Supplementary Questions Humane Research Australia NSW Inquiry into medical research using primates and other animals

1. *In your submission, you argue we need to make "retrospective assessments of animal research to be mandatory as a condition of funding and made public." Can you explain why this is so important*

Retrospective assessments are important to assess whether the stated research aims have been achieved and to assist evaluation as to how significant the data or knowledge gained was to human health. Due to a desire to obtain funding in competitive grant processes, the expected benefits of planned research may be overstated in grant applications or approval applications to animal ethics committees. **A retrospective assessment enables critique based on the actual outcomes of the research rather than the expected outcomes**. **It also enables more accurate classification of the actual severity of harm to the animals used**. Having mandatory publication of such assessments enables members of the public who as taxpayers are funding medical research, to have greater insight as to what animals have been used for and what the result of that use is. They can then have a more informed opinion as to the value, or otherwise, of animal research.

As animal ethics committees (AECs) often have so many research applications to screen, they may not be giving due consideration to monitoring or reviewing the outcomes of that research, with focus on the application itself. Retrospective assessment would aid AECs in self-assessment as to the effectiveness of their decision making - what was the cost/benefit analysis of the research that was funded? Should they be making different decisions in future?

Open retrospective assessments may also prevent repetition of animal research and demonstrate negative results, which are rarely published.

Note, in the EU, Directive 2010/63/EU (Article 39: 2) requires researchers using non-human primates and /or severe procedures to conduct retrospective assessments of their individual projects.

2. *Some submissions suggest the use of primates in experimentation are essential for studies into diseases like Hepatitis B and Covid - but you have a campaign to end primate research. What are some of the specific concerns you have around the continued use of primates in research – why do you feel it should be phased out or not continue?*

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'. It is an area of research which draws public concern, as was clear by the tabling of a petition in the NSW Parliament in March 2022, with over 109,000 people calling for a ban on primate experimentation. The animal welfare impacts associated with the advanced abilities of primates 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. It is unclear why other primates are excluded from the same protection on the grounds of moral reasoning.

In terms of primate being essential for disease research, 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 NHP models have provided disappointing contributions toward human medical advancements[1].

For example, in the field of depression, primate studies were mainly cited by other papers on animal experimentation, which suggests they are mainly contributing to subsequent animal research rather than advances to human healthcare' depressive research[2]. The results of this study suggest that studies based on in silico and in vitro approaches are taken into account by medical researchers more often than are NHP-based approaches. In addition, these human-based approaches are usually cheaper and less ethically contentious than NHP studies.

Primates are often used in HIV research but based on the primate version of the disease, simian immunodeficiency virus (SIV). This research does not equate to studying an illness in humans; but studying a different illness in primates. Because HIV and simian immunodeficiency virus (SIV) are closely related viruses, researchers study SIV as a way to learn more about HIV. In fact, SIV differs from the genetics of HIV by a staggering 50%[3]. This is illustrated by the failing of 100 different types of HIV vaccines tested in monkeys with positive results, none of which provided protection or therapeutic benefit in humans, due to major differences in SIV-infected macaques compared to HIV-infected humans[4].

Whilst primates were used in the development of the vaccine process, Pfizer and Moderna were given approval to simultaneously test their vaccines on animals (on mice and macaques) while they were conducting phase 1 trials on humans. Other data came from cell-based tests and computational assessments of the experimental vaccines. Non-animal techniques,

---

[1] Knight, A. The poor contribution of chimpanzee experiments to biomedical progress. J. Appl. Anim. Welf. Sci.2007, 10, 281–308
Bailey, J. An assessment of the role of chimpanzees in AIDS vaccine research. ATLA 2008, 36, 381–428.
Thew, M. Primate studies: Trials don't always translate. Nature 2012, 484, 167
Bailey, J.; Taylor, K. Non-human primates in neuroscience research: The case against its scientific necessity. ATLA 2016, 44, 43–69

[2] Carvalho C, Varela SAM, Bastos LF, Orfão I, Beja V, Sapage M, Marques TA, Knight A, Vicente L. The Relevance of In Silico, In Vitro and Non-human Primate Based Approaches to Clinical Research on Major Depressive Disorder. Altern Lab Anim. 2019 Jul-Sep;47(3-4):128-139. doi: 10.1177/0261192919885578. Erratum in: Altern Lab Anim. 2020 Sep 24;:261192920964278. PMID: 31838868

[3] Taylor (2016) Monkeys are still suffering for ineffective HIV research https://www.crueltyfreeinternational.org/what-we-do/blog/monkeys-are-still-suffering-ineffective-hiv-research

[4] Bailey J. Monkey-based research on human disease: the implications of genetic differences. Altern Lab Anim. 2014;42(5):287-317. doi:10.1177/026119291404200504

including the use of monoclonal antibodies, cultured cells and physico-chemical analysis, were also used to ensure the quality of each vaccine batch[5].

With xenotransplantation research being an area in which primates are used in NSW, it should be emphasised that despite the number of 'breakthroughs' reported in this area, only one xenograft of a solid organ in a living human has since been attempted. A modified pig heart was engrafted into a patient in the US with heart failure early in 2022; the recipient died after two months from a suspected porcine infection[6].

3. *Companies like Codex Research are developing alternatives to the use of animals in research – are you aware of any barriers or roadblocks companies like Codex might face in getting these alternatives into the market? Why are these alternatives not being used widely?*

The question would be best directed to Codex research, but from reading their submission and listening to the company CEO's evidence, a key barrier appears to be the nature of grant funding (labs would like to use the bioreactor technology but need funding for staffing to conduct the research). With the bioreactor technology, it is at proof-of-concept stage which could be another barrier. It is not as attractive to venue capitalists as software for example, as the return of investment is not as immediate, and funders may be lacking the scientific knowledge needed to evaluate project potential. Current NHMRC grants are not targeted at alternative methods, and the medical devises grant program is out of scope. Greater investment in new technology is needed to overcome such roadblocks.

*'The NSW government provides some excellent funding opportunities for technology start ups, such as the Medical Device Fund and the Physical Science Fund grants. A similar grant specifically aimed at alternatives to animal-based research would be a great boost to the development of this technology in NSW' (*Ed Brackenreg Submission 0225).

The alternatives are not being as widely used as merited due to a range of factors, including lack of expertise, lack of awareness, and a bias by grant funders, reviewers and journals towards animal-based research.

4. *A number of submissions from industry have called for the establishment of a Centre for Alternatives to coordinate, fund and support the development of alternatives to animals in research. Is this something you would support, and if so, why - what kind of value do you think this would bring to the sector?*

This is something HRA would support to increase knowledge and confidence in non-animal methods as well as to assist technical validation of non-animal methods. A recent article[7] reviewing the Rise of 3Rs centres in Europe highlights the **advantages as being important points of contact, playing an immense role in their respective countries as 'on the ground' facilitators of legislative requirements to not use animals where alternative methods exist**. They are also invaluable for the widespread dissemination of information.

[5] https://www.nature.com/articles/d41586-022-01110-6

[6] https://www.newscientist.com/article/2319108-man-who-received-pig-heart-transplant-has-died-after-pig-virus-found/

[7] https://journals.sagepub.com/doi/pdf/10.1177/02611929221099165

Note, HRA's recommendation is for an Alternatives Centre not a 3Rs centre, as we feel that the emphasis should be on replacement. Perhaps this could be achieved via the conversion of an animal facility to a centre of excellence for human-relevant science?

5. *Can you give some examples of alternatives to animals in research that you believe have been particularly effective or useful, or are particularly noteworthy.*

The regulatory benchmark for accepting a validated « alternative » method is in the 85% to 90% prediction range. These figures cannot be achieved with animal models. The best animal data is in the 30% to 60% range with respect to predicting safety (not taking into account the efficacy[8]).

As raised during my evidence, organ-on-a-chip appear to one of the most promising alternatives, with and the potential of a body-on-a-chip in the near future. This can be attributed to financial support for the development of this technology. In 2010, the FDA, NIH AND Defence Advanced Research Projects Agency issued a request for applications for novel research and science- based technologies and funded one of the first large efforts for MPS (organ on a chip) development by the Harvard- Wyss group, for safety and efficacy testing[9]. Such investment is required to incentive alternatives to animals in biomedical research.

Traditional animal models of drug research can be slow and potentially expose humans and animals to harm. Organ-on-a-chip technology could help bypass these issues. Emulate looked at 27 drugs, 22 of which had previously been found to be toxic in humans. This toxicity had resulted in 208 patient fatalities and 10 liver transplants, even though the drugs had been tested in lab animals before undergoing clinical trials with humans. Emulate's organ chips, on the other hand, were able to identify 87% of these drugs as toxic. Had this technology been available from the start, these drugs would never have made it to human trials[10].

Other examples of where non-animal methods have been proven to be superior include computer models of human heart cells which are able to predict side effects of various medications on the heart more accurately than animal studies[11].

The standard test on pregnant rats to find out if chemicals or drugs may harm the developing baby can only detect 60% of dangerous substances. But a cell-based alternative (EST) has 100% accuracy at detecting very toxic chemicals[12].

The limitations of animal methods are increasingly recognised by regulators. For example ,there are some biopharmaceuticals or biologics which specifically interact with proteins in human cells – therefore it is redundant to test them in humans. This is acknowledged in International Council on Harmonisation Guidelines[13].

Last year, the European Pharmacopoiea, which sets quality standards for drug companies on the continent, announced that it would, over five years, replace the conventional animal test to detect fever-inducing compounds. In the new standard test, medicines are added to vials of human blood and monitored to see whether they activate monocytes, a type of immune cell. The irony is that this

[8] Norman (2019) Limitations of Animal Studies for Predicting Toxicity in Clinical Trials. Basic to translational science. 4:7.
[9] https://journals.sagepub.com/doi/10.1177/0192623318809065
[10] https://www.fastcompany.com/90747811/safer-faster-and-more-ethical-drug-development
[11] https://eandt.theiet.org/content/articles/2019/12/is-the-end-of-animal-testing-in-sight/.
[12] https://www.crueltyfreeinternational.org/why-we-do-it/alternatives-animal-testing
[13] https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

alternative has been validated much more thoroughly than has the original rabbit test, which was developed in the early twentieth century and was incorporated into regulatory requirements by default.[14]

6. *A number of industry bodies have argued that animal research in NSW is highly regulated. Would you agree with this? What do you see as some of the shortcomings? Do you see the industry as being essentially self-regulated – and if so, do you have concerns about this?*

I disagree with this and see the industry as largely self-regulated by institutional animal ethics committees, which are heavily influenced by the research institute whose research applications they screen. An audit every four years (if resources permit) does not equate to high levels of regulation, and it is of concern that some license holders are auditing one other rather than DPI conducting the audit (as per evidence provided by Dr Sarah Toole).

Additionally, there are concerns over the independence of the DPI, given a recent instance in which the DPI was tasked with investigating themself for conducting research without AEC approval. This as recognised by the statement '**There was a subsequent failure of the investigation process by NSW DPI under its Accreditation as an Animal Research Establishment to detect and act on the problems that had occurred, demonstrating a failure of effective self-regulation under the Animal Research Act 1985'[15].**

The fact that an institute conducted research without AEC approval for years and yet still maintains its license also contradicts the portrayal of animal research in NSW as highly regulated**.**

The concerns that arise from self-regulation include lack of assurance that the research being conducted merits approval, anguish caused by members of an AEC who feel unable to speak out, and variances between institutions as to what is considered an acceptable research practice, for example some AECs have prohibited forced smoke inhalation or forced swim test protocols, whereas others permit it. Ultimately, the self-regulation is contributing to unnecessary suffering of animals, wastage of funds, and lack of translation from discoveries in animal models to human patients.

7. *One submission to this inquiry argued that the "thalidomide tragedy in the 1960s occurred in part because there was insufficient testing in pregnant animals for a drug indicated for use in pregnant women." Is that correct, or is it the case that animal research did not pick up the effects because of the differences between animals and humans? Are there cases like this where drugs have been wrongly rejected or allowed onto the market because they gave false or misleading results in animals?*

During early testing, researchers found that it was virtually impossible to give test animals a lethal dose of the drug (based on the LD50 test). In some tests, dosages of over 600 times the normal human dosage had no effect at all on rodents. Largely based on this, the drug was deemed to be harmless to humans. A basic search reveals differing accounts as to whether pregnant animals were used and which species. However, when Thalidomide was administered to pregnant rats by various routes this was without significantly interfering with embryonic development. Therefore, it could be reasoned

[14] https://www.nature.com/articles/d41586-022-01110-6

[15] SO52 Document Production Animal Pathology for NSW Field Veterinarians course at (redcated)
13 November 2017:Findings and recommendations relevant to NSW Department of Primary Industries under its Accreditation as an Animal Research Establishment under the Animal Research Act
198

that it may not have been detected dependent on the species and dosage administered even if pregnant animals were used[16].

There are some examples of treatments that would have been rejected had animal testing been required. For example, aspirin is toxic to many animals including cats, rats, and mice, but is safe for most humans. We wouldn't be able to buy it in pharmacies if it had been tested using current animal testing standards. Other examples include Gleevec (cancer drug) which causes serious adverse effects in at least five species but not when tested in human cells assays and human clinical trials, and Tamoxifen, a breast cancer drugs, which causes liver tumours in rats.

Evidently, it difficult to identify all these because since animal testing has been a regulatory requirement for decades, therefore potentially successful therapeutics for humans may have been rejected during this time during preclinical animal testing.

There are plentiful examples of drugs that made it to market after animal testing and were then withdrawn for safety reasons. These are listed on HRA's website[17]

There are also drugs still on the market for which people suffer adverse reactions; however this could still result even if animals were not used, due to differences between human responses and the potential for misuse.

Health policy has also ben adversely impacted. By the early 1940s, human clinical investigation strongly indicated that asbestos causes cancer. However, animal studies repeatedly failed to demonstrate this, and proper workplace precautions were not instituted in the U.S. until decades later. Similarly, human population studies have shown a clear risk from exposure to low-level ionizing radiation from diagnostic X-rays and nuclear wastes, but contradictory animal studies have stalled proper warnings and regulations. Likewise, while the connection between alcohol consumption and cirrhosis is indisputable in humans, repeated efforts to produce cirrhosis by excessive alcohol ingestion have failed in all nonhuman animals except baboons.

8. *One submission claimed that medical research is funded by a large number of public donations, with an implication that the amount of people making donations showed support for research involving animals. Do you think that donations from the community towards medical research is evidence of community support for animals to be used in research - or if not, why not?*

Many of the donors will not be aware that their donation is leading to animal research as that is not widely publicised by such charities. Additionally, members of the public may be supportive believing animal research to be a necessary evil, without full knowledge of other method that exist and that this narrative is no longer accurate.

A 2018 opinion poll commissioned by HRA[18] showed that 59% of those surveyed would not donate to a health or medical research charity if they knew it was funding animal experimentation (a further 23% did not know if they would). HRA operates a Humane Charities List, to direct donations to health-related charities that do not conduct, fund or commission animal research[19].

[16] https://www.sciencedirect.com/science/article/abs/pii/S0022347664806260
[17] https://www.humaneresearch.org.au/dangerous-drugs/
[18] https://www.humaneresearch.org.au/wp-content/uploads/2019/10/Awarenessofanimalexperimentationisincreasing%E2%80%93andAustraliansarenothappy-May2018.pdf
[19] https://www.humanecharities.org.au/

9. *Is there any further information or concerns you would like to share with the Committee about smoking mice experiments, particularly any that are happening in NSW?*

The issue of inertia in research institutes towards adopting new methods had been discussed during the Inquiry. HRA feels this is demonstrated by the University of Newcastle. HRA has approached the university on many occasions, with offers to facilitate relationships with companies providing non-animal research methods in the field of respiratory research for example, to replace the smoking mice model. However, the university has been non-responsive. Of course, this may be in part due to a reluctance to engage with a group opposed to animal research. However, this does not justify the hesitancy to commit to a phase out of this cruel research.

A further concern is the lead investigator previously working at the University of Newcastle continuing the nose-only smoke exposure method at the Centennial Institute which is funded by millions of dollars of NHMRC grants. With public opposition and opposition within the scientific research community itself, it is concerning that new multi-year projects are commencing using this method.

Also noteworthy is the response received from representative of the AEC approving nose-only inhalation research when questioned at the Inquiry:

> There are over eight million deaths a year from smoking worldwide, at minimum—that is the WHO estimate—and 1.2 million of those are passive smoking. So it is occurring in people who have no choice, in many cases, in that smoking exposure. In many countries, it is over a third of the population. Worldwide, it is closer to—20 per cent of people smoke. It is an absolutely massive problem. Whilst there have been gains in reducing the rates of smoking, the harms are going to continue for many decades, even for those people who have stopped. So we have an absolutely critical need to make some advances in trying to stop the progression of disease in those people who have already been exposed to smoke, those people who will expose themselves to smoke and the passive smokers.

This is an example of justifying research according to severity and scale of the disease, without giving any explanation as to why the method used is effective and relevant to humans. The research need demands the most effective method of research. This is not exposing mice to smoke. Please see the below extracts from the evidence in support. I hope this gives the panel some idea of the differing views on what research is acceptable, and the inconsistency of decisions by AECs is**. And perhaps the supportive position of the institute approving such research should be considered in light of that connection.**

LISA CRAIG: The forced inhalation study is of common concern, and I have extensive experience with those models. Animals have forced exposure to cigarette smoke five days a week. They are left two days a week in withdrawal. The particular model leaves animals hypothermic, wet and in significant distress between cigarettes. Generally those animals are smoked twice a day. **Those models are horribly unreliable. In many instances, I have seen those animals culled en masse when the researcher has decided that the progress of the study is not going the way they expected or intended**

WOJCIECH CHRZANOWSKI: **The main problem is that the lungs in rats and mice do not represent at all the physiology in humans—zero.** The other thing is that smoking is very different to humans than to animals. You cannot give a cigarette directly to the mouth of an animal. It is the same if you would like to develop the treatment, you cannot use the same devices. You cannot use the puffer for asthma

to the animal because the mouth is not fitting there. Physiologically it's very different. **As I mentioned, the aerodynamics in the lungs of animals is completely different than the one to the humans. They have two lobes, we have four, four of which are actually—both of them are different on both sides because we have a heart as well. This makes injury completely different and the deposition of chemicals completely different than what we have in human lungs. Hallmarks of the disease in the small animals in the rodent models are very different to the hallmarks of the disease in humans. If you would like to develop a treatment or even study physiology of this disease, there's actually no way of doing this properly**

ANDREW KNIGHT: The likelihood benefits, unfortunately, are low. The reasons why that occurs are well understood and well studied and, in light of that, should this research be proceeding? **Well, when it is particularly invasive and when the animal welfare impacts are particularly high, as they are in smoking towers and forced swim tests, then the research needs to be especially justifiable in order to be proceeding. It needs to be particularly good scientific quality and the likelihood benefits should be very high in order for there to even be a case. And that's not true, unfortunately. Those conditions are not met by this kind of research. It should not [audio malfunction] and it should not be proceeding.**

10. *In your submission you state that "Australia is cited as one of the highest users of animals in research globally, with New South Wales typically reporting usage of more than two million animals each year". There was some confusion about the underlined portion of this statement at the hearing. a. Can you please clarify if the two million figure refers to the total number of animals used in experimentation, or the number of animals bred in excess of need for research (aka wastage)? b. Are the number of animals considered wastage by the industry recorded? If not, do you think that they should be and why or why not?*

This number refers to the total number of animals that have been used in NSW that required animal ethics approval, so this would be broader than medical research and include environmental study for example. It does not include all animals bred and killed before use (wastage) and this should be included. Notwithstanding the waste of animal lives and money, if this information were made available, there would be a greater incentive to reduce wastage. Collating at an institutional level would highlight any license holders with poor practices. Such information is provided in the EU via the Allures Database[20]

Currently, animals culled as part of the GM production process are an example of a use that should be reported under 'Production of genetically modified animals'. However, this is not broken down to report culling specifically, as it effectively includes ALL animals used in GM production other than the final progeny which are used in a different category of procedure. The numbers of non-GM animals bred and not used are not recorded.

It is difficult to distinguish from the ARRP reports how many animals are used for medical research and teaching and therefore extract meaningful data, as well as to ensure fair reporting. Understanding human or animal biology and maintenance and improvement of human or animal health and welfare are broad categories, and the category of regulatory testing could refer to drugs or agricultural products for example. Production of genetically modified animals is categorised as a level of severity

[20] https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm

rather than project purpose. A nationally consistent method or collating and reporting animal use data is required.

11. *The Committee has received submissions stating that the full costs of animal research are often not covered by research grants and arguing that we need more funding for animal research in NSW. What is your response to this – do you think we should be increasing funding towards animal research, or should funding be focused on developing alternatives to animal research – and if so, why?*

There should be rigorous assessment of the predictive ability of animal research before allocating more funding to this method, particularly given that NSW is a proportionally high user of animals already and there has been no independent assessment of its value. Whilst understanding the intention of more funding could be to increase animal welfare standards and improve research quality (internal validity), ultimately, we cannot remove the species barrier which impacts the translational value of all animal research. Therefore, HRA recommend a focus on developing alternatives to animal research.

12. *In relation to smoking mice experiments, you stated at the hearing "it is very disappointing to see the University of Newcastle continue to use this method and for students to continue to be using that method there when, through members of the animal ethics committee, for many years we have information that has been objecting to that, but it is still continuing."*
    a. Can you please clarify what the objections were, and why the experiment was allowed to proceed despite objections by an AEC member?
    b. Do you think this is an example of AEC members having their opinions ignored? Do you believe the AEC system is working in practice, and if not can you please explain how this system is not functioning as it should?

The objections raised by AECC members and dating back to 2014 relate to:

- Protocols being changed by researchers without permission
- Requests by the AECC being rejected by researchers (for example, increasing number of technicians present to minimise restraint time and assist with monitoring)
- Health and safety concerns for technicians due to smoke exposure
- Not getting adequate answers to questions raised to researchers
- Refusal to modify protocols to improve animal welfare
- Failure to provide justification for protocol
- Inadequate plain language explanations of research
- Large number of mice requested which are not justified
- Frequent urgent variations requested
- Poor attitude by the research group to the ACEC which has impacted on young researchers' attitudes to animal welfare and the ACEC
- Concern that ACEC permitting the research because a large NHMRC grant despite the animal welfare and validity concerns
- Refusal to monitor mice over weekend to see if suffering from nicotine withdrawal symptoms

The research was seemingly allowed to continue despite the objections as approvals were made without consensus and relentless bullying, intimidation and refusals to act on the concerns raised led to AEC members with objections resigning. I am unaware of the current ACEC views on the research or the dynamics of the AEC. However, it is clear that historically this research has faced criticism, which was not adequately addressed, and much of this is alleged to result from the forceful nature of the lead researcher who instigated the nose-only method of smoke exposure.

13. *We have a submission highlighting that many AEC committee members are not properly trained and supported - is this an ongoing issue particularly for Category C and D members who are expected to provide their opinion on complex research protocols?*

As referenced in HRA's submission, 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]. The interactions HRA have had with former AEC members also suggest that training and support is insufficient.

There is a free online course provided by ANZCCART which covers the Australian Code and NZ Guide and welfare issues relating to animal use in research and teaching. This is a good introduction. However, for voluntary members without a background in research or alternative methods, it would be extremely difficult to find the time to read all the research protocols, let alone understand them and be able to challenge protocols or suggest alternatives. Whilst training could be improved, ultimately, I think there needs to be professional guidance available to AEC members, such as an alternatives centre, where members can turn to for support, or expertise on alternatives to be made mandatory within the committee, or for there to be an additional layer of oversight by a regulatory body.

14. *Do you think Animals Ethics Committees are capable of assessing whether an animal research project is valid, or whether alternatives should be used?*

As mentioned above, it would be extremely difficult to be across all alternative methods, as it is a rapidly changing field, as well as to keep informed of best practice in both research and animal welfare and behaviour, combined with regulatory changes. Some AECs may be more capable than others but certainly I would not expect most to be fully capable.

As well as technical competency, culture also plays a part, as members may not feel confident in speaking out or expressing concerns. I recently spoke with two former category D committee members and their experiences were vastly different to those presented as evidence during the Inquiry. One spoke of the existence of a 'group mentality' which did not always have the best interests of the animals as top priority.

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. It is about experimental design focuses on the desired outcome and challenging faulty logic. A like-for-like replacement is not always possible. The question should not be is this animal-free method good enough to replace my animal experiment? The question should rather which method provides the best answer to my research question? Being able to make this assessment is not an easy feat.

[21] Animal Ethics Committee education and training resources survey (2020) ARRP. https://www.animalethics.org.au/__data/assets/pdf_file/0008/1321388/AEC-survey-summary.pdf

15. *Are you aware of honours students doing research on animals in NSW – and if so, do you have concerns about this, given that students are likely repeating research experiments on animals with known outcomes? Do you think there should be laws to stop honours students conducting experiments using animals? If so, why?*

HRA was previously contacted by a student studying a Bachelor of Science with majors in immunology and early human development, at a Victorian university. The student was concerned about unnecessary animal experimentation and dissection which are components of this course. One example provided was testing cytotoxic T cell response and MHC restriction by peritoneally injecting at least 6 mice with a sarcoma virus, waiting for T cells to be differentiated and then killing them to get the spleen. This was deemed "necessary" for counting cells and generating data.

I also note the submission by a former University of Adelaide AEC member (submission 252 by Peter Anderson):

> *For example, much suffering is inflicted on animals by students so that they can submit research to gain Honours degrees and Ph.D's. One student bragged, in a University of Ade-laide newsletter, that his research had no practical value and was done only to satisfy scientific curiosity. He surgically altered small Australian marsupials' sexual organs to see how this would affect their behaviours when kept in an overcrowded cage. Amongst other things he found that he could cause male animals to mount other male animals. Con-ducting experiments merely to satisfy scientific curiosity is of course not restricted to students, and sometimes it is indulged in to provide work for academics.*

It is likely that these circumstances are evident in other states.

I also note the submission by Lisa Craig (251) stating that '*Some institutions, they borrow a lot of students—postdocs and graduates—to perform animal experimentations. And they have technical staff with that expertise that is doing it day in and day out and has the training and expertise in injections or surgery or manipulations. They are replacing the researchers—the students and the free labour that researchers use—but that is not often the case, because it is expensive. There is a difference between hiring somebody with technical expertise to perform your animal experiments and getting a postgraduate student or an honours student to give free labour*'

Within NSW, the University of School of Medical Sciences Honours Projects Booklet brings up 34 results with many animal experimentation projects including transplantation, cataracts, blindness, developing animal models, analgesia, multiple sclerosis, and gut injury.

This is of concern to HRA for a number of reasons. It establishes a precent of using animals in research, does not equip students with skills needed to peruse advanced new approach methodologies, and is wasteful of animal lives in the projects where outcomes are known and the animals are simply used to demonstrate existing knowledge, which could be taught by other methods. There is also the potential of animal welfare impact if the students are not adequately trained or experienced. To reduce the number of animals used and bring about a change in future generations of researchers, HRA recommend that honours students are prohibited from using animals. This would also encourage supervisors to expand the research methodologies they use.

16. *Some submissions have argued that a phase out of the use of animals in research, or even just tightening regulations around animal research, could push animal research overseas where animal welfare laws may not be in place - what is your response to those claims?*

This is based on the concern that animal welfare standards are worse overseas. In some cases, they may well be, although the evidence provided by Lisa Craig implies that Australia is not leading on animal welfare for animals used in research, so perhaps we could learn from other jurisdictions rather than the other way around. For countries where animal welfare laws are absent or poorly administered, Australia should lobby for higher standards. **If research quality in animal research is as high as claimed, and animal welfare directly correlates to the quality of research conducted, then surely Australian researchers would not want to outsource to such countries in any case?**

However, abuses in animal laboratories occur in many countries, including those who argue that they have robust animal welfare laws such as the US and EU.[22] There is never a guarantee of high animal welfare or high impact research. It should also be noted that Australian pharmaceutical companies heavily outsource their animal research overseas already.

There is a global need to transition away from animal research. However, Australia can only start by reducing the use of animals in our own jurisdiction and communicating effectively why this is needed, which could potentially impact on other countries. If Australia and other leading biomedical research countries simply continue using animals because we feel the research may be conducted to a lower standard elsewhere, then nothing will change.

17. *There has been a lot of focus on NHMRC funding at the inquiry. Are they the only source of animal research funding in Australia? Are there other sources of funding in Australia, and what are they? Is some of this funding easy to obtain without proving a level of justification?*

At a national level, the Federal Government funds health and medical research directly through the Medical Research Future Fund (MRFF), the National Health and Medical Research Council (NHMRC), and the Biomedical Translation Fund (BTF), and indirectly through block grants to universities. It also contributes funding through grants to both public and private research institutions and organisations, such as CSIRO and Cancer Australia. The Department of Education's funded Australian Research Council Fund (ARC) supports fundamental and applied research.

The Australian Research Council administers the National Competitive Grants Program (NCGP), a significant component of Australia's investment in research and development and has responsibility for Excellence in Research for Australia.

AusIndustry delivers the BTF on behalf of the Department of Health. The Fund stimulates private investment in the sector by providing companies with venture capital through licensed private sector fund managers to develop biomedical discoveries into products, services and outcomes.

Other sources of funding are state and territory Government, charitable donations, private investment and philanthropic funding.

Obtaining funding is not easy to obtain, but in common with others represented at the Inquiry, HRA is concerned that the peer reviewers or grant panels may have a bias forwards non-animal methods and

[22] https://www.humanesociety.org/sites/default/files/docs/HSUS_Inotiv-Investigation-Report.pdf
https://www.theguardian.com/environment/2021/apr/12/animal-testing-suspended-at-spanish-lab-after-gratuitous-cruelty-footage

lack experience in other methods, which can disadvantage applicants using non-animal technologies[23]. There is also a history of giving funding to previous applicants, which can serve to perpetuate more animal research. See the evidence provided below:

> WOJCIECH CHRZANOWSKI: **But for me, as a researcher, if we apply for funding overseas the models are accepted. If I apply for NHMRC funding, I get a comment, "You need an in vivo model. You cannot progress any work because you need an in vivo."**
>
> ALASTAIR SLOAN: **I think currently the situation of grant funding in Australia is deeply flawed. It means, quite simply, that money simply follows money. If you have had 20 years of funding and you delivered on that funding, you are likely to get your next grant funded**

Additionally, according to the Code, research using animals need only have potential benefit which can be difficult to quantify. Certainly, much of the animal research that HRA profile in our cases studies do not show sufficient justification, such as the forced swim test or forced inhalation research.

18. *At the inquiry, one witness stated that "If the regulations become too stringent, it would mean that New South Wales research would not be competitive with overseas research. And it probably means that less national research funding would flow into New South Wales and this would affect, undoubtedly, the quality of medicine and our hospitals". What is your response to this argument – do you agree that additional regulations on the use of animals in NSW is likely to affect the quality of medicine and NSW hospitals?*

'Undoubtedly' seems a highly inflated claim. Taking the UK for example, having an additional level of regulation (the Home Office approves each application following AEC approval), this has not resulted in a reduction of quality.

Additional regulations which favour non-animal methods could actually have a positive impact on the quality of medicine and NSW hospitals by providing human-relevant data instead of data based on animal models. It presents an opportunity for NSW to be a leader and attract new researchers and drive innovation. I refer to the evidence below:

> WOJCIECH CHRZANOWSKI: I would go probably even further. With the three innovation precincts, which we have now, why not establish an innovation precinct in replacement of animals, or a discovery centre and bring together really powerhouse brains, which we have in the State, bring them together and establish something which is world-class, the first in the country, probably the first in the world. I will give you a very simple example. A few years ago I started working with a company in Korea, ROKIT. It is a 3D printing company. I focused at that moment on bioprinting. Today they have a factory that is producing the skin replacement after burns after injuries and they have, literally one of the buildings the size of a university building. It is only production of skin replacement. The company after five years moved from literally one bioprinter to hundreds of bioprinters printing the skin. Why can't we do it here? Why can't we have a replacement for liver, heart, lungs? We have wonderful research

[23] https://www.biorxiv.org/content/10.1101/2022.03.24.485684v1.full

happening across the board, why not bring it all together and create a world-class facility, discovery centre, or even an innovation precinct in this space?
ALASTAIR SLOAN: You will likely find yourself attracting researchers from across the country into New South Wales, because it is something that will attract half of my lab. I'll have to move States.

Codex Research Submission 0225 The move to replace animal-based research with better alternatives is an idea whose time has come. More and more people are coming to feel that conducting experiments on animals is ethically wrong, and we are seeing the results of this social movement in new efforts by governments in Europe and the US to move away from animal experimentation. At Codex Research, we believe that alternative technologies have great potential to not merely substitute for animal-based research, but to dramatically improve our research outcomes. These are still early days in what we see as an inevitable development of a new field of technology, which means NSW has a great opportunity to participate in this process. This has the potential for a huge boost to the NSW economy.

19. *At the inquiry, when asked about the level of transparency within the animal research one witness stated it was "as open as it can be". Do you agree with this statement? If not, can you please explain some of the ways you feel the animal research industry should be more 'open' and 'transparent'*

I would respond that it is as open as the current legal framework requires it to be, but that falls short of the level of transparency needed to enable thorough public scrutiny of animal research. I also pose the question to the Inquiry members, even after involvement in this Inquiry, where you have been privy to information not in the public domain, how much do you know about animal research in NSW? How much Government funding is provided for animal experimentation? How much is directed to non-animal method? What is the success rate in NSW? What are dogs and cats used for? Who is supplying dogs and cats for research? I expect many of the answers would be unknown.

HRA notes that the one of the most frequently cited examples of transparency provided during submissions and at the Inquiry is the mixed composition of animal ethics committees, including an animal welfare representative. However, with the deliberations of animal ethics committees not being made publically available, nor the AEC application or project progress or completion reports, and very infrequently their annual reports, this is not broad transparency and restricted to the very small number of people on the AEC, who then cannot share that information.

The below are recommended to enable the industry to be more open and transparent. Please note, this does not only apply to AECs and researchers, but to the industry more broadly, including regulators and funders. In many cases, this should not create additional levels of bureaucracy or intensify workloads, it is simply making publically available data and documentation which is already being collected or should be available.

- Commitment to implementation of the proposed Australian Openness Agreement
- Whistleblower protection
- Publication of DPI audits
- Reporting of number, nature and outcome from notifiable incidents or adverse incidents

- Pre-registration of all animal experiments to prevent duplication (see www.preclinicaltrials.eu and www.animalstudyregistry.org for examples)
- Clarification of how many scientific license applications are rejected
- Reporting on how many AEC applications are rejected in their entirety
- AEC annual reports to be public
- List of license holders to be public
- Breakdown animal v human health funding and number of animals
- Reporting on animals bred and not used
- Release of Government funding breakdowns for animal and non-animal method
- Outcomes- retrospective assessments
- Plain language summaries of research funded by Government
- Information on what research is being contracted out overseas
- Enable access to Wallacia breeding colony to animal protection NGOs
- Outcomes of complaints to ARRP to be shared with the complainant