Summary Evidence for Petition Debate

Petition: **End the use of animals for toxicity test & prioritise non-animal methods (NAMS)**
Date & Time: **Monday 19th February 2024 at 4.30pm**
Location: **Westminster Halls, Grand Committee Room**

The petition raises the subject of prioritising modern scientific techniques collectively known as New Approach methodologies (NAMS) that do not require the use of animals to prove the safety of the same chemicals and drugs over and over again. The team behind the petition have worked extensively with key experts in their fields (listed over the page) to create a briefing to provide a comprehensive overview of both the background, the current situation and how a new future could look. Shortcuts to the key sections of the document are below:

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Expert references & points of contact

All the experts listed are ready and willing to help you should you need any further information and welcome questions and interest in this subject. Likewise petition creator Maria Iriart, at admin@thecampbeagle.com.

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For any questions on the science of NAMs vs animal studies, the economic opportunities for UK businesses, "future-proof" job creation in science / STEM careers, with a perspective as CEO of a UK SME with a global presence in this space.

1.0 Summary Evidence

1.1 No explicit UK legal requirement

In the UK, there is no explicit legal requirement to use animals for testing pharmaceuticals and chemicals. International guidelines do however include animal tests as the standard expectation. To use a non-animal method it must be formally validated and accepted as a "replacement". If no officially accepted non-animal method exists, the UK Home Office will automatically grant a licence for the animal testing to go ahead. In practice this means tests that use animals are ***functionally*** required by law even though there is ***no explicit*** legal requirement to use animals in this way. This is in direct conflict with Animals in Scientific Procedures Act (ASPA 1986, revised 2012) which states:

> *"…the principle of replacement is the principle that, wherever possible, **a scientifically satisfactory** method or testing strategy not entailing the use of protected animals must be used instead of a regulated procedure."*

Yet animal use per se has never been validated or approved and is certainly not scientifically satisfactory.

Since 2021 medicines are regulated independently under the Human Medicines Regulations 2012 which does not mandate animal testing specifically. The latest version - Schedule 8, states that the materials to accompany a UK marketing authorisation for new drugs must include:

"The results of the following in relation to the medicinal product and its constituent active substances -
(a) Pharmaceutical (physico-chemical, biological or microbiological) tests;
(b) Pre-clinical (toxicological and pharmacological) tests; and
(c) Clinical trials."

The UK is part of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which publishes guidelines and standards for testing, e.g., Guidance M3(R2) on non-clinical safety studies. The latter lists all sorts of tests on animals for pharmacology and toxicity assessments. However, it also mentions that;

> *"This guidance should [..] reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles [..]. Although not discussed in this guidance, consideration should be given to use of new in vitro alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods."*

The ICH guidelines are an expectation to enable smoother trade between participating countries. They are *not a legal requirement.*

The Government response to the petition states: *"In the UK it is required by law that all new drugs are tested within two species".* This is ***untrue*** as confirmed by a question raised recently by Giles Watling MP.

A very complex and intensely bureaucratic regulatory system has been built up to control the safety testing of products ranging from industrial chemicals to pharmaceuticals and vaccines. Many animal tests are currently required for risk assessment to support the marketing and use of these products. To replace the accepted animal tests requires considerable effort to reassure the regulatory authorities that the alternative methods provide an adequate assessment of risk, and to overcome bureaucratic inertia.

Intensive efforts are needed to accelerate the validation and regulatory acceptance of alternatives through bodies such as the OECD and ICH, as well as ECVAM and the European Commission. This includes showing human relevant data matches previously obtained data from animal use, this ignores the fact that NAMS are human relevant and that animal models are not predicative of human biology.

1.2 The Science and Non animal Methodologies (NAMs)

NAMs are human-specific techniques that represent superior science. They are designed to provide results that are human relevant and therefore not hampered by the non-predicative translation of one species to another. NAMs are not a choice between an animal life or a human loved one, they provide an opportunity to use superior, cutting edge new approaches that are specific to humans making them more accurate.

NAMs are available right now, for example, a liver on a chip has 87% accuracy for human toxicity. Compare this with 92% - 96% of drugs being abandoned at human trial stage. Half of those failures are due to unanticipated human toxicity and most of the rest are due to efficacy reasons not identified in non predicative animal models. It is obvious we need to modernise our methods to accelerate new drugs to market and save effective medicine from being discarded that could save many human lives.

Conversely, adverse drug reactions kill thousands of people in the UK and costs NHS England billions each year. Tests on human cells and tissues can predict dangerous drug side effects where animal tests and even human trials fail.

1.3 Toxicity Testing

Animal testing is used in pharmaceutical, agricultural and industrial research to predict human toxicity, and yet analysis suggests that animal models are poor predictors of drug safety in humans. The cost of animal research is high, financially, time delays in drug approval, and in the loss of potentially beneficial drugs for human use.

Using animals to predict toxicity safety of human pharmaceuticals can:

1) Falsely identify a toxic drug as “safe”
2) Falsely label a potentially useful therapeutic agent as toxic.

An analysis of 2,366 drugs concluded that:

> *“Results from tests on animals (specifically rat, mouse and rabbit models) are highly inconsistent predictors of toxic responses in humans, and are little better than what would result merely by chance, or tossing a coin, in providing a basis decide whether a compound should proceed to testing in humans” (1). Similar results were found for non-human primates and dogs (2).*”

When a human-toxic drug is identified as "safe" by animal testing, the most likely outcome by far is that the drug will fail in clinical testing, often due to unacceptable adverse human effects, and sometimes significantly harming volunteer research subjects in the process. Drugs that survive clinical trials and attain market approval may still be recalled later due to toxicity identified only after months or years of human use.

Of 578 discontinued and withdrawn drugs in Europe and the USA almost half were withdrawn or discontinued in post-approval actions due to toxicity (3). There are many notable examples of cases in which animal trials did not predict severe human toxicity, a few are listed below:

Isuprel
Developed for treatment of asthma caused over 3,500 deaths in Great Britain alone, despite safety in rats, guinea pigs, dogs, and monkeys, all of which had received doses far exceeding those administered in humans (4,5).

Thalidomide
Famously caused devastating phocomelia in an estimated 20,000 to 30,000 infants before it was withdrawn. However, animal tests failed to reveal significant teratogenicity in 10 strains of rats; 11 breeds of rabbit; 2 breeds of dog; 3 strains of hamsters; 8 species of primates; and various cats, armadillos, guinea pigs, swine, and ferrets (6).

TGN1412
An antibody to treat human autoimmune disease given at 1/500th the dose found safe in animal testing to 6 human volunteers in a phase I trial (7,8), rendering them all critically ill within minutes and leaving them all with long-term complications (9–11).

BIA-102474-101
Developed for a range of disorders from anxiety to Parkinsonism, caused deep brain hemorrhage and necrosis in all 5 human volunteers during a phase I clinical trial after it was administered in doses that were 1/500th of the safe dose for dogs. One volunteer died (12).

Fialuridine
Developed for treatment of hepatitis B, caused the deaths of 5 volunteers during phase II clinical trials despite being safe in mice, rats, dogs, monkeys, and woodchucks in doses that were hundreds of times higher. Two other volunteers only survived after receiving liver transplants (9).

When animal tests falsely identify a safe chemical as "toxic," the almost certain outcome is abandonment of further development. Undoubtedly many potentially beneficial drugs have failed animal testing and been lost to patients, even though they would have been both safe and effective, the magnitude of this type of "error" is unknown. Many highly beneficial drugs would have failed animal testing and never been brought to market except that they were developed before animal testing was required E.g. penicillin (fatal to guinea pigs), paracetamol (toxic in dogs and cats), and aspirin (embryo toxicity in rats and rhesus monkeys).

Contract research organisations account for most of the animal testing done in the United States and Europe. Statista, a global data portal for market and economic sector statistics, estimates the global markets for animal testing in 2018 at $7.4 billion for drug discovery, $11.2 billion for preclinical development and safety, $58.5 billion for clinical development, and $2.3 billion for central laboratory testing.

Reproducibility of animal studies within species, even when carried out under rigorous protocols, is questionable. Using a database of more than 800,000 animal toxicity studies performed for 350 chemicals under rigorous guidelines, a reviewer found toxicity was repeatable just 70% of the time in the same species (13). Another reviewer found that results for a single chemical often differed with animal model, strain, dose, and delivery route. About 26% of chemicals demonstrated contradictory results on repeat testing in the same species.

The absence of toxicity in animals (dogs, rats, mice, rabbits and monkeys) provides essentially no insight into the likelihood of a similar lack of toxicity in humans: the former contributes no, or almost no, evidential weight in relation to the latter. Quantitatively, if, for example, a new drug has (based on prior information, such as similarity to other drugs, data from in vitro or in silico tests, and so on) a 70% chance of not being toxic in humans, then a negative test in any of these five species will increase this probability to an average of just 74%. The most controversial species, dogs and monkeys, the use of which, as opinion polls show, the general public object to particularly strongly, were the least predictive for humans in this respect, raising the probability from 70% to just 72% and 70.4% respectively. Therefore, animal tests provide essentially no additional confidence in the outcome for humans, but at a great ethical, and financial, cost (14).

1.4 Funding and The National Centre of the 3Rs (NC3Rs)

It is very difficult to accurately identify how much the UK spends on human relevant NAMs research. However, calculations suggest it is close to insignificant at less than 1%. For example:

> 1) In 2019, the UK government's gross expenditure on research and development (R&D) was £ 38.5 billion. Around 40%, £ 15.4 billion, is spent on basic research which uses many animals and is largely publicly funded. The annual budget of the NC3Rs is around £10 million, of which around £ 6.375 million is for “replacement” although this is not all NAMs as includes replacing one species with another. This equates to just 0.016%.
>
> 2) NAMs funding represents between 0.2% and 0.6% of total biomedical research funding in the UK and ~0.02% of the total public expenditure (£10.45B for 2019-2020) on R&D. (15)

There is an urgent need for greater funding to improve the human relevance of research and greater human safety by accelerating the uptake of NAMs. The Government consistently points to the NC3Rs as the main source of funding for NAMs. However, the NC3Rs annual budget is only around £10 million and evidence provided to the All-Party Parliamentary Group (APPG) on Human Relevant Science in May 2021 indicated that around 16% of grants have focused on the ‘refinement’ of animal research, with around 20% focusing on reduction, neither of which address translational problems. Core funding for the NC3Rs is provided by the MRC and BBSRC. Since their combined budget allocation for 2021/22 was over £1 billion, a negligible proportion of this is being allocated to the NC3Rs. Appropriate funding will be essential for enabling the UK to realise its scientific and economic potential in the field of human relevant research.

ASPA 1986, Section 20B has enshrined the concept of the development of alternative strategies as a legal requirement. The SOS must support the development and validation of alternative strategies. Alternatives must be developed and promoted at a Governmental level, not just at a scientific level. Although the SOS has statutory duties to support the development of non animal testing this is often overlooked.

We refer you to https://www.humanrelevantscience.org/wp-content/uploads/APPG-report-March-2022.pdf for more information on funding and the lack of uptake of NAMs.

The NC3Rs commissioned Dr Frances Rawle, former Director of Policy, Ethics and Governance at the Medical Research Council (MRC), to produce a detailed review of the current 3Rs landscape. (16) https://nc3rs.org.uk/sites/default/files/2023-02/Rawle%20project%20report.pdf This is highly critical of the lack of funding and availability of information of "replacements." Extract from conclusions is that:

> *"…so the best strategy for improving this situation would be to ensure that the expert peer review organised by the funders explicitly covers this area."*

This is the subject of our last petition where we suggested an advisory NAMs specialist committee, even an independent report reached the same conclusion.

1.5 Dogs

The Government's own commissioned Ipsos Mori survey on UK public attitudes to animal testing in 2018 showed that 86% of people find it unacceptable to test on dogs for the purpose of medical research, *even when that research is said to be for the benefit of human health.*

MBR (Marshall BioResources) Acres near Huntingdon breeds up to 2,000 puppies a year to be sold to repeat dose toxicity laboratories. The same USA based company also flies in many thousands of beagle puppies to Europe including the UK. Most of these pups, with proven sentience equivalent to that of a 3-year-old child, are forced to ingest or inhale pharmaceuticals, industrial or agricultural chemicals for 28, 90 or 120 days. They are then killed by suffocation or by being bled out. Euthanasia drugs cannot be used as this could effect post-mortem results.

Ingesting is via a forced procedure called 'gavage', involving a flexible tube pushed manually down a dogs throat into its stomach without any pain relief for 1-3 times daily. This considered a mild severity classification.

Of all dogs used in research Beagles are the breed most often used in research because of their intermediate size and loving nature. Kevin J. Stafford, author of The Welfare of Dogs, speculated that:

> *"Their existence for some time as 'the' laboratory dog may make it easier for handlers and research scientists to use them without becoming too emotionally attached to them."*

The total amount granted by MRC in grants for research involving the use of dogs licensed under ASPA 1986: 2020 - £2,911,281 (2019 - £3,691,116).

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