the announcements from funders and regulators risk giving the misleading impression that NAMs are more advanced than they actually are, says Lloyd. And, he adds, drugs fail in clinical trials for reasons other than inadequate animal models. These include small sample sizes or other flaws in the design of animal experiments that can falsely suggest a potential drug is effective — problems that NAMs can have too. "My concern is that there will be just as much failure in clinical trials using NAMs as there has been using animal models," he says.

Some animal studies remain essential for the foreseeable future, researchers say. Biological systems, such as entire organs with intricate networks of blood vessels and nerves, interacting endocrine and reproductive systems or the ageing of tissues are difficult to recreate and study in organoids or organs-on-chips, says Robin Lovell-Badge, a biologist at the Francis Crick Institute in London.

Human behaviour and cognition also remain mostly impossible to model in a lab dish, says Sarah Bailey, a neuropharmacologist at the University of Bath, UK. When it comes to unpicking the complexity of biology, she says, "we will still need to use animals in basic discovery science for a while to come".

Diana Kwon is a freelance science journalist in Berlin.

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