The veterinary voice in animal welfare

Inquiry into the use of primates and other animals in medical research in NSW: Sentient's responses to questions

Dr Rosemary Elliott's responses to questions asked during the Inquiry

Question two: Do you agree that there is a cultural problem in terms of the attitude to the use of animals in research?

We see widespread evidence of a cultural problem in terms of the attitude to the use of animals in research and this has been evident during the Inquiry's hearings. There is a strongly held belief, which is unsupported by evidence, that animal use is essential in medical research and that any harms to animals in the process are justified by the severity of human disease. This is ethically unacceptable. As veterinarians, we object to the status quo of animals being kept in barren environments, where they are subject to a host of stimuli that leave them chronically stressed and frequently in pain. Analgesia and anesthesia are often denied, partly due to concerns that they will impact experimental outcomes. This is despite increasing recognition that pain relief improves both animal welfare and research quality via minimisation of pain-related physiological, psychological, and behavioural distortions. Many procedures performed on animals in the name of human medical research are overtly cruel, with death or unnecessary suffering as an endpoint.

The following are some of the cultural barriers to acknowledging the low level of success of animal use in medical research that are delaying the necessary shift towards the use of non-animal alternatives:

- Very limited understanding of the sophistication of non-animal methods of research
- Misuse of the term 'human-relevant' research, with assumptions that it refers to testing directly on human volunteers from the outset, or 'using people as guinea pigs'
- Lack of critical analysis of animal research, such as researchers who fail to validate their research or subject it to scientific scrutiny, but instead make claims of success in the form of personal opinion. This is not acceptable evidence but is influential in a parliamentary Inquiry due to the social status held by medical researchers.
- Elevating the necessity of animal research way beyond its efficacy and efficiency by accepting the high failure rate of pre-clinical trials using animals (approximately 90 to 95%) as 'part of the scientific process'.
- Lack of acknowledgement of extensive evidence that animals do no provide accurate models of human disease
- Conspiracy theories about whistle blowers such as animal technicians who give evidence about poor animal welfare practices, through claims they have been 'planted' by certain political parties

- Concerns by researchers that if regulations are 'too stringent', NSW research will receive less funding than international research
- Resistance to change and portraying any suggested change to the use of animals in research as an immediate and total ban that would be detrimental to scientific progress
- Sensational stories about purported successes based on animal research, for example hailing the success of xenotransplantation with the recent pig heart transplant in the US without acknowledging that the patient died from suspected porcine infection
- A simplistic ethical stance that is reflected in questions to witnesses such as 'how many animal lives are worth a human life?" rather than adopting a One Welfare approach, which acknowledges that the welfare of human and non-human animals is interconnected, and that human health and wellbeing can be achieved without harming animals.
- Citing the severity of human disease to justify the use of animals in medical research rather than proving animal research is making a difference. This is a statement of value. The severity of human disease does not alter the impact on animal suffering.

The cultural problem that exists in the research community regarding the use of animals in research has been widely acknowledged in the literature. Due to technical problems on the day of the Inquiry, we were unable to table the following 2015 paper[1] by Dr Aysha Akhtar, a neurologist and preventive medicine specialist and Fellow at the Oxford Centre for Animal Ethics, who questions why animal experimentation is viewed as the default option for preclinical testing given questions about its validity.

Supplementary Questions

1. We have heard at this inquiry that it is not mandatory for all research institutions to have a vet on site, and some do not have one at all. Does this concern you? If so, why?

Yes, we find this very concerning. It must be considered that the public has a duty of care to seek veterinary advice for sick animals in their charge under relevant state animal protection legislation. It would be expected that a parallel duty exists for animals used in research, given that these animals are often the same species as those kept as pets (rats, mice, rabbits, cats, dogs), and/or are species with the same capacity for suffering. Without a veterinarian being on site, animals who suffer from pain, illness, injury or unexpected reactions to procedures may be denied medical assistance for hours of perhaps days. This is neglect.

We reference an article in the Global Journal of Animal Law, 2014, that contrasts this "with the statutory appointed Named Veterinary Surgeon role in the UK, the designated veterinarian of the EU, and attending veterinarians in the US. The role of the Named Veterinary Surgeon in the UK is well-defined by the use of supportive guidance notes issued by the Veterinary Surgeons professional body. This not only aids those acting in the role but provides another impetus to

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594046/

perform the role competently; the bringing of the role under the remit of professional conduct rules. Other international jurisdictions also refer to the specific expertise required of laboratory animal veterinarians and training programs which allow attainment of this.[2]"

Our concern extends to the exemptions in the Code that allow researchers to legally perform surgery on animals - surgery that would be restricted to veterinarians in other contexts. Researchers may have internal training (which is not provided by vets) and may or may not be supervised by vets. This is stated in 2.4.18: "Investigators must (ii) ensure that procedures are performed competently, and that the investigators are: (a) competent for the procedures they perform, or (b) under the direct supervision of a person who is competent to perform the procedures." We fail to see how non-veterinarians can be expected to perform 'surgery' on animals within best practice standards, and how these researchers are attaining surgical competence - something that requires at least five years of training for veterinarians. This situation poses grave welfare outcomes for animals used in research given the highly invasive nature of surgery. Animals used in research are the same species and/or have the same capacity for suffering as all other animals, and therefore surgery must be considered an act of veterinary science as it is in other contexts.

2. You express some concerns in your submission about the effectiveness of the Animal Ethics Committee oversight regime, and in particular the role and experience of Category C members. Can you give us some details about your concerns, and do you think more support and training for Category C members might be useful in defining their role?

We are concerned about the inherent biases involved in role allocation within AECs. These biases include peer pressure from others within the group. We think that support and training would certainly be beneficial for Category C members in this regard, but this would not sufficiently compensate for power imbalances. It can be intimidating stating one's concerns in the face of peers who have more formal and revered qualifications. Category C members are also often the only member with a vested interest in the animal's experience above all other considerations. Veterinary members, while ostensibly representing animals' health and wellbeing, are bound to the industry and have a vested interest in ensuring animal research continues; being strongly embedded within the animal research culture is an impediment to unbiased assessment.

We also see an urgent need for the addition of a committee member who has expertise in finding alternatives to using animal models.

Furthermore, according to section 2.3.11 of the Code, if a consensus can't be reached, even with some mitigation to research protocols, the AEC should proceed towards a majority decision despite an individual member who retains strong objections to the proposed use of animals. Evidence presented to this Inquiry includes a Category C member who was unable to prevent the use of forced inhalation in mice.

[2] Animal Research Regulation in Australia – Does it Pass the Test of Robustness? By Alexandra Whittaker, Global Journal of Animal Law (GJAL) 1/2014

> "2.3.11 Decisions should be made based on consensus. Where consensus cannot be reached after reasonable effort to resolve differences, the AEC should explore with the applicant(s) ways of modifying the project or activity that may lead to consensus. If consensus is still not achieved, the AEC should only proceed to a majority decision after members have been allowed a period of time to review their positions, followed by further discussion."

In the first two days of hearings for this Inquiry, we heard two alarming examples of failure in the current regulatory regime:

- Research using sheep with death as an endpoint had been going on for years at a major university in NSW and was reported anonymously. Evidence from HRA, when asked how this research could be occurring without AEC approval, identified the hierarchical nature of universities as a factor as the illegal research had been common knowledge but when someone complained, the academic said 'get a life, I'll do what I want'; also, people just assume someone else has gone through AEC committee approval due to multiple researchers being involved (in this case a university and the DPI). We heard that the Minister did not recognise this complaint as an offense under the Animal Research Act, which is inconsistent with the Act itself.
- It remains unclear whether the Animal Research Review Panel has taken any action over research that subjected mice to a 90-minute forced swim test; this research had presumably been given AEC approval to use the test to research cardiac conditions in humans.

We oppose the mandatory confidentiality clauses that members of Animal Ethics Committees are asked to sign. This contributes to the lack of transparency about approved research on animals and what this entails. We also have concerns about the recruitment of members of AECs and do not believe that support or training, such as for Category C members, would suffice. We know of examples where Category C members were told at the initial interview that their role is to 'facilitate, not hinder, research' and who withdrew their application upon being informed of the true nature of the research, which was highly invasive with death as an end point. This is a dynamic that serves to deter those who have the best interests of animals at heart. The essential problem with the AEC process is that it is a form of industry self-regulation. The best way to protect animals from suffering and harm through research is to replace the AEC process with an independent review of all research proposals.

3. Do you think the fact that some Animal Ethics Committees are continuing to approve controversial experiments (such as forced swim tests for depression studies), while other Animal Ethics Committees are rejecting them because of animal cruelty concerns and questions around their validity undermines community confidence in the animal research regime? What would you

like this committee to recommend to the Government from this inquiry to overcome some of the issues in relation to Animal Ethics Committees?

Yes, we agree that this could serve to undermine community confidence in the process. The makeup of AECs is intended to reflect community attitudes to what is and is not ethically acceptable. The great variation in what different AECs will and will not approve demonstrates the need to better qualify ethical thresholds to ensure that approvals adequately meet community expectations. Currently the AEC process does not consistently protect animals from treatment that in other contexts would qualify as animal cruelty.

To better reflect community expectations and improve the transparency of the approval process, we recommend that:

- At least two members on the panel have a demonstrated knowledge of and commitment to alternatives to animals in medical research;
- An update be provided to complainants for complaints lodged via the Animal Research Review Panel at the end of the investigation;
- There be increased powers of investigation and more decisive action to penalise breaches
- All applications made to Animal Care and Ethics Committees be made publicly available, as well as committee decision making - including determined relevance within the wider research landscape, cost/benefit analyses, pain mitigation strategies and the provision of adequate environmental and social enrichment, and well-justified reasons why alternatives to animal models were not pursued
- Confidentiality clauses for members of AECs be abolished
- Mandatory public reporting of the number, species and types of interventions carried out on these animals
- There be pre-registration of all animal experiments to avoid duplication, as well as publicly available publication of all negative results and the fates of all animals involved in research (including those bred but not used)
- Statistics be made publicly available on all animal-related adverse events that occur within institutions, both related to research and while running business
- The names of all license holders be made publicly available
- CCTV cameras be installed in all institutions both wherever animals are housed or experimented on, and
- That a certain percentage of inspections of institutions also be made unannounced.
- Ideally, the current AEC process would be abolished and replaced by an independent process. Having AECs based in research institutions amounts to self-regulation, particularly given the lack of consistency in decisions about what is acceptable in terms of animal use, the lack of public transparency and the mandatory confidentiality clauses signed by all AEC members.

4. One member of the Committee suggested that witnesses had been 'selective' in the data they presented to this inquiry, suggesting they had selectively chosen data which supports their argument. They gave the example of the statistic cited by Sentient that in relation to Alzheimer's, where you said "99.6 per cent of all research performed does not translate in human trials". Would you like to respond to this assertion about 'selective' use of statistics – can you expand further why you used these examples and what the example demonstrates?

While the figure of 99.6% is particularly high, it is not much higher than the average failure rates of all human trials - figures put this average as anywhere between 92 to 96%.[3] Meaning, it is not just Alzheimer's Disease (AD) research that fails so dramatically, but the vast majority of all drug research. Dr van Ekert cited in her response the 99.6% figure in reference to AD, and these averages. Using averages allows one to demonstrate what happens most commonly - not present specific figures that suit an agenda. **To the best of our knowledge, there are no studies of any kind that demonstrate a high predictive value of animal models for human drugs or disease.[4]**

Reasons for these high failure rates include widespread issues with study quality, as well as issues *inherent* in using animals as a means of modeling disease and drug responses in humans. We believe it is important to highlight these to emphasize the need for alternatives to animal models, because these inherent problems cannot be overcome.

Some have argued that these alarming failure rates are just the nature of doing research. Systematic reviews - a far more reliable means of assessing causation compared to individual opinion - instead point to bad science. Systematic reviews[5] are the gold standard in evidence-based medicine, and provide a transparent means for gathering, synthesizing, and appraising the findings of studies on a particular topic or question by using scientific methodology. Systematic reviews can help researchers and clinicians keep up with literature by summarizing a large body of evidence and helping to explain differences among studies on the same question. Meta-analysis is the statistical method used to combine results from relevant studies, and the resultant larger sample size provides greater reliability of the estimates of a treatment effect. Systematic reviews and meta-analyses of experimental investigations can clarify whether and how translation from animal to clinical research could progress and can provide a unique opportunity to review the appropriateness of the animal models used.

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[3] According to a submission by Cruelty Free International on Environment Protection and Biodiversity Conservation Amendment (Prohibition of Live Imports of Primates for Research) Bill 2015#: "Recent data obtained from 13 large pharmaceutical companies for drug approvals made between 2007 and 2011 found that **95 percent** of drugs fail in human trials, because they are not safe or do not work, even though they will have 'passed' tests involving non-human primates." In a more recent update, based on a report by Biotechnology Innovation Organisation (BIO), the world's largest trade association representing biotechnology companies, universities and related organisations in the United States and 30 other nations, the failure rate of drugs after pre-clinical tests, including animal tests, was **92%** between 2011 and 2020.

[4] Chp 17 of Andrew Knight's book, Ray Greek and Lisa A. Kramer https://brill.com/view/title/35072

[5] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7479780/

We heard evidence from Professor Andrew Knight that every systematic review of the use of animals in medical research has identified a common set of methodological flaws that reduce their reproducibility and reliability, and therefore the ability to produce the hoped-for benefits in human health care. Methodological flaws noted by Dr Andrew Knight include: a lack of statistical justification of sample sizes, lack of sufficient sample sizes (meaning we can't make predictions for species), a lack of random allocation of animals to treatment and control groups, lack of blinding (where researchers are not aware whether the animal has been in an intervention or control group) - all of which distort scientific outcomes. These flaws were identified and weeded out decades ago in human clinical research but remain persistent in animal research because the culture has not improved in terms of researchers subjecting their own work to scientific scrutiny. All these flaws distort scientific outcomes. These errors are very prevalent so the results cannot make reliable predictions in the same species, let alone in other species.

Kilkenny et al. (2009)[6] conducted one of the largest and most comprehensive systematic surveys to date, assessing the experimental design, statistical analysis, and reporting of published animal experiments. 271 papers were examined, which included 72 studies using mice, 86 using non-human primates, and 113 using rats. Most (99%; 269/271) of these papers were published between 2003 and 2005. They covered a wide variety of experimental fields, were published in a comprehensive range of journals, and were funded by leading grant agencies within the United Kingdom and the United States. However, only 59% of these studies clearly stated the hypothesis or objective of the study and the number and characteristics of the animals used. Details, such as animal strain, sex, age, and weight, are all scientifically important and can potentially influence results. Nevertheless, in many cases these details were omitted.

Furthermore, at least 50 per cent of preclinical research results cannot be replicated when other scientists re-run a study. Reasons for this include variation in the way animals are housed and handled (environmental factors). For example, a recent meta-analysis[7] examined differences in outcomes for rodents housed in 'enriched' housing (containing running wheels, nest boxes, additional space or other items that allow natural behaviours like digging, climbing, exploring and hiding) compared to conventional housing ("shoeboxes" — small, barren cages typical in laboratories). They found that conventional housing causes rodents to be more stressed, increasing stress-related morbidity. For example, if given cancer, they developed larger tumours. The analysis also highlighted concerning methodological problems and poor reporting of experimental details. The rodents used were male-biased, with few studies using female animals. And, despite investigating housing effects, two-thirds of the studies analyzed did not fully describe animals' living conditions. The authors suspect that the reliance on "CRAMPED" animals — cold, rotund, abnormal, male-biased, enclosed and distressed — could help explain the current low

[6] Kilkenny C., N. Parsons, E. Kadyszewski, M.F. Festing, I.C. Cuthill, D. Fry, J. Hutton and D.G. Altman (2009) Survey of the Quality of Experimental Design, Statistical Analysis, and Reporting of Research Using Animals. PLoS ONE,4(11), p. e7824.

[7] https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-021-01184-0

success rates of biomedical research, and issues with repeatability if housing factors aren't standardised.

Laboratory procedures and conditions exert influences on animals' physiology and behaviors that are difficult to control and can impact research outcomes and impede extrapolation to humans. Animals in laboratories are involuntarily placed in artificial environments, usually in windowless rooms, for the duration of their lives. Captivity and the common features of biomedical laboratories—such as artificial lighting, human-produced noises, and limited space and lack of environmental enrichment—can prevent species typical behaviors, causing distress and abnormal behaviors among animals. They are also exposed to social stressors, whether this is isolation or aggressive interactions between conspecifics. Among the types of laboratory-generated distress is the phenomenon of contagious anxiety. Examples include cortisone levels rising in monkeys watching other monkeys being restrained for blood collection and blood pressure and heart rates elevating in rats watching other rats being decapitated.

Animals used in laboratories commonly experience stresses incurred during handling, restraint, and other routine laboratory procedures; and in particular, the stressful routes of dose administration common to toxicity tests. Orogastric gavaging, for example, involves the insertion of a tube into the esophagus for the forced administration of test compounds. These stressors can alter physiological, hormonal, immune statuses, cognitive capacities, behavioral repertoires, neurochemistry, genetic expression, and nerve regeneration, in ways that are not always predictable. The results may include alterations in the progression of diseases, in bodily responses to chemicals and test pharmaceuticals.[8] For example, stressed rats develop chronic inflammatory conditions and intestinal leakage, which add variables that can confound data. In one study, mice were genetically altered to develop aortic defects. Yet, when the mice were housed in larger cages, those defects almost completely disappeared. Providing further examples, typical noise levels in laboratories can damage blood vessels in animals, and even the type of flooring on which animals are tested in spinal cord injury experiments can affect whether a drug shows a benefit.

To control for potential confounders, some investigators have called for standardization of laboratory settings and procedures. One notable effort was The Flaws and Human Harms of Animal Experimentation 409 made by Crabbe et al.[9] They investigated the potential confounding influences of the laboratory environment on six mouse behaviors that are commonly studied in neurobehavioral experiments. Despite their "extraordinary lengths to equate test apparatus, testing protocols, and all possible features of animal husbandry" across three laboratories, there were systematic differences in test results in these labs. Additionally, different mouse strains varied markedly in all behavioral tests, and for some tests the magnitude of genetic differences depended on the specific testing laboratory. The results suggest that there are important influences of environmental conditions and procedures specific to individual laboratories that can be difficult—perhaps even impossible—to eliminate. Alternatives to animal models would avoid these confounding factors and therefore improve research reliability.

[8] https://brill.com/view/book/edcoll/9789004391192/BP000019.xml

[9] https://www.science.org/doi/abs/10.1126/science.284.5420.1670

We chose the example of AD research to highlight the significant impacts that such high failures can have on society. According to the Alzheimer's Association:[10] estimates of AD prevalence in the US are 16% of people aged 65-74 years, 45% of all 75–84-year-olds, and 36% of people aged 85 years and older. Total payments in the US in 2019 (in 2019 dollars) for all individuals with Alzheimer's or other dementias are estimated at $290 billion. Among people aged 70, 61 percent of those with Alzheimer's dementia are expected to die before age 80 compared with 30 percent of people without Alzheimer's dementia. This is a disease for which effective treatment is urgently needed because it costs society a lot of money and impacts a lot of people.

Unfortunately, among the ten most common causes of death, AD is the only one with no effective approach for prevention, slowing disease progression, or cure. Most basic science research of AD has used animals, predominantly mice (transgenic, inbred, and wild type), but also rats and, to a lesser degree, other species, such as rabbits, dogs, and non-human primates. Many animal models have been attempted, yet no individual animal model or combination of models replicates the clinicopathological complexity of human AD. Despite the 2,204 AD clinical trials (including 1,329 completed, terminated, suspended, and withdrawn drug studies) listed at ClinicalTrials.com on July 24, 2017, only four drugs are currently FDA-approved for treatment of the disease alone or in combination. The drugs produce very small changes, of dubious clinical relevance, on cognitive and behavioural measurement scales; they typically have mild impact on symptoms in only a minority of patients, have no effect on disease progression or mortality, often lose any effectiveness within several months, and may produce serious adverse effects.[11]

If we were to ask the public whether they would want their taxpayer dollars being preferentially allocated to more efficient options, of course the answer would be affirmative. Yet AD research, like other medical research, is stuck in an antiquated and unvalidated system of animal testing that has poor reproducibility, poor reliability, and unacceptably low predictive values. Insufficient resources are being allocated to exploring more effective means of meeting these research goals. This resistance to change in the scientific community is impacting on human health as well as animal welfare.

5. A number of researchers told the committee that there aren't alternatives to animals available yet for their field of study. Is this correct, in your opinion? If there are areas of research where alternatives are not available, can you please give your view as to why this is the case – do you think it is a lack of funding, or are there other issues causing a delay?

We are not experts in alternatives to animal models, so cannot comment on their availability or applicability to various research goals. However, we wish to cite EU reports on non-animal

[10] https://www.alz.org/media/documents/alzheimers-facts-and-figures-2019-r.pdf

[11] Animal Experimentation: Working Towards a Paradigm Change, Kathrin Herrmann and Kimberley Jayne Copyright: 2019 Publisher: Brill, Chapter 20 Animal Research for Alzheimer Disease: Failures of Science and Ethics John J. Pippin, Sarah E. Cavanaugh and Francesca Pistollato pp. 480-516

alternatives to researching degenerative diseases[12], with 568 models, ranging from biochemical and computational approaches to different types of cell cultures and procedures using ex vivo human material; respiratory diseases[13] using in vitro cell and tissue cultures, human ex vivo, in silico approaches; and breast cancer[14] and immuno-oncology[15] using human based models.

Unlike the UK and some other EU member states[16] Australia has no dedicated national centres for the development of replacements to animal use in research - this is a contributing factor to the lack of availability of alternatives to animals in medical research in NSW. The NHMRC does not dedicate funding, specifically, to the development of animal-free research methods and this is what is needed. We agree with Humane Research Australia's suggestion of establishing an independent Australian Centre for the Development and Validation of Alternatives.

Another reason we propose for the lack of animal-free alternatives is that of path-dependency. Animal testing was developed, and required, in an era when we did not have the ability to develop alternatives. We now have the technical sophistication to do so, but our regulatory system and institutions are tied to antiquated animal models, and there is little incentive to change this. Those charged with performing medical research are taught and subsequently teach animal models; they do not have the expertise to use alternative models, nor the institutional incentives to critically evaluate the efficacy of these models. Medical researchers also hold powerful influence in society, so even where they may not be adept at critically appraising the efficacy of their animal models or at seeking alternatives, the claims of success that they make in the form of a personal opinion have impact - even if such claims objectively hold less weight than systematic reviews. Using alternatives requires a larger paradigm change in the scientific community.

AECs - those charged with approving projects - are also insufficiently equipped to critically evaluate the availability and appropriateness of alternatives to animal models, so when, invariably, researchers state that there are none available, this is not challenged. The regulatory system fails to sufficiently look at the bigger picture and analyse our progress with regards to the 3Rs, including the most crucial, which is "replacement."

The Government requirement for regulatory animal testing of drugs before human trials prevents researchers from opting out of this. We are optimistic that this could change, given what we have seen with the cosmetics industry. Overseas developments regarding the regulation and use of animals in medical research are also promising. The US is likely set to end the FDA (Food and Drug Administration) requirement for animal testing of new drugs. The 2021 FDA Modernization Act,

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[12] https://op.europa.eu/en/publication-detail/-/publication/5d9512e7-a89b-11eb-9585-01aa75ed71a1/language-en

[13] https://op.europa.eu/en/publication-detail/-/publication/42ab9f04-f98d-11ea-b44f-01aa75ed71a1/language-en/format-PDF/source-search

[14] https://op.europa.eu/en/publication-detail/-/publication/2bdc3c07-1a63-11eb-b57e-01aa75ed71a1/language-en/format-PDF/source-search

[15] https://publications.jrc.ec.europa.eu/repository/handle/JRC125256

[16] http://alttox.org/mapp/regulatory-policy/european-union-programs-policies/eu-3rs-centers-initiatives/

H.R. 2565 and S. 2952 will reform the drug approval process and drive the use of non-animal testing methods. It was approved with an overwhelming majority in the US House of Representatives and is waiting to be passed by the Senate. In the US, some pharmaceutical companies under the FDA Act are actually ahead of the regulators as they are pushing for non-animal alternatives.

6. Would you support a 'deadline' or 'target' for a phase out of the use of animals in research, and if so, what would that look like in practice?

Yes. This would rely on there being appropriate replacements. Measures should include: the establishment of dedicated centre/s to advance the development and use of alternatives; redirecting funding to human-predictive research methods; (re)training scientists in non-animal research methods; and redesigning university curricula to focus on non-animal approaches. We are also aligned to Professor Andrew Knight's[17] views on this matter, and we propose that:

- Prior to designing any new animal study, researchers should conduct a systematic review to collate, appraise, and synthesize all existing, good-quality evidence relating to their research questions. Such systematic reviews should be similarly required by grant agencies, ethical review committees, other animal-experiment licensing bodies, and journals. Systematic reviews are studies in and of themselves. In recognition of their intrinsic value, and their necessity for informing further research, they should also be readily funded by grant agencies.
- To ensure that all such evidence is publicly available, researchers and editors should always publish negative results. Studies that fail to show a treatment effect are often considered less interesting and are, consequently, much less likely to be published. The subsequent exclusion of such results from systematic reviews leads to over-estimations of treatment efficacy and partly explains the widespread failures in humans of treatments apparently efficacious in animals.
- Within the field of human studies, clinical trial registers allow researchers to learn about existing and prior clinical trials, including those with negative outcomes, before results are formally published. A similar international initiative to register animal studies and their results is warranted
- We also wish to see detailed consideration of non-animal alternatives in applications and sound justification of why these could not be employed. This should be bolstered by the addition of 1-2 AEC committee members with an expertise in animal alternatives.

[17] https://brill.com/view/book/edcoll/9789004391192/BP000019.xml

7. You note in your submission that in 2020, 36,441 (43%) of research animals in NSW were exposed to procedures that either resulted in their death or subjected them to unnecessary surgery or pain and distress due to physiological challenge. As veterinarians, what is your reaction to these statistics- does that concern you, and what do you think the NSW Government should be doing in response to these statistics?

This is highly concerning, particularly because we do not know whether any pain relief was provided, the details of the nature of the experiments, or their utility (which would allow the public to weigh up the cost/benefit of such invasive experiments).

The government should:

- Requiring mandatory pain relief and provision of adequate environmental and social enrichment;
- Mandate that CCTV cameras be installed in all institutions both wherever animals are housed or experimented on, to improve accountability and provide reassurance to the public that, if animals are forced to endure harmful procedures, they are treated humanely;
- Require more reporting around 3Rs, including: a comprehensive analysis of alternative models to animal use and why these were not used; and reporting of improvements to procedures and husbandry that minimize actual or potential pain, suffering, distress, or lasting harm and/or improve animal welfare in situations in which the use of animals is unavoidable. At present, scant information is provided about the living environments of animals in laboratories, such as enrichment, opportunities to express species-specific behaviors, and whether individual animals are kept in isolation from other animals. This is of interest to the public;
- Place bans on any research (including medical research) that involves: ▪ Forced inhalation ▪ Forced swim tests ▪ Unconsciousness without recovery ▪ Major surgery with recovery ▪ Major or minor physiological challenge ▪ Production of genetically modified animals, and ▪ Death as an endpoint ▪ Lethal testing

8. Some researchers have argued they want to keep researching on primates due to their biological similarity to humans – however, do you think this similarity also raises concerns on an ethical and welfare level about using these animals? What is Sentient's view on the use of primates in research?

We do not think that primates should be used in medical research. We would only support non-invasive observational studies such as in sanctuaries or veterinary research performed for the benefit of the species.

Primates' advanced cognitive, psychological and social characteristics of primates make it problematic for their welfare when kept in confined environments. Laboratory environments cannot provide sufficient social and environmental enrichment. Their long memories allow them to remember certain people and procedures associated with pain and distress, which increases their suffering. They also have the capacity to anticipate stressful events, suffering therefore not only from the procedures themselves but from the stress of anticipation.

There is also no evidence that research on primates reliably translates to human health. We strongly recommend the Committee evaluate such claims about the efficacy and translatability of primate research to humans, given the serious animal welfare implications of continuing their use. The researchers arguing for their use should be providing systematic reviews - not just individual anecdotes - to prove that such research is a reliable means of producing meaningful outcomes for humans, because the data we have seen suggests otherwise.

- According to a submission[18] by Cruelty Free International on Environment Protection and Biodiversity Conservation Amendment (Prohibition of Live Imports of Primates for Research) Bill 2015: "Recent data obtained from 13 large pharmaceutical companies for drug approvals made between 2007 and 2011 found that 95 percent of drugs fail in human trials, because they are not safe or do not work, even though they will have 'passed' tests involving non-human primates."
- HIV/AIDS vaccine research using NHPs represents one of the most notable failures in animal experimentation translation. Immense resources and decades of time have been devoted to creating NHP (including chimpanzee) models of HIV. Yet all of about 90 HIV vaccines that succeeded in animals failed in humans. After HIV vaccine gp120 failed in clinical trials, despite positive outcomes in chimpanzees, a BMJ article commented that important differences between NHPs and humans with HIV misled researchers, taking them down unproductive experimental paths. Gp120 failed to neutralize HIV grown and tested in cell culture. However, because the serum protected chimpanzees from HIV infection, two Phase 3 clinical trials were undertaken —a clear example of how expectations that NHP data are more predictive than data from other testing methods are unproductive and harmful. Despite the repeated failures, NHPs remain widely used for HIV research.
- Due to their costs, the number of primates used in studies is so small that it is impossible to reliably translate results to the same or even other species (large sample sizes are required to improve research replicability and reliability).

[18] https://crueltyfreeinternational.org/latest-news-and-updates/bio-updates-figure-failure-rate-drugs-after-pre-clinical-animal-tests-92

- Additionally, Kilkenny et al. (2009)[19] conducted one of the largest and most comprehensive systematic surveys to date, assessing the experimental design, statistical analysis, and reporting of published animal experiments. Such reviews are a good way of assessing research quality. The review included 86 studies using non-human primates. Studies covered a wide variety of experimental fields, were published in a comprehensive range of journals, and were funded by leading grant agencies within the United Kingdom and the United States. However, only 59% of the studies analysed clearly stated the hypothesis or objective of the study and the number and characteristics of the animals used. Details, such as animal strain, sex, age, and weight, are all scientifically important and can potentially influence results. Nevertheless, in many cases these details were omitted.[20] This is not good science.

9. A number of researchers have argued that the regulatory regime overseeing animal experimentation in NSW is 'robust' and 'rigorous' – would you agree with this? If not, how would you describe the regime, and what (if any) are your concerns?

"Rigorous" means "extremely thorough." The system is too prone to error for this term to be appropriate. These kinds of claims were made throughout the Inquiry but with no actual evidence to back them up. Instead, we have heard evidence of experiments operating without AEC approval, and 90 minute forced swim tests being approved despite the serious animal welfare implications of this and the dubious benefit to humans. A recent study by Professor Andrew Knight analyzed the number of times that studies involving forced swim tests were later cited in clinical papers on human depression and found that the median citation number was zero - that is, clinically focussed human research was continuing in a parallel world and the FST is not contributing significantly to the understanding or cure of MDD.[21]

We would describe the regime as dysfunctional. Ostensibly, it is meant to apply a utilitarian framework to assessing the worthiness of research by considering animal impact, as well as benefit to humans. As we have outlined, most research performed on animals fails to translate to humans; that is, there is no or very minimal benefit to humans. This is despite the extreme costs to animals involved. This critical analysis is absent in the existing assessment methods. Citing the severity of human disease is often used to justify the use of animals in medical research rather than proving animal research is making a difference. This is a statement of value. The severity of human disease does not alter the impact on animal suffering.

Our concerns include:

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[19] https://pubmed.ncbi.nlm.nih.gov/19956596/

[20] Animal Experimentation: Working Towards a Paradigm Change Series: Human-Animal Studies, Volume: 22, Editors: Kathrin Herrmann and Kimberley Jayne, Chapter 14 Critically Evaluating Animal Research, Author: Andrew Knight, Pages: 321–340

[21] https://brill.com/view/journals/jaae/aop/article-10.1163-25889567-bja10026/article-10.1163-25889567-bja10026.xml

- The functioning of AECs, as outlined in above questions. This includes a lack of standardization in the AEC approval process, which undermines public confidence, and allows experiments to be passed in contexts where they would otherwise be rejected
- A lack of sufficient scrutiny regarding the utility of animal models to address research goals
- Insufficient incentives to develop and use alternatives to animal models
- No requirement for pre-registration of animal experiments, resulting in unnecessary experimental repetition and thus excessive use of animals
- A lack of transparency:
    - Most information about how animals are used in research is received by the public via exposes. For example, baboons are being purpose bred at a facility in Wallacia for 'important biomedical research' at the National Health and Medical Research Council (NHMRC) in Sydney, where they have been used for at least 30 years. There is no transparency about what is done to these animals to "tackle priority medical issues identified by the Federal Government including diabetes, kidney disease and complications arising from pregnancy." The public were only made aware of the use of these primates for research after 3 baboons accidentally escaped in 2020.
    - We could find no details on the DPI website about how animals are used in research or about recent ethics committee approvals of research projects.

10. We heard from an animal care technician during this inquiry who had worked in the US and here in Australia. She highlighted that in the US, if there are welfare issues, there is an independent welfare body someone can complain to with the authority to investigate. She had major concerns that the same did not occur here in Australia – that the oversight body was the institution itself (or the Animal Research Review Panel which is still part of the research industry) with no independent and separate regulatory oversight. Do you have concerns about this state of regulation of animal research in NSW? Do you think the 'self-regulation' system we have is problematic, and will continue to lead to animal protection issues?

Yes, we do hold grave concerns about self-regulation in the scientific community and the failure of the current system to protect animals from harm. Sentient fully supports independent oversight. Transparency is central to the scientific method and ethical conduct. We trust that genuine transparency, by way of independent oversight, will lead to greater scrutiny of animal research projects, which in turn will lead to greater reduction and replacement of animals in research. As it stands, there are insufficient incentives or technical knowledge to adopt alternatives to animal models, and unacceptable levels of animal suffering as a result of, for example, inappropriate projects being approved by AECs, and animals receiving insufficient pain relief and environmental enrichment.

We are also concerned that no concrete actions have been taken in response to the 2020 Australian Senate Motion, which called on the Federal Government to: (i) ensure national

transparency and accountability in the use of animals in research, and (ii) invest in the methods and technology needed to end the use of animals for research purposes.

11. At the hearing, we heard about the 'FDA Modernization Act' in the US, which would remove the mandatory element of doing animal studies for drug trials. Would you support similar initiatives in Australia, to phase out any mandatory requirements to test on animals? What effect would that have?"

This would be an important step in aligning Australia with other leading research countries, including the United States and EU member states. As well as advances in the US, it should also be noted that in September 2021, the European Parliament voted overwhelmingly in favour of a resolution to phase out animal use for research, testing, and education, through the adoption of an action plan. This resolution stems from the following observations in the EU:

- the overall use of animals in laboratories has failed to undergo any significant decline despite enshrining the "3Rs" principles of replacement, reduction and refinement in the European Directive 2010/63/EU on the Protection of Animals for Scientific Purposes;
- rising public opinion against the use of animals with almost three-quarters of Europeans in favour of phasing out animal testing, and
- the increase in development and application of non-animal new approach methodologies (NAMs)

These international changes will increase the demand for scientists able to find more efficient means of getting drugs past human trials. If Australia does not do a better job of funding alternatives and training scientists in alternative testing modalities, we're going to be losing a huge market opportunity and we could lose researchers who wish to pursue innovative, non-human alternatives.

Relying on animal models slows down our ability to efficiently develop cures for disease, makes for an expensive drug development process, and significantly compromises the welfare of millions of animals. Australia should be incentivizing the development of the most predictive technologies to provide the safest and most effective medicines for patients in the least possible time. Removing this requirement would provide the needed incentives to increase funding and adoption of alternatives and increase training in the use of alternatives.

12. During this inquiry, we've received evidence of cruelty happening at research facilities in Australia – for example, animals not receiving proper analgesia, mass killings from excess breeding stock, animals having their tails and toes cut off. Do you see a link between incidents of cruelty like this, and a lack of transparency in the animal research industry? If so, how are the two related? Can you explain how transparency could help ensure incidents like this will reduce in occurrence? Are there other changes that will help reduce cruelty incidents?

Yes, we do see a link. The more transparent a system, the more its practitioners are held accountable, resulting in higher standards of practice. To increase transparency, we advocate that the following measures be adopted:

- Independent oversight - including for audits, the complaints process, and adherence to the 3Rs principles (notably, that of "replacement").
- Reporting around 3Rs: a comprehensive analysis of alternative models to animal use and why these were not used; and reporting of improvements to procedures and husbandry that minimize actual or potential pain, suffering, distress, or lasting harm and/or improve animal welfare in situations in which the use of animals is unavoidable. At present, scant information is provided about the living environments of animals in laboratories, such as enrichment, opportunities to express species-specific behaviors, and whether individual animals are kept in isolation from other animals. This is of interest to the public.
- Documentation of funding for animal and non-animal research and on development of alternative methods. And a comparison to the funding directed towards research using animal models, with year-by-year comparisons to gauge progress. The NHMRC, as the largest funding-body of biomedical research, is the appropriate organization to make the details of funded animal research available. The NHMRC already provides lists of funded projects. However, from the project descriptions in these lists, it is unclear whether the research uses animals. It should be easy to add this detail.
- Updates be provided to complainants for complaints lodged via the Animal Research Review Panel (or equivalent) at the end of the investigation.
- Increased powers of investigation and more decisive action to penalise breaches.
- All applications made to Animal Care and Ethics Committees should be made publicly available, as well as committee decision making - including determined relevance within the wider research landscape, cost/benefit analyses, pain mitigation strategies, and comprehensive reasons why alternatives to animal models were not pursued
- Confidentiality clauses for members of AECs be abolished.
- Mandatory public reporting of the number, species and types of interventions carried out on these animals.
- Mandatory (not voluntary) public reporting of the fate of ALL animal species used in research (not just for domestic dogs and cats), including the number rehomed and those bred but not used directly in experiments.
- Pre-registration of all animal experiments to avoid duplication, as well as publicly available publication of all negative results.
- Statistics be made publicly available on all animal-related adverse events that occur within institutions, both related to research and while running business, and the response to these.
- The names of all license holders be made publicly available (not the names of individuals).

- CCTV cameras be installed in all institutions both wherever animals are housed or experimented on.
- That a certain percentage of inspections of institutions also be made unannounced.
- Inspection reports to be made publicly available.
- See examples:
    - The European Commission "ALURES" animal use reporting system - the EU's statistics database on animal use in research.[22] This details the number of animals used, where they were obtained, the type of research, the degree of invasiveness, species, whether animals were reused, and whether the animal testing was performed to satisfy EU or non-EU requirements
    - Non-technical summaries (NTS) of animal research are mandated by the EU Directive 2010/63/EU (European Parliament, 2010, Article 43). NTS provide information on the objectives of a project; predicted harm and benefits and the number and types of animals to be used; and a demonstration of compliance with the requirement of replacement, reduction, and refinement. We suggest these summaries clearly describe what happens to animals undergoing procedures in a way that the public can understand. This type of openness would provide the public with a more impartial way to evaluate the animals' experiences against the intended benefits of the research conducted upon them.

1/8/2022

Dr Katherine van Ekert, Vice President
Dr Rosemary Elliott, President

[22] https://webgate.ec.europa.eu/envdataportal/content/alures/section1_number-of-animals.html