Submission No 250

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

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Dear Committee members,

I'm a Veterinary Professor of Animal Welfare and Ethics at the University of Winchester Centre for Animal Welfare in the UK. I'm originally from Australia, completing a PhD in 2010 at Griffith U, which examined the benefits and harms resulting from animal use within research and education, and alternatives available. I've published numerous academic studies in this field, along with my 2011 book *The Costs and Benefits of Animal Experiments*.

Thank you for the opportunity to contribute to this Inquiry. I will address the terms of reference. Please let me know in due course if I can further assist.

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

NSW and Victoria have persistently been the largest Australian user states, of animals for scientific and educational purposes annually (https://www.humaneresearch.org.au/statistics/). Most recently (2018) animal use reported in NSW was 2,253,943 animals. This is in the context of Australia being the 4th largest user of such animals globally both per capita and in terms of overall numbers (Knight 2013). Hence, the number of animals use in NSW are particularly high. The animal welfare and ethical impacts associated with such use are explored below.

It is essential both ethically and legislatively, that scientific and educational animal use undergoes a harm-benefit analysis. This is a key responsibility of ethics committees, and of governmental bodies with oversight responsibilities.

The high level of animal use in NSW requires a high level of social benefits to justify. Unfortunately, these are not apparent when analysing the outputs of invasive animal use within research or education generally. Many such studies have now been published, as summarised in Knight (2019):

> To provide more definitive conclusions [of the social utility of scientific animal use], *systematic reviews* of the human clinical or toxicological utility of large numbers of animal experiments are necessary. A systematic review is "a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the

results of the included studies" (Moher et al., 2009). In recent years, systematic reviews have become widely utilized to investigate a broad range of clinical and other research questions. Their aims are to retrieve as much high-quality evidence as possible, relevant to the research question, and to minimize bias during the selection, analysis, and reporting of results. Any conclusions reached should, accordingly, be as close as possible to biological, physical, chemical, or other truths.

A large number of systematic reviews of animal experiments within various research fields have examined their utility for advancing human healthcare, and the results have not been good. Of 20 published systematic reviews examining human-clinical utility located during a comprehensive literature search, animal models demonstrated significant potential to contribute toward clinical interventions in only two cases, one of which was contentious. Included were experiments approved by ethics committees on the basis of claims that medical advances were likely to result; highly-cited experiments published in leading journals; and chimpanzee experiments, utilizing the species most generally predictive of human outcomes. Seven additional reviews failed to demonstrate utility in reliably predicting human toxicological outcomes, including those associated with the greatest public health concerns, such as carcinogenicity and teratogenicity. Results in animal models were frequently equivocal or inconsistent with human outcomes (Knight, 2011). Since then, numerous additional reviews have yielded similar results. Baker et al. (2014), for example, examined human neurological disease, which has been extensively studied in animal models, resulting in relatively few human treatments (Cheeran et al., 2009; Vesterinen et al., 2010). Similarly, despite reports of the efficacy of more than 1,000 treatments in animal models of multiple sclerosis (MS), very few treatments have progressed to the marketplace (Vesterinen et al., 2010). This usually indicates failures of efficacy or safety concerns in humans. And, despite the widespread use of animal models within stroke research, virtually no interventions described as effective in animal models have proven similarly effective in human patients (Cheeran et al., 2009). There are many other examples.

The limitations of animal models, that result in their poor utility for advancing human healthcare, are described in detail in Knight (2019) and elsewhere.

Additionally, it is not only harms to animals and potential social benefits that should be evaluated. As noted (Knight 2019): "Others potentially affected include patients and consumers. The social and ethical implications are profound, when consumers suffer serious toxic reactions to products assessed as safe in animal studies, or if patients with serious conditions are denied effective clinical interventions, partly because potentially more efficacious research fields are under-resourced (Knight, 2011)." The latter is a major problem. Similar concerns have been raised by numerous other researchers who have examined the social utility of animal research (e.g. Pound et al. 2004).

Key references

- Pound, P., Ebrahim, S., Sandercock, P., Bracken, M. B., & Roberts, I. (2004). Where is the evidence that animal research benefits humans?. *BMJ*, *328*(7438), 514-517.
- Knight, A (2013). The australasian regulation of scientific animal use: a chimera of protection. In Sankoff, P., White, S., & Black, C. (Eds.). *Animal law in Australasia: Continuing the dialogue*.
- Knight, A. (2019). Critically evaluating animal research. In *Animal Experimentation: Working towards a paradigm change* (pp. 321-340). Brill.

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

Animal research is a particularly expensive research field (particularly due to costs associated with animal sourcing, care and housing). Providing scientifically adequate animal numbers (to enable statistical validity) – particularly in the case of species such as primates which are costly – can become prohibitively expensive. Hence the vast majority of animal studies are undersized, with insufficient subject numbers limiting their statistical predictivity. Because such studies frequently cannot reliably predict outcomes in larger populations (even of the same species), the overwhelming majority of animal research funds spent on these studies, is inefficiently used (or indeed, wasted). This also partly explains, why many animal study results cannot be reliably duplicated (the 'reproducibility crisis').

Unfortunately, research funds are very finite, and we should ensure these are spent on the research strategies and tools most likely to deliver key public benefits – such as human healthcare advancements. Funds, facilities and skilled personnel consumed by animal research, become unavailable to other research fields. The superior cost effectiveness of human clinical research, in achieving human health benefits, has been noted by Pound et al (2004) and others.

Key reference

- Pound, P., Ebrahim, S., Sandercock, P., Bracken, M. B., & Roberts, I. (2004). Where is the evidence that animal research benefits humans?. *BMJ*, *328*(7438), 514-517.

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

A wide range of alternative research and teaching methodologies exist, described elsewhere (Knight 2011, Knight 2012). A range of measures are strongly warranted to increase the implementation of the 3R principles, the methodological quality of animal research, and the reliability of results and to overcome some of the barriers that currently prevent reliable extrapolation to human outcomes (Knight 2013):

> Compliance with each of the 3Rs and the arrive guidelines and other best practice standards, during the design, conduct, and reporting of experiments, must become mandatory. Such standards should cover animal sourcing, housing, environmental enrichment, socialization opportunities, appropriate use of anesthetics and analgesics, handling, non-invasive endpoints, and a range of measures designed to minimize sources of bias and to ensure methodological quality. Compliance with such standards should be a necessary condition for securing research funding and ethical approval; licensing of researchers, facilities, and experimental protocols; and publication of subsequent results. Compliance would also facilitate subsequent systematic reviews.
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> Where journal space constraints limit the description of methodological details, these should be included in supplementary online databases, which are now widely available (Kilkenny et al., 2009). This would also facilitate the transfer of alternative technologies, such as the development of new alternative methods, between institutions (Gruber and Hartung, 2004).
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> To enable animal researchers and technicians to meet the necessary standards, training and continuing professional development in 3R methodologies and the design, conduct, and reporting of animal research should be compulsory. The existing lack of focus on replacement methods (in favor of refinement methods) must be addressed.
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> The adoption of measures, such as these, would increase the reliability of research results and would facilitate their use within systematic reviews. 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, greater efforts must also be made by researchers and editors to publish negative results. Studies that fail to show a treatment effect are often considered less interesting and are, consequently, less likely to be published. The subsequent exclusion of such results from systematic reviews leads to overestimations 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 (Hooijmans et al., 2014).

Many of these measures will require cooperation and coordination between researchers, regulators, licensing bodies, ethical review committees, funding bodies, journals, and authors. And of course, the necessary willingness, among all parties, to change. If these measures were to be successfully implemented throughout the broad field of animal research, then we may be able to predict treatment effects accurately within the animal species under study.

However, interspecies differences will remain in absorption, distribution, metabolism, and elimination pathways or rates, resulting in differing toxico- or pharmaco-kinetics and dynamics and, subsequently, differences in the organ systems affected and in the nature and magnitude of these effects. Such factors, which reflect the intrinsic complexity of living organisms, will continue to pose barriers to extrapolation to humans that will remain insurmountable, in many cases.

Key references

- Knight, A. (2011). *The costs and benefits of animal experiments* (p. 245). Basingstoke, UK: Palgrave Macmillan.
- Knight, A. (2012). The potential of humane teaching methods within veterinary and other biomedical education. *Altex Proc*, *1*, 365-375.
- Knight, A (2013). The australasian regulation of scientific animal use: a chimera of protection. In Sankoff, P., White, S., & Black, C. (Eds.). *Animal law in Australasia: Continuing the dialogue*.

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

From Knight (2019):

A wide variety of stressors have the potential to cause significant stress, fear, and possibly distress in laboratory animals. These stressors may be associated with the capture of wild-sourced species, such as primates, to supply laboratories or breeding centers; with transportation, which may be prolonged for some animals; with laboratory housing and environments; and with both routine and invasive laboratory procedures (see Knight, 2011). An *invasive* procedure is an intervention that interferes with bodily integrity through puncture, incision, or insertion of an instrument or foreign material, as in surgical and some experimental procedures (Knight, 2011).

A large minority of all procedures are markedly invasive. These include procedures resulting in death (whether or not the animals are conscious); surgical procedures (excluding very minor operative procedures); major physiological challenges; and the production of genetically-modified animals. Few regions report procedural invasiveness, but Canada does. From 1996–2008 inclusively, the proportion of markedly invasive procedures reported in Canada ranged between approximately 29%–44% (Canadian Council on Animal Care, 2009). These procedures were defined by the Canadian Council on Animal Care (2009) as resulting in moderate to severe stress or discomfort (Category D); or in severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals (Category E) compared to procedures resulting in little or no discomfort or stress (Category B) or minor stress or pain of short duration (Category C).

A sizeable majority of all procedures utilize no anesthetics of any kind. Few regions report anesthetic usage, but Britain does. During two recent decades (1998–2009), the proportion of procedures conducted in the UK without anesthesia fluctuated between approximately 59%–69% (Home Office, 2010). For example, in 2009, at the end of this period, 66.7% of cases did not utilize any form of anesthesia. General anesthesia was provided throughout or at the end of terminal procedures in 9.5% of cases. In 17.1% of cases, general anesthesia with recovery was provided, and in 6.7% of cases, local anesthesia (Home Office, 2010).

To assess animal impacts further, it is helpful to know the frequency of analgesic (pain-killer) use, and the level of correlation between markedly invasive procedures and anesthetic or analgesic use (See Herrmann and Flecknell (2018) for a review of original animal research proposals). Painful or invasive procedures warrant anesthesia and/or analgesia. Animal welfare is adversely affected when animals undergoing such procedures are denied these; or conversely, when they are provided without sufficient need (due to their potential side effects), although this is rare in practice. It would also be helpful to study the prevalence of environmental enrichment and socialization opportunities. Unfortunately, such information remains largely unreported.

Key references

- Knight, A. (2019). Critically evaluating animal research. In *Animal Experimentation: Working towards a paradigm change* (pp. 321-340). Brill.

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

From Knight (2019):

The core ethical principle underpinning modern animal experimentation regulation and policy is that the likely benefits of such research must outweigh its expected costs. This utilitarian harm-benefit analysis underpins all fundamental regulation governing animal experimentation. …

When considering harms and benefits overall, one cannot reasonably conclude that the benefits accrued for human patients or consumers, or those motivated by scientific curiosity or profit, exceed the harms incurred by animals subjected to scientific procedures. On the contrary, evidence indicates that actual human benefit is rarely, if ever, sufficient to justify such harms. And those harms are not limited to the many millions of animals used. Others potentially affected include patients and consumers. The social and ethical implications are profound, when consumers suffer serious toxic reactions to product assessed as safe in animal studies, or if patients with serious conditions are denied effective clinical interventions, partly because potentially more efficacious research fields are under-resourced (Knight, 2011).

> A paradigm change in scientific animal use is clearly warranted. Instead of uncritically assuming the benefits of animal research, we must subject it to much more rigorous and critical evaluation. Where animal research continues to persist, a broad range of measures must be implemented to improve substantially its methodological quality and compliance with the 3Rs and to maximize the reliability of subsequent results (Knight, 2011).
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> When such research fails to meet the harm-benefit standards expected by society, which underpin legislative instruments … then such research should cease; and the resources consumed by it directed into more promising and justifiable fields of research and healthcare.

Key references

- Knight, A. (2019). Critically evaluating animal research. In *Animal Experimentation: Working towards a paradigm change* (pp. 321-340). Brill.

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

No comment.

(g) any other related matters.

No comment.