Submission No 269

INQUIRY INTO USE OF PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH IN NEW SOUTH WALES

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Use of primates and other animals in medical research in New South Wales

(a) The nature, purpose and effectiveness of medical research being conducted on animals in New South Wales, and the potential public health risks and benefits posed by this research;

Bioscience research is based upon three pillars: laboratory-bench research, animal research and data from human experiences. Each of these provides knowledge which informs and supports the others. Practically every medicine and treatment available to doctors and vets has thus been developed and tested using animals. From insulin for diabetes (discovered and refined using dogs), through penicillin, vaccines, technologies and transplants, to the processes by which we train surgeons, all our medical progress to date has unavoidably involved some use of animals. In a recent and topical example, the rapid development of vaccines to treat COVID-19 (both m-RNA and viral vector-based vaccines) in response to the global pandemic was only possible because of decades of existing animal studies of coronaviruses and potential avenues for treatment. These were rapidly scaled up to move from proof-of-concept studies in mice that were relevant to the new virus, to full challenge-studies in primates. Misinformed claims that no animals were used in developing and testing these vaccines, or that animals played only a minor role, are simply untrue.

To be at the forefront of science-based medical research, providing both the understanding that underpins new concepts, and the training and testing that allows them to be used in humans, inevitably means using animals. Well-developed and considered policies around the use of animals in science offers protection to both the research and the animals involved by driving a humane approach to high quality science. Indeed, basing policies on uninformed and unrealistic ideas of the efficacy of both animal and non-animal models leads to the worst conceivable outcomes for humans, animals and society; from failing to adequately safety test medical treatments and devices, to lower animal welfare standards.

The odd framing of the terms of reference for this inquiry are increasingly apparent as each question is addressed. For instance, in light of readily available data, the question (a) above, effectively asks, what risk to public health is there from a component of the pharmaceutical testing regime that usually predicts human safety more than 90% of the time?

One of the near-universal and demonstrable benefits of animal research is the protection of public health. We could, by analogy, ask *"what are the public health risks of flood defences?"* The answer in that context is *"very little risk indeed"*, particularly since animal tests are just one component in a suite of safety tests.

We are asked to consider an extremely broad notion, which should be discussed with far greater context and specificity. In ensuring pharmaceutical safety, for instance, the concordance between animal and human safety averages 86%. Yet, if you were talking about a primate's ability to predict human kidney safety then the concordance is 100%. Gastrointestinal safety would be 77% and most results cluster around 92%. Because of this variance, research into the efficacy of animal models tends to focus on the specific application of the research. Programmes are usually required to state what species, for what purpose, in light of which condition.

However, average figures on the utility of animals in drug testing can reasonably be used to conclude that animal data add significant weight to safety evaluations and can be said to "predict" safe human outcomes 86% (on average) of the time.

Animals in drug testing

There are numerous international bodies and consortia looking at the question of animal use in different contexts. In 2016, the UK's National Centre for the 3Rs has worked with 37 relevant bodies including regulators, academia and industry to examine whether the use of a *second species* should always be mandated in drug safety testing. The NC3Rs, run in cooperation with other regulators such as the FDA in the USA, also presides over a "Crack It" challenge that hopes to replace *second species* animals by bringing computational modelling approaches to the point that they are fit-for-purpose by 2025. Funding for this is provided by Bayer AG, Eli Lilly and Company, Genentech Inc., Gilead Sciences Inc. GSK, Merck Healthcare KGaA, Roche and the Engineering and Physical Sciences Research Council.

Meanwhile the IQ consortium of pharmaceutical companies is seeking to drive excellence in research and has compiled a translational database of human/animal safety reactions, from which we have taken some of the impressive data cited above. Non-human primates show the strongest predictions of adverse effects, whereas the beagle dog performs most strongly in predicting an absence of clinical adverse effects. Combining data from rodent and non-rodent species, as is usual in toxicity testing, increases the predictivity of both safety and adverse events.

In pharmaceutical testing, as in other areas of research, the animal model is just one component, and is used alongside *in vitro* and *in silico* data. These "pre-clinical" tests are intended to see whether a compound is likely to be enough for stage one human trials only. They are not expected to "predict" what might happen in large human populations and are not expected to identify all drug side effects. Rather, the researchers are looking for specific indicators of toxicity in the heart, the liver or a range of other organs. These could mean lasting damage if the substance were given to healthy volunteers, and it is testament to the reliability of this process that there are so few disasters in stage one clinical trials. The current tests used for preclinical safety work extremely well.

While pre-clinical tests provide some preliminary data, human drugs are tested in humans, through four stages of clinical trials (three pre-approval and the fourth stage once a drug is prescribed widely in the human population), and any subsequent "failure" of a drug due to safety or efficacy hangs squarely on the whole testing paradigm rather than a part of it. Removing animals from this process would not improve the failure rate but would certainly increase risks to people participating in stage one clinical trials, as well as removing crucial safety data that could indicate, however infrequently, important issues such as carcinogenicity, before they manifest in human populations.

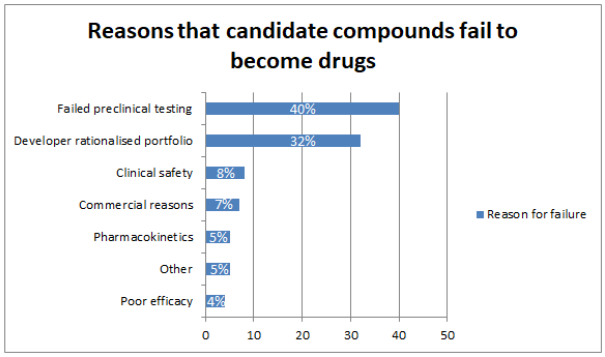
Most adverse drug reactions in the wider human population are, however, not due to a failure of testing. Most are preventable and known risks.

A paper on adverse drug reactions (ADRs) commonly cited by activists finds that most can be prevented. In http://www.bmj.com/content/329/7456/15.long 72% of the ADRs studied are classified as "avoidable". The authors write that "*Most reactions were either definitely or possibly avoidable. Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin, the most common reaction being gastrointestinal bleeding.*" This shows that in most cases the ADRs were known effects. The authors found that aspirin accounted for 61% of hospital admissions.

The authors further note that *"Nevertheless, it is impossible to be absolutely certain of a causal link between a drug and an ADR. For example, with low dose aspirin, up to half of the cases of bleeding may have occurred anyway, irrespective of aspirin use."*

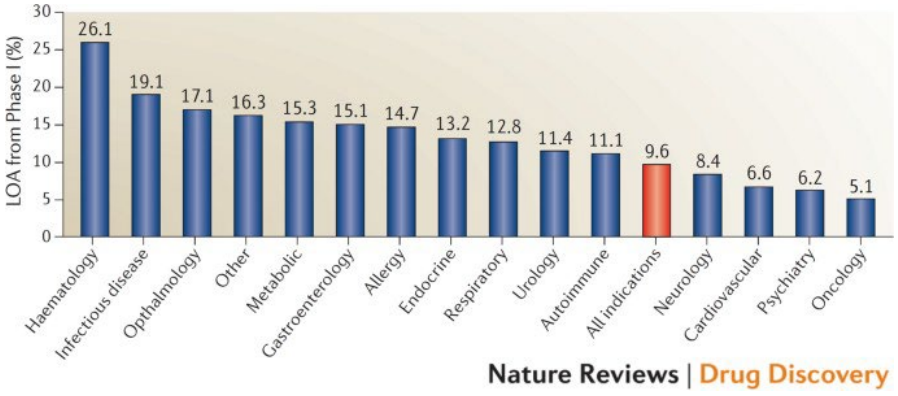
Differing 'success' by disease

Some conditions are more easily researched and treated than others, and there are numerous external factors affecting the chances of a drug making it to the clinic that are often commercial in nature.



Waring, M., Arrowsmith, J., Leach, A. et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov ***14,*** *475–486 (2015). https://doi.org/10.1038/nrd4609*

Through examination of the data only, the drugs with the lowest translational value to humans are cancer drugs, yet these are also advanced to human trials despite disappointing preclinical results because the disease is considered sufficiently serious that it justifies greater risks.



Mullard, A. Parsing clinical success rates. Nat Rev Drug Discov ***15,*** *447 (2016). https://doi.org/10.1038/nrd.2016.136*

Other safety tests

The benefits of animal research thus vary by application. For instance, testing that a product is safe for pets is important given that some 40% of Australian households have at least one dog. The purpose of those tests is not to hurt the dog undergoing the trials – that would mean the product isn't safe for pets – but they might be put down at the end of the testing process to check for hidden signs of disease. Similarly, animal testing is conducted to protect industrial workers, human consumers and natural assets like groundwater in the event of a spillage.

The adverse effects of untested products could not be controlled or necessarily treated following exposure without adequate safety data. Animal testing allows this data to be gathered while providing a humane death for animals suffer during exposure.

This approach means minimal risks to the health of the public and pets, but more significant risks are removed.

Treatments rejected due to animal testing

There is a widely held idea that animal testing is the basis of a go / no-go decision on marketing a drug, but this is rarely the case. No scientific study reaches the clinic in isolation, and drugs or therapies are not approved or rejected solely on the basis of animal data, but on all data. A compound that shrank a human tumour *in vitro* would not be immediately abandoned if the same effect was not seen in a particular mouse study, but further research would be expected to find out whether the original effect was indeed relevant to patients.

Previous calls by authorities to revisit "rejected" drugs for overlooked therapies are largely premised on the idea that medications are licensed on the basis of their *applicability to one disease*, when actually they may have effects relevant to several different conditions. The problem of "missing cures" is more of a problem with the drug development model and licensing process that limit their use. Indeed, millions of dollars in fines have been issued to drug companies for the promotion of compounds being used beyond their narrow, approved application.

Beyond this, many drugs fail to reach the clinic for commercial reasons and there may sometimes be attempts to revive them. Other drugs may be revisited when they initially failed preclinical testing (in both animal and non-animal methods), but new studies have revealed ways to repurpose them.

Animals in basic and translational research

Attempting to attribute percentage values to research into how basic biology works is largely meaningless since it cannot be clear how, if and when the information gleaned will be relevant. All current attempts to even estimate how long basic research takes to manifest in the clinic are flawed due to the use of different metrics and definitions used by various researchers and institutions. A previously 'useless' piece of information can yet prove to be critical as a fuller picture emerges.

Very often, criticisms of animal models will focus on these kinds of ambiguities as "evidence" of inefficacy. Similar tactics are used by climate change denialists asking why, if we know the climate is changing, we cannot predict the weather?

Nobel prizes for physiology or medicine, more than 80% of which have directly involved the use of animals, recognise game-changing discoveries which have shaped our understanding of life sciences. They are usually awarded decades after an initial discovery due to the inevitable uncertainty of their impact.

(b) the costs associated with animal research, and the extent to which the New South Wales and Federal Government is commissioning and funding the importing, breeding and use of animals in medical research in New South Wales;

Carrying out humane and high-quality animal research is undoubtedly expensive. The animals must be kept in highly controlled conditions, monitored by trained staff and with veterinary and behavioural expertise available. Nevertheless, this expensive and challenging research is done because of the enormous benefits it brings to society as a whole. Research on living animals is a small but vital component of not only basic biological sciences that allow us to understand ourselves and our world, but all of the translational sciences that are underpinned by them, including human and veterinary medicine, ecology and rural studies. Some of the key scientific questions of our time will only be answered through research involving animals.

(c) the availability, effectiveness and funding for alternative approaches to animal research methods and technologies, and the ability of researchers to meet the 3 R's of Replacement, Reduction and Refinement

We are unable to comment on the specific resources available to support the 3Rs in New South Wales. More generally, although support in meeting the 3Rs is provided through worldwide programmes, many researchers and their institutions have found that systematic application and the development of the 3Rs is challenging, requiring support, monitoring and active oversight to work most effectively.

(d) the ethical and animal welfare issues surrounding the importing, breeding and use of animals in medical research

These aspects of research usually require regulation and specialist provision so that the welfare of the animals over their entire lifetime can be accounted for. As with other terms in this inquiry the ethical and welfare issues will be distinctly different for each species of animal, which have specific needs and requirements.

There is little that can be generalised between various classes of research, and different species of animals feature more or less across different research activities. The answers that can be given to these questions will therefore differ depending on which animal and which purpose is being considered. That said, animal protection regulations around the world, including in Australia, are built around principles of minimising the number of sentient animals used in experiments, while monitoring for and limiting any suffering. This is balanced against a societal need to support scientific research that ultimately benefits both humans and animals.

The moral aspects of animal research are to a large degree dependent upon the circumstances in which its undertaken, for instance it is generally accepted that animals should not be used if there is a fit-for-purpose alternative. The anti-vivisection movement founder, Frances Power Cobbe acknowledged in 1894, that the original philosophical basis of the movement would be fatally undermined if animal research should lead to medicines. This of course subsequently happened leaving the idea that animal use is always wrong as a priori, circular argument.

(e) the adequacy of the current regulatory regime regarding the use of animals in medical research, particularly in relation to transparency and accountability

We are not placed to comment on the suitability of current regulations in NSW at this time.

(f) overseas developments regarding the regulation and use of animals in medical research

The UK remains a beacon of good regulation on lab animal use and has numerous essential features, such as disallowing animal use in the face if a valid alternative and a national centre for finding alternatives.

Twelve years on, and despite the difficulties of translation and harmonisation, the EU Directive has (we believe) successfully raised the standards of animal research across Europe. There is still some poor practice, but there are also excellent examples and great willingness to adopt good practices.

A referendum on the use of animals in experiments recently took place in Switzerland, with 71% of the vote against a ban.

(g) any other related matters