2 March 2022

Dear Committee Members

**Re: Inquiry into the use of primates and other animals in medical research in NSW**

I am writing on behalf of Humane Research Australia (HRA), a not-for profit organisation advocating scientifically valid and humane non-animal methods of research. HRA works professionally and ethically to develop community-wide awareness of animal experimentation; pursues all reasonable channels to eliminate such experimentation and champions the benefits of realistic, scientifically effective alternatives to all forms of animal usage in research and teaching. Formally known as the Australian Association for Humane Research Inc, which was founded in October 1979, the organisation has acquired extensive knowledge and expertise on the issue of animals in medical research.

Thank you for your time and attention to this vital inquiry. We note that in 1989 there was a Commonwealth Enquiry into animal experimentation (1). The committee recommended that:

1. The Commonwealth, State and Territory Governments publish annually accurate and comprehensive information on the extent and forms of animal experimentation, conducted within their respective jurisdictions
2. That the Commonwealth establish a separate fund for research into the use of alternatives to animal experiments

Over 30 years later, these recommendations are yet to be implemented, which demonstrates the low priority replacing animals in medical research is awarded in Australia. This is despite Australia being cited as one of the highest users of animals in research globally (2) and NSW typically reporting usage of an excess of two million animals per year. We hope this Inquiry will lead to tangible outcomes which support human-relevant research.

HRA is opposed to all animal experimentation but is cognisant that despite evidence demonstrating the failings of animal research — approximately 90% of drugs found to be safe and effective in preclinical research, of which animal testing is currently mandatory, failing to make it to human clinical use (3)— an immediate ceasing of animal experimentation is unlikely and not a goal of this committee. There are many barriers at play that create resistance to such a paradigm change, including culture, adherence to the status quo, the fear of sunk costs, journal editorial policy, tradition, and careers built on animal research. HRA has therefore sought to propose practical recommendations and to provide relevant resources that can be of assistance to the committee to guide a transition from animal-based medical research to methods which are based on human-biology.

Whilst accepting this is a NSW Inquiry and attempting to keep our submission specific to NSW, a national approach is needed, as is clear from the structure of federal funding bodies,

the federal *Australian Code for the Care and Use of Animals for Scientific Purposes* (hereafter 'the Code'), the federal Therapeutic Goods Administration, and collaborative research across Australia. We hope that the information gathered can at a minimum be shared with stakeholders across Australia and that a consistent approach is considered.

HRA will address all the terms of reference and provide guidance on approaches HRA feel could best address the scope of the inquiry.

Due to the specialist nature of our organisation, HRA would welcome the opportunity to give evidence at a hearing.

**(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;**

NSW is to be praised for publishing annual reports detailing their animal use in research statistics, which give some indication of the nature and purpose of research. However, the effectiveness of this research is not clear and given that there is increasing recognition of the limited translation of animal research to human patients globally (4) it can be assumed that these same translational issues occur in NSW.

The effectiveness of research is a crucial term of reference as research using animals is often defended as a 'necessary evil'. However, when questioned in May 2020 as to whether the Government has investigated the limitations or effectiveness of animal models in medical research in the Senate; the response provided was that no such investigation has taken place.

Simply stating that the use of animal models in medical research is necessary without explaining how, if at all, the research has translated to human patients is commonplace. For example, when three baboons escaped at the Royal Prince Alfred Hospital in February 2021, there was heightened public awareness of the use of non-human primates (hereafter 'primates') and objections were raised. A petition by HRA calling for a ban on primate research jumped from 60,000 signatures to over 100,000 signatures in a matter of days.

Professor Annemarie Hennessy, a senior adviser at the Wallacia primate facility from which the baboons were transported, stated that baboons at the facility had been used in "*important biomedical research*" in Australia for at least 30 years and that research at the lab has been used to tackle priority medical issues identified by the federal government, including diabetes, kidney disease and complications arising from pregnancy (5). HRA does not contest that medical research is necessary to advance human health; however there needs to be rigorous questioning of the research methods most applicable to human-biology, and standard responses fail to demonstrate the precise outcomes of the research. The severity of a disease does not justify the use of animals; and indeed, the decades of animal-based research, costing billions of dollars, which have failed to provide cures for

humans, despite curing disease in the mouse, for example, are a strong indication that a new approach is needed (6,7,8).

HRA is not disputing that knowledge gained from animal research has resulted in human benefits. However, HRA proposes that the benefits are overstated, and that superior methods based on human-biology are much needed to progress human health in the modern era.

Reviewing the effectiveness of medical research is a complex task. When questioned, it is likely that researchers will be of their opinion that their research has value. But how is this value evaluated? There are many claims and counter claims about the predictive value of animal research, particularly in the field of human healthcare advancements. Such arguments have often relied on citing specific cases in which animal research has or has not proven predictive for human patients, and has, or has not, proven useful in developing new therapeutic interventions. Although even a single significant advancement is to be applauded, it must be considered in the context of a great number of failed cases, which indicate the unreliable and ineffective nature of animal models. It would be prudent to seek more consistently successful models that could produce a higher rate of significant contributions

There is therefore a need to take a measured approach to evaluating the utility of animal research. Although even a single significant advancement is to be applauded, it must be considered in the context of a great number of failed cases, which indicate the unreliable and ineffective nature of animal models. It would be prudent to seek more consistently successful models that could produce a higher rate of significant contributions.

Systematic review plays a fundamental role in assessing the predictive value of animal models, because it can either confirm the translation of research findings, or lack thereof, from a broader and objective basis, rather than anecdotal evidence or isolated cases selected to support a certain position. Such reviews have suggested that animal research is not scientifically valid and imply that its use is instead continued for historical and cultural reasons. For example, Knight (9) found that of 20 clinical reviews, in only two cases (one of which was contentious) could animal models be assessed to have contributed significantly towards the development of human clinical interventions.

It is also suggested that the committee refer to international efforts already underway. An EU project is retrospectively monitoring research impact at society level, considering a list of indicators categorised as; funding/economic, dissemination, scientific and technological, regulatory and policy, public and social engagement, and education, training, and job opportunities (10). A synopsis report of a survey addressed to EU funding recipients to gather their (subjective) feedback about perceived importance and impact of their research can also be reviewed (11).

Additionally, analysis of 'breakthroughs' reporting could be employed. A UK paper illustrates the exaggerated results of biomedical studies using animals (12). The report looked at 27 examples of animal research that were highly publicised in the UK national media in 1995, and which were claimed to provide a "breakthrough" for human health. Each study was followed up more than 20 years later to determine if any actual human benefit had transpired. Only one out of the 27 animal studies reviewed for the report resulted in actual benefit to humans.

Whichever method/s are used to guide the evaluation, it is inaccurate to simply correlate the use of animals as essential due to a subsequent treatment being approved for humans following animal trials. At best, animal experiments can suggest new hypotheses that might apply to humans. The below must be asked of animal research. Is the research:

1. reliably and sufficiently translatable to humans
2. providing data that could not be provided in another way, and;
3. is the data critical to ultimate human benefit?

Instances which have led to medical advances may simply be a consequence of findings extrapolating to humans by chance, without any guarantee that the same results could not have been achieved using alternative methods.

For example, the clinical trials of nimodipine and low-level laser therapy were conducted concurrently with the animal studies (13), while the clinical trials of fluid resuscitation, thrombolytic therapy, and endothelin receptor blockade went ahead despite evidence of harm from the animal studies (4). This suggests that the animal data were regarded as irrelevant, calling into question why the studies were done in the first place and seriously undermining the principle that animal experiments are necessary to inform clinical medicine (3).

And what about scientific curiosity? Knowledge for knowledge's sake may be a questionable use of funds and in many cases, animal lives. Such examples are referenced in HRA case studies. For example, research published by the University of New South Wales in which rats were fed a fast-food diet of pies, lamingtons, and dim sims to investigate linkages with obesity. With human data already having established the link between a fast-food diet and obesity, and key differences in the gastrointestinal pathway of humans and rodents, surely research funding could have been better spent, when the grants process is so competitive and should be dependent on vigorous assessment of grants for their merit (14).

The majority of animals used in medical research in Australia are used in basic (fundamental research), as opposed to applied research. It is the opinion of HRA that much basic research using animals it to satisfy scientific curiosity and develop hypothesis that are in reality only relevant to animals and simply lead to more research and more publications. Clinical relevance is poor. For example, one study found that fewer than 10% of highly promising basic science discoveries enter routine clinical use within 20 years (15).

**Recommendations:**

- Extensive independent report evaluating the impact of animal-based research in NSW to be commissioned.
- Retrospective assessments of animal research to be mandatory as a condition of funding and made public
- Grant evaluation reports to be made public for all publicly funded research
- Animal care and ethics committee applications for animal-based research to be made public, to enable scrutiny of the proposed cost/benefit assessment
- Statistics of adverse drug responses to be made public
- Clinical trial failure rates to be made public
- Greater scrutiny of basic research using animals
- Pre-registration of all animal experiments to prevent duplication (see www.preclinicaltrials.eu and www.animalstudyregistry.org for examples)

**(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;**

HRA is reliant on reviewing research publications and analysing grant project descriptions to try and discern whether animals are used. This is because limited detail is provided by research institute as to what procedures are conducted in animals, for what purpose, and with what funding.

A breakdown of what research involves animals should be obtainable, since researchers planning to use animals need to seek approval by an animal ethics committee; therefore, it is reasonable for funders to request records of which grants involved animal ethics committee approval and publish this information in grant summary documentation. Currently, this is not made public by significant grant funders at State or Federal Level, including the National Health and Medical Research Council (NHMRC). Through the federal budget estimates process, it was confirmed that during 2019–20, approximately $380 million was expended on active grants that indicated they require animal ethics review as part of the NHMRC-funded research (about 40% of total funding). Whilst HRA appreciates that some research may use both animals and non-animal methods and that planned animal research may not eventuate, these challenges do not preclude the necessity of this data being transparent. The published data would enable trends to be monitored, as well as meet the expectations of health consumers and taxpayers.

There is also an imperative for researchers to seek replacements for animals, although limited funding is allocated to enable this (see Term of Reference C). Transparency in the funding allocated for the development and validation of alternative methods, and any associated trends in reduced animal use for grant funded projects would be useful to track.

**Note: the costs associated with animal research extend beyond the funding allocated, to the costs to patients when animal data does not translate to humans, or from the abandonment of treatments that fail in animals that may be effective in humans (16). As this quote illustrates (17):**
**'*If you sought out the wrong substances in drug development and they never make it to therapy because of a misleading animal experiment, then this is far more costly than any animal experiment you could possibly have done'* (Thomas Hartung MD, Professor at Johns Hopkins Bloomberg School of Public Health).**

**For this purpose of the Inquiry, we anticipate these factors to be considered under reference 1.**

**Recommendations:**

- A consistent process be introduced for publicly funded research to record expenditure that involves the use of animals that is accessible to the public.
- HRA recommends that expenditure for the development and validation of non-animal methods (we are not aware of the existence of any such funding programs in NSW currently) is also recorded and reported against.

**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;**

There are 'alternatives' to using animals. New – and not so new – methods and technologies that can replace live animals in research, testing, education and training include:
1. *In-vitro* methods (performed with microorganisms, tissues,
whole cells or parts of cells in test tubes, Petri dishes etc.)
2. *In-silico* (computer-based) methods
3. Studies with human volunteers
4. Simulators (virtual reality (VR)-based or physical model (PM)-based)

HRA suggests that the committee review the following HRA publications, which detail alternative approaches to animal research and the benefits thereof:

Better ways to do research
https://www.humaneresearch.org.au/wpcontent/uploads/2020/06/BetterWaysToDoResearch.pdf

A business case for funding non-animal methodologies
https://www.humaneresearch.org.au/wp-content/uploads/2021/02/Final-business-case-Feb-2021.pdf

Optimising inhalation research: transitioning to human-relevant research

https://www.humaneresearch.org.au/wp-content/uploads/2021/11/Optimising-inhalation-research-transitioning-to-human-relevant-research.pdf

Other relevant reports which are recommended reading are:

Accelerating the Growth of Human Relevant Life Sciences in the United Kingdom
Alliance for human-relevant science
https://www.humanrelevantscience.org/accelerating-the-growth-of-human-relevant-life-sciences-in-the-united-kingdom-2/

The economic impact of the UK's New Approach Methodologies sector
Animal Free Science

The Research Modernization Deal
PETA
https://www.peta.org/wp-content/uploads/2020/12/peta-2021-research-modernization-deal.pdf

The above reports highlight the scientific, as well as the economics gains from non-animal research methods, which offer huge growth potential and opportunity for innovation. For example, in September 2021, US-based organ-on-a-chip provider Emulate Inc. announced that it had raised almost $225 million in investment (18). In the UK, In absolute terms, the New Approach Methodologies (NAMs) industry turnover, which include the use of human cells and tissues; artificial intelligence; and organ-on-a-chip technology, grew by £452 million over the period of 2017-1, reflecting an uptake in demand for goods and services provided by the industry (19).

In terms of perspectives from Australian researchers, we would encourage that greater insights into alternatives and their use/barriers to use, and application of the 3Rs, be sought from researchers.

Some examples of NSW research institutes meeting the 3R's are provided in annual Animal Use in Research Statistics but beyond that, this knowledge is held by research institutions with limited transparency. A 2019 paper by the NHMRC (20) stated that increased funding to develop replacement options was identified as a key enabler to implement the 3Rs. The same report identified the lack of appropriate scientific or technological innovation as the primary barrier to implementation of the 3Rs. **A survey of animal ethics committee members in 2020 revealed strong support for training and education on replacement methods, indicating that there may be a knowledge-gap for those tasked with evaluating and approving research proposals (21).**

HRA believes that there is increasing recognition of the potential of non-animal methods and that Australian researchers who seek to use such methods do have avenues within Australia. For example, Phenomics Australia recently announced investing over $2 million to

2023 to expand modelling services using CRISPR engineered cell lines, iPS cells, tissue cultures, organoids, as well as 3D bioprinting and “on-a-chip” systems (22). Many researchers have signed onto a statement calling for increased funding for non-animal research methods and issued supporting statements outlining their personal motivations (23). Furthermore, the use of non-animal research methods is evident from Australian case studies HRA has compiled recently (24) which showcase a range of methods, from computer modelling to human-population studies.

However, the alternatives field is underdeveloped in Australia in comparison to within Asia, Europe or the US and this can be attributed to lack of Government action to establish funding programs or a centre for replacing animals. To our knowledge, there is very limited funding available besides some small-scale university 3R grants, and no funding programs for the development and validation of non-animal methods. Currently, Australian researchers interested in the field of alternatives are reliant on limited overseas funding and whilst there are some exciting projects underway in Australian via international funding sources, additional funding would facilitate more innovative research of this nature.

Researchers will ‘follow the money’ yet currently there is stagnation as no institution is taking responsibility for funding alternatives, despite a legislative obligation to only conduct research for which there is no alternative to animal use. If no funding is committed to develop, refine and validate alternatives, progress will remain stalled. Whilst it is argued that Australian researchers can rely on international alternatives data, a cultural change is needed to encourage adoption of alternatives and that can only be achieved through leadership, commitment and mentorship of Australian researchers, leading to generational change in research practices. Funding is a crucial first step.

Many of the new research technologies require expertise in areas such as bioengineering or computational systems and may fall outside the skill sets of biomedical researchers; therefore, investment is required to develop this specialist workforce and infrastructure. Incentives could include; scholarships, grants, sponsorships to attend relevant conferences and mentoring.

HRA proposes that intensifying efforts to develop, validate and implement human- relevant research will result in increased translation and commercialisation of medical research. Where there is the potential to minimise or eliminate animal testing, this should be encouraged, not only due to the requirement for human-relevant research, but also to fast-track research. Performing unnecessary or duplicative animal research is time consuming and it can take months to refine the most appropriate animal ‘model’, which remains at best, a model.

**HRA would like to emphasise that the 3Rs relate to animal welfare principles, but do not ensure that the research is merited.** For example, a researcher may seek to establish whether a marmoset is a suitable ‘model’ for particular type of vision research and thus the researchers investigate biological mechanisms of commonality between the human and the

marmoset. Because of the nature of the research question (attempting to create, refine or validate an animal model), an alternative method would be unlikely to be considered. Animal welfare alone does not suffice to make animal research ethical if the research does not have sufficient scientific value.

**When considering 'alternatives to animals', it is important to note that conducting biomedical research without animals is not simply a case of looking for a direct replacement for an animal model (25). It is about experimental design focused on the desired outcome and challenging faulty logic. A like-for-like replacement is not always possible. HRA is not confident that this is comprehended by Animal Care and Ethics Committees in NSW.**

**Additionally, HRA are concerned that the claim that 'an entire biological system' is needed is overused as an automatic default to justify animal experimentation. A recent study showed that the current choice of a specific animal model in a project application for the use of animals seems to be based on traditional acceptance and standard responses rather than robust substantiation for the choice of an animal model (26). Non-animal models may lack the integration and longevity of an intact organism. They are designed to stimulate human biology up to a certain level of organisation and complexity. However, despite the current limitations, they are superior to the inaccurate animal model. A whole living rat does not represent a whole living human.**

**Recommendations:**

- An ongoing, federally funded research funding stream for the development of non-animal based scientific testing
- A commitment to developing an Australian Centre for the Development and Validation of Alternatives.
- State and territory funding for the development of non-animal based scientific testing via incentives such as awards, scholarships or research grants.
- Training for journal and grant peer reviewers in non-animal methods
- All applications to animal ethics committees to provide evidence that alternatives have been sought such as systematic reviews
- To encourage more progressive thinking than the 3Rs—this is missing the 'Relevance R' and simply maintaining the status quo.

**SUGGESTED 5Rs to REPLACEMENT: (27)**

- ✓ **Recognise failing preclinical models and discontinue funding**
- ✓ **Redirect funding to human-predictive research methods**
- ✓ **(Re)train scientists in non-animal research methods**
- ✓ **Redesign university curricula to focus on non-animal approaches**
- ✓ **Resolve to phasing out animal use in science, with defined timetable and metrics**

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

Medical research using animals raises questions as to the ethics of using non-consenting sentient animals and subjecting them to harms for which they will derive no benefit. A 2018 opinion poll commissioned by HRA revealed that only 23% of those polled believe that humans do have the moral right to use animals in research, while 60% do not believe humans have the right and 17% are uncertain (28).

Regardless of the ethical position held, most people would agree that the animal welfare needs of animals used in laboratories is paramount and would not be accepting of procedures that cause severe suffering.

HRA will focus on the below research procedures, of which the animal welfare and ethical considerations are profound and there is no public license.

**Forced Inhalation Research**

Inhalation research is currently being conducted at the University of Newcastle and the Centennial Institute (29) with mice exposed via nose-only or whole-body exposure to cigarettes or other hazardous inhalants. In a whole-body exposure chamber, the animals are immersed in the test atmosphere, whereas in nose-only or head-only exposure systems, exposures are localised primarily to the head and/or nasal regions. 'Animal models' of diseases for which cigarette smoking has a correlation, such as chronic obstructive pulmonary disease, are created to study disease pathogenesis. This requires subjecting mice to smoke inhalation experiments for up to 18 weeks in duration. In addition, other invasive procedures may be carried during the experiment, such as injections. There are animal welfare impacts such as weight loss and hypothermia; ongoing suffering likely to be incurred from the disease induced; and ultimately death at the end of the experiment.

There are severe limitations to the translation of findings due to biological differences between humans and mice and differing responses to interventions between species. It is impossible for a mouse to accurately mimic human inhalation. For example, it is impossible for a mouse to accurately mimic human inhalation due to their quadrupedal stance and obligate nasal breathing. It is therefore time that new approach methods, such as the lung-on-a-chip or advanced computer modelling and simulation be utilised (30) especially in the field of basic research by academia, where most forced inhalation studies are conducted, and could be replaced without regulatory obstacles.

**Forced Swim Test**

In the forced swim test, animals, typically mice or rats, are made to swim in a cylinder of water. They swim frantically, trying to find an escape, until they stop struggling and subsequently float. HRA has sourced a research publication confirming that Macquarie University (31) and the University of Wollongong has used this test in recent research (32).

The claim is that when animals spend more time floating, they are deemed to be more "depressed." This claim is made in spite of evidence that floating is actually a learned and adaptive behaviour, one that saves energy and is beneficial for survival (33). An analysis of publicly available data from four major pharmaceutical companies revealed that the test was less predictive than chance at determining if a compound would have antidepressant efficacy in humans (34).

Many of the world's top pharmaceutical companies (Roche, Bayer, Johnson & Johnson, AbbVie, GlaxoSmithKline, Pfizer, AstraZeneca, Bristol-Myers Squibb, and more) have formally ended their use, funding, and/or commissioning of forced swim tests (35).

As determined by the stated pharmaceutical companies, the forced swim test does not teach us anything reliable about human depression—nullifying any scientific justification for carrying out the test; and it causes acute suffering and distress to the animals who are used—presenting a compelling ethical argument against using the test.

Relevant alternatives include testing on human platforms. For example, novel compounds might be identified using mathematical or computer modelling of human systems, or by a drug-repurposing program. These compounds might be tested on human tissues or cells using advanced in vitro methods, such as in organoids or microfluidic systems. Pharmacogenomics (precision medicine) has particular relevance to medications for depression (36). Epidemiology is another tool for understanding how to prevent and treat human depression. Further, funds can also be allocated to support and improve access to existing mental health treatment.

HRA's critique extends beyond the forced swim test to other 'tests' used in behavioural neuroscience which offer nothing more than inferences. As expressed in a 2017 article (37) '***more than 20 diagnostic features of depression in humans but neither a motor deficit (when confined within a tank of water) nor a reduction in struggling (when suspended upside-down) is on the list. Similarly, anti-anxiety drugs increase activity on the open arms of the Elevated Plus-Maze but most people would regard any reluctance to 'walk the plank' (i.e. to venture onto the open arms of the maze) in the drug-free state as a sensible decision after a risk assessment, rather than a sign of a psychiatric illness'***.

Regardless of the research undertaken, standard laboratory housing and practices contribute to poor animal welfare. Studies have shown that routine laboratory practices—such as handling, blood collection, gavage, and witnessing other animals being subjected to procedures—are associated with a stress response, and that animals do not readily habituate to these practices (38).

Certainly, the quality of life of animals used in research is of concern, particularly for social species with advanced cognitive abilities, such as dogs, cats and primates, for which a laboratory environment cannot meet enrichment needs. Whilst there may be reduced

empathy for the wellbeing of rodents; mice and rats, alongside fish, are the species most used in medical research and their welfare should not be unnoticed, neither should their lack of relevance. For instance, a recent study led by Stanford immunologist Mark Davis, PhD, suggests that experimental mice - who spend their entire lives in artificial, ultra-germ-free environments - may be a poor model for adult humans' more battle-hardened immune systems (39).

**Primate Research**

53 primates were used in research in NSW in 2019, according to the Annual Use in Research Statistics Report. Of these, 31 were for the purpose of researching human or animal biology, six for human or animal welfare, and 16 for stock breeding. Whether these primates were killed or to be used in more research is not reported.

Our investigations suggest that much of the primate research conducted in NSW relates to studies into preeclampsia, diabetes and vision/cognition.

Primates are genetically the closest living creatures to humans. Their sentient ability is thought to be very similar to ours, as primates have complex social interactions. In contrast, a laboratory setting is far removed from the natural habitat. The average laboratory cage of the rhesus macaque is 7 million- fold smaller than their natural home range (40).

Primate research is particularly contentious, presenting a clear ethical dilemma of using animals with high cognitive abilities, a long lifespan, and well-developed social structures as mere 'tools for research'. The animal welfare impacts associated with their advanced abilities are profound in a research setting, where they may associate previous negative experiences such as invasive procedures with future occurrences.

The use of great apes (chimpanzees, orangutans, bonobos and gorillas) for biomedical research is not permitted in Australia. **The special status granted to great apes on the grounds of moral reasoning should not exclude other primates from the same protection.**

If the research involves the use of non-human primates, the NHMRC Policy on the Care and Use of Non-Human Primates for Scientific Purposes also applies (41). Accordingly, primates must not be used for scientific purposes except when; i) no alternative to the use of non-human primates is suitable to achieve the stated aims of the project, and ii) the potential effects on the non-human primates are justified by the potential benefits. Yet it doesn't provide guidance on how to do this, so it's left to the subjective discretion of researchers and animal care and ethics committees to determine what procedures are justified.

It has been argued that primate research is essential to advance human health. Indeed, this is a common assumption due to their close genetic relationship to humans. Yet, we are separated by 25 million years of evolution. There are major anatomical, genetic, dietetic, environmental, toxic, and immune differences. Systematic reviews of primate research indicate that the perceived benefits to humans **are overstated and that non-human**

**primate models have provided disappointing contributions toward human medical advancements (42, 43, 44, 45).**

The publication 'Replacing Primates in Medical Research' (46) provides a detailed analysis of the extent to which experiments on primates have been replaced by advanced non-animal alternatives. The report includes five case studies that demonstrate the need and potential for replacing non-human primates in medical research.

**DOGS**

A 2018 opinion poll commissioned by HRA revealed that 70% of those polled oppose the use of dogs in research (28). With much of the population being dog owners, Australians can empathise with the suffering that dogs in research are subjected to, without the opportunity to live as a loved-family member. No amount of laboratory enrichment can compensate for the social deprivation they endure.

Dogs are used in Australian laboratories for toxicity testing, infection inducement, 'immunomodulatory methods ', aversive stimuli behavioural testing, and more. HRA has also exposed some of the most shocking procedures taking place in Australia, including the use of beagles for pharmaceutical drug testing, and the use of healthy greyhounds for heart surgery experiments, terminal blood donation, and to test dental implants and deep brain stimulation devices.

Not only is the use of dogs ethically objectionable to the majority of Australia, but it has also been shown to be ineffective. In 2013, a ground-breaking scientific study (47) showed that the use of dogs in testing human drug safety is not scientifically justifiable. In analysing data from over 2,366 experiments, the study found that the prediction success of using dogs was little better than tossing a coin. A 2020 US report by the National Academies of Science, Engineering and Medicine recommended the development of a strategic road map to incorporate new approach methodologies, or innovative non-animal approaches, into its biomedical research (48).

**CATS**

Many Australians are surprised to learn that cats are being used in highly invasive procedures in Australian laboratories. As with dogs, using a companion animal with complex social needs as a research tool is objectionable to many.

The types of experiments cats were subjected to include use in; central nervous system testing, immunomodulatory methods, infection inducing, long term attachment / insertion, neuromuscular block/electroimmobilisation, toxicity testing, and other disease testing. Many of the case studies HRA have profiled relate to sight and hearing (49).

A study by Rattay et al (50) compared the anatomical auditory nerve differences between the cats and humans in order to determine if results from the cat ear are really transferrable to humans. The study found a number of differences, as expected, and stated:

"*Shorter total lengths of SGNs in cat, thinner processes, smaller cell bodies and fundamental differences in myelination are obvious reasons not to rely on a cat model when signalling in human auditory nerve is discussed as these differences between the species may lead to important differences in auditory nerve function*."

Given this, one must seriously question why the Australian researchers engaged in these experiments spend valuable time and resources using cats, rather than investing in advanced human biology-based methods of research, in order for results to be directly relevant to human health outcomes.

**Recommendations**

- Prohibit the use of forced inhalation research in NSW legislation
- Prohibit the use of the forced swim test in NSW legislation
- Commit to a phase-out of primate research
- Commit to a phase-out of research using dogs
- Commit to a phase-out of research using cats
- Introduce mandatory rehoming of suitable dogs and cats used in research (current rehoming guidelines are voluntary)
- Introduce a mandatory retirement age for dogs and cats used in research of 6
- Fate of all species used in research to be reported

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

Lack of transparency has been referred to previously in relation to the lack of detailed information released about animal research in NSW and the outcomes of this research, as well as the cost to taxpayers. Upon questions in Parliament, the NSW Health Minister responded this cannot be disclosed due to the Animal Research Act. Also raised previously is the annual animal use in research statistics reports, which are complimented by The Animal Ethics Infolink website (51). Both are commendable and do contribute towards accountability.

Additionally, HRA note that a draft Australian Openness Agreement on Animal Research is open for consultation (52) and hope this will encourage research institutes to be more open in their communications. However, it is non-binding and in its current format, there is no obligation on regulators to report on their performance in meeting greater transparency.

Of frustration to HRA has been the inability to obtain a list of accredited animal research establishments in NSW which is provided by most other Australian states and territories. This withholding demonstrates a clear lack of transparency by the regulator, although it is appreciated that resistance will have been shown by the research institutions.

In terms of adequacy of the system more broadly, HRA is concerned that the system of self-regulation via institutional animal care and ethics committees is not robust. Category C members (animal welfare representative) must possess a 'demonstrable commitment to, and established experience in . . . the welfare of animals', which suggests that their utility will be limited to promoting better welfare for the animals (through housing, environmental enrichment, or, for those more knowledgeable, stronger analgesics) but not whether the experiment is actually justified. Due to a number of factors including biases within the AEC, bullying, social pressure, or the chair being a senior person in the research institution, even if opposition is felt, it may not be expressed or acted upon.

HRA note that the Animal Research Act will be revised as part of the current process of legislative reform. We are pleased that the NSW Research Review Panel looks likely to continue but suggest the below measures to strengthen the panel:

- At least two members on the panel must have a demonstrated knowledge of and commitment to alternatives to animals in medical research
- An update to be provided to complainants for complaints lodged via the Animal Research Review Panel at the end of the investigation
- Increased powers of investigation and more decisive action to penalise breaches

In respect to the third point, recently, HRA became aware of sheep inhalation research occurring without animal ethics committee approval at a Sydney research institute (53). Despite breaching the Code, the only repercussion has been that the student involved cannot publish his or her PhD based on the data. Moreover, information provided in confidence to HRA suggests that there have been weak responses to allegations of misconduct by ACEC members and a preference to simply monitor questionable research such as forced inhalation research in place of more decisive action, such as bans, phase outs or the enforcement of penalties. It is important to have an investigative panel, but if it is to be a 'toothless tiger', it will not serve its rightful purpose. It also brings to light questionable animal research by students, who may be encouraged to use animals by their supervisors regardless of its relevance.

Lastly, according to a ARRP annual report, there were no inspections of research facilities in 2018-19. We understand this is due to staff shortages. This is totally unacceptable and does not instil confidence in the inspections system.

**Recommendations**

- Publish adverse incident statistics
- Make list of license holders publicly available

- Provide details on the numbers of animals bred, but not used, for medical research, instead being killed for no purpose
- CCTV cameras in research facilities
- Ability to visit primate breeding colony for media and animal welfare organisations, in accordance with biosecurity measures
- Ministerial approvals for lethal dose tests to be made public
- Plain language non-technical summaries of research projects
- NSW Government to call for a revision to the 2013 National Code. The code currently specifies that research institutes should 'consider making available all annual reports and summaries of external reviews/inspection reports'. We recommend that this should be mandatory.
- Greater scrutiny of undergraduate and postgraduate animal use
- Consideration of a national body for animal ethics reviews. The equivalent for human ethics is Belberry, which provides streamlined scientific and ethical reviews of human research projects across the country.

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

Around the world, government-funded initiatives are acknowledging the need to further develop and validate non-animal methods of research, investing millions of dollars in alternatives and reflecting practical commitment to the replacement of animal research. This may be enshrined in legislation. In South Korea new federal legislation has been proposed that would prioritise funding for human biology-based approaches in biomedical research (54), whilst the UK Animals in Scientific Procedures Act 2012 revision has enshrined the concept of the development of 'alternatives' as a legal requirement (55). The wording in ASPA 2012 reads:

20B Alternative strategies

(1) The Secretary of State must support the development and validation of alternative strategies.

**Centres for Validation of Alternative Methods:**

- BraCVAM – BRA: Brazilian Center for Validation of Alternative Methods.
- CaCVAM - Canadian Centre for the Validation of Alternative Methods
- ECVAM - The European Centre for the Validation of Alternative Methods.
- ICCVAM - the Interagency Coordinating Committee on the Validation of Alternative Methods (U.S.).
- NKCA – The National Knowledge Centre on Alternatives to Animal Experiments (Netherlands).
- JaCVAM - Japanese Center for the Validation of Alternative Methods.
- NC3RS – National Centre for the 3Rs (UK)
- SKoCVAM - the Korean Center for the Validation of Alternative Methods.
- Swiss 3R Competence Centre
- ZEBET - the Centre for Documentation and Evaluation of Alternatives to Animal Experiments (Germany).

**Country-Specific**

Netherlands

The Dutch government announced its plan to phase out toxicology tests for chemicals, food ingredients, pesticides, veterinary medicines, and vaccines by 2025. Their Transition Program for Innovation without the use of Animals sets out the means to achieve this through collaboration between the science, health care, government and business community (56).

United States

US Senators Cory Booker and Rand Paul introduced the FDA Modernization Act to end animal testing mandates that demand experimental drugs must be pushed on animals before they are used on humans in clinical trials (57).

In the interests of transparency, The USDA Animal Care Public Search Tool (58) allows members of the public to search for:

- A list of persons licensed or registered under the Animal Welfare Act
- Inspection Reports
- Animal Welfare Enforcement Actions
- Teachable Moments
- Research Facility animal use annual reports

European Union

EU legislation regular risk-based inspections and improves transparency through measures such as publication of non-technical project summaries and retrospective assessment. The development, validation and implementation of alternative methods is promoted through

measures such as establishment of a Union reference laboratory for the validation of alternative methods supported by laboratories within Member States and requiring Member States to promote alternative methods at national level (59). The European Commission ALURES Statistical EU Database on the use of animals for scientific purpose database has been created to increase transparency in animal research and includes data on animals bred but not "used" for scientific purposes (60).

The European Parliament passed a recent resolution calling for an action plan to end the use of animal experimentation. Passed with a resounding vote of 667 to 4, the resolution calls for the European Commission to establish an EU-wide action-plan with ambitious yet achievable targets and milestones to accelerate progress in phasing out the use of animal methods in scientific research and education. The plan should prioritise funding towards the development of non-animal science and technologies. Developed over a year, with collective support from the scientific community and campaigning by animal protection organisations within the EU, this historical resolution is a welcome indication of changing times (61).

Switzerland

Two initiatives recently failed by a referendum vote (62):

1. Animal testing. The testing ban would have prohibited experimentation on animals and humans and would have prohibited the import of any new products developed using such testing. According to the Swiss Federal Statistical Office, 44% of the population participated in the vote but, of the votes cast, only 20.9% voted in favor of the ban.
2. Non-human primate rights. The Basel-Stadt measure would have amended section 11 of the canton's constitution, entitled "guarantees of fundamental rights," to provide "the right of non-human primates to life and to physical and mental integrity."

Belgium

The Brussels-Capital Region of Belgium, which encompasses the city of Brussels and 18 surrounding municipalities, officially banned commercial animal testing involving cats, dogs, and primates as of January 1, 2020 (63).

UK

There was a recent debate on animal testing in the UK Parliament arising from e-petitions 581641 and 590216. The first petition, which calls for all animal testing in the UK to be banned, has attracted 236,000 signatures. The second, which calls for a phasing-out of animal experiments, has attracted more than 83,000 signatures and remains open (64).

**(g) any other related matter**

When reviewing animal research proposals, reviewers only need to consider the potential benefit of a project. HRA recognises that there are uncertainties and that is the nature of scientific research. However, given the high failure rates of medical research, it is our position that there needs to be greater scrutiny of the relevance of animal models by regulators, journal editors, grant funder reviewers and animal ethics committees. Sadly, there are countless examples of non-translatable clinical science based on laboratory animal research, mostly mouse models. The drugs or other interventions "worked" (were nontoxic and clinically effective) in animal models but were abandoned for use in people due to toxicity or lack of therapeutic efficacy. These include the below (8):

- Type 1 diabetes—all 195 methods that prevented or delayed diabetes in mice failed in people
- HIV pre-clinical and phase 1,2 and 3 trials—30-40 vaccines in clinical trials failed whereas all vaccines worked in non-human primates
- Alzheimer's disease—300 different interventions effective in mice, not effective in humans
- Amyotrophic lateral sclerosis (ALS)—100 potential drugs in established animal models, all failed in human clinical trials

**It may be argued that improving study design will improve the predictive value and reproducibility of animal research, which could overcome this lack of translation. However, HRA does not support this claim. The weaknesses in the internal validity of animal experiments cannot be overcome by simply improving study design. This is 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," can never be achieved. Inherent species differences mean that nonhuman animals cannot serve as analogues for understanding the specific biological details necessary to develop safe and effective drugs for humans (65).**

We also contest that creating genetically-modified animals is the solution to human-relevant data. In 2019, there were 2,792, 976 genetically modified animals produced in NSW. **Yet genetically- modified based advances have not had a significant increase in improving the rate of success in medical research, and a recent assessment analysing; the degree of animal pain and suffering, the number of people who stand to benefit, and how likely genetically-modified animal models are to contribute to a breakthrough, concluded that the practice is not justified (66).** Whilst animal research continues, HRA recommends that there is greater oversight of genetically modified breeding for medical research to reduce 'wastage' and review impact.

Clearly, some diseases are uniquely human, and we need human-relevant research to make real progress. Furthermore, the rapid evolution of personalised (precision) medicine

utilising genomics, proteomics, systems biology and bioinformatics demonstrates we understand the uniqueness of each individual—that we develop diseases and respond to treatments differently. Indeed, there is increasing evidence that biomedical research must not be limited to the traditional reductionist view but rather take a system's-based approach to disease, if to properly understand biological mechanisms in humans. For example, the studies of neuroendocrinology (nervous and endocrine system), the gut-immune, gut-brain (central nervous system), and recently, gut-lung axis, have identified strong connections between multiple body systems.

Evidently, understanding the cause of disease in humans, must consider factors unique to the human population, as the associative cause of many diseases has already been identified and widely accepted. The Adverse Child Experiences study, cited over 15 thousand times, clearly demonstrates the association between adverse childhood experiences, and disease later in life (67). Allostatic load theory compliments this work—it explains the biological embedding of these early life experiences, and of the effect of stress (wear and tear over the lifetime) on the brain and its causative role in disease—its origins in neuroendocrinology, which led to the Nobel prize in 1950 (68, 69). Continuing to rely on animal models is not fit-for-purpose. The ability of human nature, not physiological mechanisms alone, can contribute to and cause much of the disease and suffering humans experience. Relying on animal models completely overlooks the complexity of humans.

Yours sincerely,
Rachel Smith
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