Submission No 261

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

Organisation: People for the Ethical Treatment of Animals (PETA)

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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS (PETA) SUBMISSION TO THE PARLIAMENT OF NEW SOUTH WALES INQUIRY ON THE USE OF PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH IN NEW SOUTH WALES

30 March 2022

All correspondence regarding this submission should be directed to:

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PETA Australia

The Director
Portfolio Committee No. 2 – Health
Parliament House
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30 March 2022

Dear Director:

We are writing on behalf of People for the Ethical Treatment of Animals (PETA) Australia, PETA UK, and PETA US in response to the request for information on the use of primates and other animals in medical research in New South Wales. The scientists and policy experts who work for PETA entities have a proven track record of productively assisting many international regulatory and government agencies and companies. This assistance includes providing expert opinions, regulatory advice, and technical support in a broad range of fields. Given the breadth and depth of our expertise, we believe that we can make a valuable contribution to the inquiry and can confirm we are available to provide oral evidence remotely at the forthcoming hearing.

Our evidence that follows provides a review of the use of primates and other animals within biomedical research and testing, as it falls within the terms of reference. While we have not commented on specific projects or procedures carried out in New South Wales, we have outlined a strategy for why and how the use of primates and other animals could be ended in research in New South Wales.

The scientific concerns over using primates and other animals in research

Extensive research demonstrates the poor translatability of basic and applied research and predictive failures in safety and efficacy testing using animals to understand human disease and test therapeutics. Inherent species differences mean that other animals cannot reliably serve as analogues for understanding human disease and developing safe and effective treatments for humans.[1] Systematic reviews published in peer-reviewed journals document the limitations in translating results from studies using animals into treatments for humans in numerous disease areas. Some examples include cancer,[2] cardiovascular disease,[3] diabetes,[4] HIV/AIDS,[5] immunology,[6] nerve regeneration,[7] neurodegenerative disease,[8] sepsis,[9] and stroke.[10] The majority of "highly promising" basic science discoveries are based on animal studies, but it is estimated that fewer than 10% of these enter clinical use within 20 years.[11] A more recent analysis found that – contrary to public perception – studies using animals have not furthered our knowledge in the field of human health or led to the development of treatments for conditions affecting humans.[12] The authors note, "[I]f research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced."[13]

While it remains the case that primates are "genetically very close to humans,"[14] critiques of the relevance of studies on primates to humans determined that "this genetic similarity does not result in sufficient physiological similarity for monkeys to constitute good models for research,

and that monkey data do not translate well to progress in clinical practice for humans."[15] Systematic reviews have documented the inapplicability of data from primates for numerous areas of investigation into human disease. A 2014 paper examined key differences in various aspects of gene expression and protein function in primates and humans that have contributed to the problems in attempting to extrapolate biomedical data from monkeys to humans in research areas as diverse as Alzheimer's disease, Parkinson's disease, stroke, and SIV/HIV.[16] For research into infectious diseases, use of even our closest relative, the chimpanzee, was found by the US National Institutes of Health and the US National Academy of Sciences' Institute of Medicine (now the National Academy of Medicine) to have "rarely accelerated new discoveries or the advancement of human health for infectious diseases."[17,18] In light of these conclusions, it is evident that other species of primate, with whom we share less of our DNA, or other animals, would not offer more reliable data.

The poor translation of results from animals to humans is further undermined by factors such as poor study design, publication bias, and confounding effects inherent within the laboratory environment. For example, University of Oxford scientists found that a lack of measures to reduce bias in experiments on animals likely results in an overestimation of the benefits of the treatment studied, thus confounding the trustworthiness and the rationale given for justifying further research using animals.[19] Poor internal validity also means that many experiments using animals are unable to be replicated. A 2015 investigation concluded that between 50% and 89% of all preclinical research, a large part of which involves animal testing, could not be reproduced.[20] Even though the so-called reproducibility crisis has been heavily discussed, measures applied to improve experimental design have been unsuccessful.[21,22,23,24]

Weaknesses of experiments on animals cannot be overcome simply by improving study design, because external validity, or the "extent to which research findings derived in one setting, population or species can be reliably applied to other settings, populations and species",[25] can never be achieved. Inherent species differences mean that other animals cannot serve as analogues for understanding the specific biological details necessary to develop safe and effective drugs for humans.

If finite public funds are to be used responsibly, they must fund research that leads to effective treatment for humans.

The potential public health risks of using primates and other animals in research

Primates used in biomedical research are frequently infected with unintended zoonotic pathogens, including those listed on the Australian national notifiable diseases list[26] such as campylobacteriosis, cholera, cryptosporidiosis, salmonellosis, shigellosis, measles, Hepatitis A, tuberculosis, flaviviruses, and malaria; as well as opportunistic zoonotic infections, including alpha, beta, and gamma herpesviruses, Simian type D retroviruses, Simian foamy virus, Simian immunodeficiency virus, adenoviruses, parvoviruses, fungal infections, *Trypanosoma cruzi*, *Giardia*, *Yersinia enterocolitica*, *Shigella flexneri*, and *Helicobacter* spp. West Nile virus, *Listeria*, tularemia, and *Burkholderia pseudomallei*, are also particularly common in immunocompromised primates.[27,28,29,30,31,32] Immunocompromised monkeys may be more likely to shed these pathogens in their faeces, saliva, urine, or blood. Uncontrolled and undetected infections in primate colonies pose a threat to research integrity and worker safety.[33] The scope

and consequence of the importation of primates into Australia and their subsequent movement between facilities has been underappreciated. It is critical that we start looking closely at the public health risks associated with the poorly monitored movement of primates and the lack of transparent pathogen reporting.

Recent studies report that the pharmaceutical industry is reducing its reliance on tests on animals because of the extensively documented difficulties in applying results from other species (including primates) to humans.[34,35] It has been estimated that from 2005 to 2008, European pharmaceutical companies have decreased their use of animals by more than 25%.[36]

Primates are often required for the testing of pharmaceuticals, despite there being no scientific justification this practice.[37] Indeed, clinical trials of the drug TGN1412 led to multiple organ failure and disfiguring injuries in the six previously healthy clinical trial participants – even though the drug was found to be safe in cynomolgus macaques who were given a dose 500 times higher than the human dose.[38] More recently, clinical trials of a pain relief drug candidate called BIA 10-2474 resulted in the death of one man and the hospitalisation of five more. A preliminary investigation report stated that "no toxicity, especially neurological (central or peripheral) comparable to that observed in the accident in Rennes, appears to have been demonstrated in animals, despite the use of four different species and high doses administered over long periods".[39] The final report notes that primates were given doses equivalent to 100 times the highest dose given to humans and that the animal studies were of "good quality".[40] As well as primates, the drug had also been tested in mice, rats, and dogs.[41]

Despite being high-profile, these are by no means isolated cases. In 2012, a Hepatitis C vaccine which appeared promising in preclinical studies, including tests on cynomolgus monkeys, resulted in the hospitalisation of nine patients and the death of one due to heart failure.[42] The preclinical research in primates showed that the liver efficiently extracted the compound.[43] Since the tragedy, a team of scientists in Canada has created a new computational model which can predict the cardiotoxicity that occurred in the trial participants, and using the compound that failed in the Hepatitis C drug trial, the researchers found that the adverse events "could have been predicted using our new computational model".[44]

In the field of regulatory toxicology and environmental protection, continued dependence on unreliable animal tests lessens the level of protection that can be afforded. Since tests on animals are known to lack reliability, relevance, and – in the case of those designed to detect certain carcinogens and endocrine disruptors – validation to modern standards, basing regulatory and chemicals management decisions on the results of such tests could lead to the misclassification of substances with damning consequences for the protection of humans, the environment, and animals. Animal tests are designed to measure the effects of large doses of single substances administered to small animals with short lifespans. They cannot address the long-term effects of the cocktail of low doses of chemicals to which human beings – large animals with long lifespans – are exposed. In addition, species differences render animal tests intended to identify subtle effects such as disruption to human endocrine or immunological systems or neurobiology highly unlikely to meet their objective, especially when looking at low doses of substances. Consider, for example, studies conducted using rats or mice to assess whether a chemical causes cancer in humans. The rodent cancer bioassay has come under scrutiny since the 1970s for its

inability to predict human outcomes. Two assumptions underlie the bioassay: (1) rodent carcinogens are human carcinogens, and (2) high-dose chemical exposure in rodents is indicative of an environmentally relevant dose.[45] Both assumptions have been shown as incorrect by 50 years' worth of data. The test also lacks predictivity and demonstrates poor reproducibility, with factors such as stress, differences in diet, and even the strain or sex of the animal used likely to affect results.[46,47,48] One review found a concordance of only 57% in carcinogenicity classifications for duplicate studies.[49]

As stated above, there is mounting evidence that animals are not reliable models of human diseases and cannot be used to accurately predict human responses. As a consequence, data derived from animal studies may be viewed as a significant barrier to drug development or safety assessment and thus delay public access to potential new therapeutics. In a recent paper co-authored by scientists from the UK Medicines and Healthcare products Regulatory Agency, it was reported that the forced swim test – a test purportedly designed to gauge the antidepressant qualities of drugs – and equivalent tests cannot predict the efficacy of potential new antidepressant drugs and could rule out effective new drugs for humans.[50] Transitioning towards human-relevant methods will likely improve patient access to treatments more safely and in less time.

The costs associated with animal research and opportunities for use of non-animal methods

A 2018 academic report on the economic landscape of non-animal methods states it clearly: "Many animal tests are simply too costly, take too long, and give misleading results."[51] Of more than 1,000 compounds tested on animals for improving stroke outcome, many of which reduced brain damage in rodents, none that reached clinical trials in patients improved stroke outcome.[52] Speaking about Alzheimer's disease, the chief science officer of the Alzheimer's Drug Discovery Foundation has commented, "We've cured mice engineered with this disease over 500 times. The mouse models don't translate into humans."[53] At the most conservative US estimate, the failure to reproduce preclinical research equates to approximately US$28 billion per year spent on misleading experimentation,[54] not to mention the costs to society of delaying effective treatments and disregarding potentially helpful interventions.

There is growing scientific consensus that far more is to be gained from enhanced support for human-relevant research methods and technology that are better suited to solving human biomedical and regulatory assessment paradigms than from reliance on animal studies. For example, it is estimated that organ-on-a-chip technology, which emulates tissue and organ physiology *in vitro*, could reduce total drug development costs by up to 25%, saving approximately US$700 million.[55]

The United Kingdom's innovation agencies, Innovate UK[56] and the Medicines Discovery Catapult and BioIndustry Association[57] have published reports that highlight concerns around the translation of animal models to human clinical benefits, alongside the potential business opportunities for human-relevant non-animal research methods. Additionally, Innovate UK has identified non-animal technologies as emerging technology with the potential to drive future economic growth and attract international investment.

When tests on animals are banned, we see a thriving expansion in innovative, humane non-animal approaches that can have numerous applications, as was evident when the European cosmetics testing ban came into effect. It should be noted that this ban was implemented irrespective of the availability of non-animal replacement methods for all human health endpoints. In the advent of the testing ban, Europe invested heavily in the development of non-animal testing methods and saw fantastic returns. For example, scientists may now use high-tech, sensitive tests such as three-dimensional tissue models produced from human cells to evaluate whether chemicals irritate the skin and eyes. These humane tests are a great success story: they not only spare animals suffering but have also been found to produce more accurate, human-relevant results in comparison to tests on animals.[58] An impact assessment published by the European Commission recognised that the provisions of the cosmetics animal testing ban "are generally seen as a crucial accelerator of research and validation of alternative methods by all stakeholders".[59] In addition, the report stated, "The search for alternative methods is by now also more and more recognized as the search for better science and forms part of an overall shift of paradigm in safety assessment." The ban has been influential internationally, and cruel cosmetic tests are now illegal or policies are in development to ban such practices around the world, including a ban on the use of animal test data for cosmetics across Australia.[60]

The future of science lies in humane and human-relevant technology such as organs-on-chips, micro-models of the brain, and computer models that can predict what happens in human beings more accurately than tests on primates do.

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

Australia is thought to have the fourth-highest rate of experimentation on animals in the world, using an estimated 5.3 million animals per year,[61] and New South Wales uses the most nationally.[62] However, the exact figure is unknown because there is no national system for collating statistics on animal use.[63] In addition to this, there is a significant lack of transparency and openness about even basic information, and Freedom of Information requests are denied by state governments, including New South Wales, or obstructed by universities.[64] This has led to poor awareness among the Australian public that animals are even used in experiments in Australia[65,66] and heavy criticism of the current regulatory frameworks.[67,68]

Internationally, there are growing ethical concerns over the use of primates and other animals in experiments. Indeed, the cosmetics testing and marketing ban, first implemented in the UK as a voluntary ban[69] and then included in the EU Cosmetics Regulation,[70] resulted from decades of public and political support premised on the fundamental belief that the harm caused to animals used in testing cannot be outweighed by the potential benefits of new cosmetics products.[71,72] A 2018 Ipsos MORI poll[73] found that public acceptance of experiments on animals is conditional on there being "no alternative", but the majority do not feel well informed about "work to find alternatives". Public support for investment in non-animal methods is also high – 75% of respondents to the 2018 poll backed increased efforts to develop "alternatives" to animal use. In Australia, 73% of the general public supports the allocation of a proportion of medical grants to funding scientific alternatives to experiments on animals.[74] As well as scientific advancement, public opinion should be a major factor driving policy change towards ending the use of primates and other animals in experiments.

Overseas developments regarding the regulation and use of animals in medical research
The transition away from using animals to model human disease or as tools to predict human responses to drugs and towards human biology–based methods is changing policy around the world:

- In September 2021, Members of the European Parliament almost unanimously supported a Motion for a Resolution calling on the European Commission to develop an action plan, with a timeline and milestones, to phase out experiments on animals and accelerate the transition to innovation without the use of animals in research, regulatory testing, and education.[75]
- The Netherlands has initiated the government-coordinated Transition Programme for Innovation without the use of animals (TPI) to help fulfil the country's ambition to be a frontrunner in innovation without animal testing. The TPI brings together regulators, scientists, funding bodies, and industry to offer them a platform for identifying and developing innovative activities within their fields that will increase the pace of the transition to animal-free research.[76]
- The US Environmental Protection Agency (EPA) released the first update to its New Approach Methods Work Plan for reducing the use of animals in testing. The plan lists concrete steps that the agency will take in the next three years to reduce tests on vertebrates for pesticides and chemicals, including establishing metrics to monitor the agency's progress; developing, establishing confidence in, and accepting non-animal tests; offering educational opportunities on the use of non-animal methods; and engaging with stakeholders. The EPA work plan highlights that non-animal methods have the potential to increase the "rigor and sophistication" of chemical assessment by the agency.[77]
- Also in the US, the Food and Drug Administration Modernization Act of 2021 proposes to amend the Federal Food, Drug, and Cosmetic Act to lift the compulsory requirement to test all new drugs on animals in favour of "alternative testing methods".[78]

It is crucial that Australia does not fall behind these international developments. Now is the time for the government of Australia to commit to developing a strategy for ending experiments on animals and prioritise funding for sophisticated non-animal methods. The Parliament of New South Wales has the opportunity to take the lead in such a strategy.

A strategy for ending the use of animals in research and testing
In light of the growing body of evidence that data resulting from studies on primates and other animals cannot be readily extrapolated to humans and the development of non-animal testing methods and technologies that can replace the use of animals, it is essential that plans are drawn up to phase out experiments on animals.

The work of PETA entities to end the use of animals in several specific areas of experimentation has met with success. PETA scientists have developed the Research Modernisation Deal (RMD),[79] which maps out a strategy for ending the use of animals in biomedical research and regulatory testing and highlights the economic, public health, and animal welfare benefits of applying and developing advanced animal-free methods. We have included a copy of the RMD for your information.

In order to end the use of animals in experiments and prioritise investment in non-animal methods, we recommend the development of a strategy that includes the following critical steps:

1. Immediately eliminate animal use in areas for which animals have already been shown to be poor and unreliable predictors for humans and have impeded progress
2. Conduct critical scientific reviews to identify the areas in which the use of animals can be ended
3. Implement transparent, robust prospective and retrospective evaluations for all projects, allowing for a public commenting period so that external experts can contribute to them
4. Harmonise and promote international acceptance of non-animal testing methods for regulatory toxicity testing requirements
5. Increase funds for non-animal studies and decrease funds for animal studies
6. Educate and train researchers and regulators in the benefits and use of non-animal research and testing methods

For Australia to maintain its position at the forefront of global science and innovation, it must embrace scientific and technological progress and have the courage to challenge the status quo. Now is the time to take the next step and formally commit to the ultimate goal of ending animal use. The Research Modernisation Deal offers a strategy for reaching this goal.

The ethical and animal welfare issues surrounding the import, breeding, and use of animals in medical research

While we urge the Parliament of New South Wales to commit to ending experiments on primates and other animals for the benefit of humans, other animals, and science, we also support opportunities to improve the welfare of primates, as well as other animals, who are currently housed in laboratories. We recommend that a central panel of experts in primate ethology be convened to establish clear and well-defined standards for the ethological appropriateness of environments in which primates are held.

It is well established that primates held in impoverished conditions – deprived of companionship, sufficient space, and sufficient environmental complexity – they experience a harmful chronic stress response and develop behavioural abnormalities, including stereotypic and self-injurious behaviour.[80] For example, primates experience increased stress from common laboratory procedures such as cage cleaning,[81] physical examination,[82] blood draws,[83] and restraint.[84,85] Numerous studies have demonstrated that even minor changes in primates' captive environment, including temporary changes in cage size or location, increase stress levels.[86,87] In fact, the mere physical presence of human experimenters and technicians increases stress in primates.[88,89] The lack of adequate psychological and social stimulation in the laboratory, along with frequent subjection to common laboratory procedures, leads to chronic stress that negatively affects primates not only psychologically but also physiologically. Primates held captive in laboratories and subjected to experimental procedures exhibit signs of extreme distress, including pacing, rocking, head-twisting, and eating their own faeces. Highly traumatised primates will bite their own flesh, pull out their own hair, and engage in other forms of severe self-mutilation.[90,91,92,93]

Primates in laboratories display aberrant immune-system functioning, including increased stress-related hormones, dysregulation of the hypothalamic-pituitary-adrenal axis, and depressed immune-system functioning.[94] Stress-induced immune dysregulation and systemic inflammation

result in significant health consequences, including increased vulnerability to infection,[95] delayed wound healing and recovery from surgery,[96] and accelerated aging.[97]

The myriad physiological and psychological effects experienced by primates in laboratories introduce numerous insurmountable confounding variables into biomedical experimentation relying on these animals.

The absence of clear standards for what would qualify as an ethologically appropriate environment for primates has heretofore been interpreted by experimentation facilities as a licence to confine primates, sometimes alone, to small, sterile cages – with little consideration of the impact of such bleak conditions on the welfare of the animals.

At its foundation, an 'ethologically appropriate environment' is an attempt to approximate the living situation of free-roaming animals within a captive environment. As Honess and Marin have commented, "Producing an environment that encourages animals to indulge in an appropriately balanced repertoire of natural behaviours that resembles as close as possible that of wild conspecifics will result in animals [who] are significantly more psychologically healthy than those with restricted, disproportionate repertoires. This will in turn result in healthier animals through a reduction of injury associated with excessive aggression and self-injurious behaviours, lower stress levels and associated vulnerability to opportunistic infection and neurological damage [and] a more accurate model for research."[98]

For primates, such an attempt at approximation must take into account social housing, access to the outdoors, exercise spaces, home cage enrichment, and considerations pertaining to noise and music:

- Social housing is universally acknowledged as a key factor in the welfare of primates in laboratories, and it is well documented that housing primates alone is detrimental to these animals' development, physical health, and psychological well-being. Ethologically appropriate environments for primates must provide for each primate of a species known to be social in nature to be housed with other primates. Group housing should be viewed as the appropriate situation, pair-housing as a compromise, and single housing as an extremely rare occurrence.
- Access to outdoor environments provide primates with more visual, olfactory, and auditory stimulation as well as greater opportunities for exploration and manipulation of one's surroundings than indoor environments. Outdoor housing also exposes animals to natural perceptual stimuli such as sunlight, transitions at dusk and dawn, natural sounds, and temperature variations. Studies have documented decreased stress (as indicated by lowered cortisol levels) in marmosets who were given access to an outdoor enclosure,[99] increased activity in rhesus macaques moved to outdoor spaces,[23] and increased levels of aggression in primates who were moved from outdoor to indoor enclosures for the winter.[23] Also, self-biting, self-injurious, and self-directed stereotypic behaviour has been significantly reduced by providing primates with outdoor housing. Therefore, ethologically appropriate environments for primates must include safe access to outdoor enclosures.
- Primates should also have regular access to rooms or outdoor enclosures that provide sufficient space and appropriate substrates for normal locomotion, including quadrupedal walking and running, vertical climbing and clinging, leaping, and swinging. Factors to

consider include size, shape, and orientation. Many structures, such as perches or ladders, limit behaviour to horizontal and vertical movement. Providing adjustable structures that can be moved between sessions can ensure that an animal has access to a variety of inclines that may promote a range of positions and movements not normally accommodated in the home cage. Ethologically appropriate environments for primates must include exercise spaces.

- Enrichment of the physical environment is often limited to the provision of a perch, a mirror, and a toy or other manipulanda. The evidence now available in the scientific literature suggests that such a regimen is inadequate. Inadequate enrichment standards fail to promote not only psychological well-being but also normal brain development and function.[100] Data on the relationship between the brain and enrichment provide powerful reasons for expanding the programme of enrichment that primates receive on a daily basis. Ethologically appropriate environments for primates must ensure adequate cage structure and complexity and provide a variety and number of frequently rotated enrichment objects.
- Noise is a widely recognised stressor for a variety of animals used in laboratories, including primates. Noise from caging must be minimised by use of appropriate materials to soften metal-to-metal contact areas and improve acoustics in rooms, including to reduce echo and amplification. The evidence is clear that music is aversive to primates and can cause distress.[101] The lack of control over the stimulus in type and volume and the inability to escape from it may compound any unpleasantness of exposure to the sounds per se. Ethologically appropriate environments for primates must reduce noise in laboratories and not subject them to music.

We thank you for the opportunity to submit comments on the use of primates and other animals in medical research in New South Wales. We give permission for our submission to be published in full on the website and would be happy to meet with you to discuss pragmatic ways to make the transition to animal-free science.

Yours sincerely,

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