**Submission No 351**

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

**Organisation:** Medical Advances Without Animals Trust (MAWA)

**Date Received:** 25 May 2022

MEDICAL ADVANCES WITHOUT ANIMALS

# REPLACING ANIMALS IN MEDICAL RESEARCH

NSW Legislative Council Portfolio Committee No 2 - Health
Inquiry into the use of primates and other animals in medical research in NSW
Submission from The Medical Advances Without Animals Trust (MAWA)

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MEDICAL ADVANCES WITHOUT ANIMALS

# THE MAWA TRUST
## REPLACING ANIMALS IN MEDICAL RESEARCH

**NSW Legislative Council Portfolio Committee No 2 – Health**
**Inquiry into the use of primates and other animals in medical research in New South Wales**
**Submission from The Medical Advances Without Animals Trust (MAWA)**

Via email: PortfolioCommittee2@parliament.nsw.gov.au

Thank you for your invitation to provide a submission to the *Inquiry into the use of primates and other animals in medical research in New South Wales* conducted by the NSW Legislative Council Portfolio Committee No 2 - Health. MAWA's comments and recommendations are set out below.

**PREAMBLE**

The following information provides the context for MAWA's comments on the terms of reference.

About MAWA

The Medical Advances Without Animals Trust (MAWA) is a registered charity established in 2000 by Ms Elizabeth Ahlston and A/Prof Garry Scroop, with Prof Stephen Leeder AO, then Dean of Medicine, the University of Sydney, and later Editor-in-Chief of the Medical Journal of Australia, as its first Chair. Since Prof Leeder retired from MAWA's Board in 2013, The Hon Kevin Rozzoli AM has served as MAWA's Chair.

MAWA's aim is to advance medical science to improve human health and therapeutic interventions without using animals or animal products in fundamental biomedical research.

MAWA takes a leading role in replacing animals in medical research in Australia. MAWA's approach is positive. Rather than focusing on practices that it does not support, MAWA concentrates on finding and implementing solutions by engaging with scientists and academics. MAWA works cooperatively and productively with the research community to achieve progress. By maintaining this position and building relationships with researchers and institutions, MAWA has been successful in promoting its ideals, developing collaborations and partnerships, and identifying funding opportunities.

MAWA's Expertise

MAWA is managed by a Board which includes eminent scientists in medicine and other members with valuable expertise in the broad range of areas crucial to MAWA's operations. MAWA has also established a Scientific Advisory Panel which is called on for advice and review of research projects submitted for MAWA funding. Membership of MAWA's Advisory Panel comprises senior scientists, researchers, academics and medical consultants with expertise across a range of disciplines, many with international profiles and considered to be leaders in their field. A number of experts in law, ethics, philosophy and other relevant disciplines are also represented on, or are available to, the panel.

## How MAWA Operates

MAWA operates as an independent medical and scientific trust fund to encourage and facilitate the development and utilisation of non-animal-based experimental methods to replace the use of animals in medical research. MAWA Board members are aware that an increasing number of medical scientists are attempting to replace animals wherever possible and that new graduates, in particular, are increasingly concerned with the ethical dilemmas they must face when using animals or animal products in their research projects. It is expected that by funding non-animal research and the training of scientists in alternative methods, the entrenched reliance on the use of animals will be reduced. MAWA also encourages, through promotion and education, the wider adoption of such methods and techniques.

## MAWA's Focus

Of the "3Rs" (Replacement, Reduction and Refinement) MAWA's focus is on Replacement and "absolute replacement", meaning research that avoids the use of all members of, and products derived from, the kingdom Animalia, which includes lower order animals such as nematodes, flies, animals in early developmental vertebral stages, as well as animal products such as animal tissue, animal cell lines, animal derived antibodies, stains, bio-inks. reagents etc, rather than "relative replacement", which may utilize some of the lower order species, embryonic, foetal and larval forms, or animal products.

Recognising that until recently, Replacement in basic research was viewed as the most neglected of the 3Rs (as opposed to toxicology where many alternatives have been validated), and that toxicological testing accounts for only a small proportion of the animals used in research in Australia, MAWA has concentrated its support on replacing animals in basic research where substantially greater numbers of animals are used.

## MAWA's Research Portfolio

MAWA's research focus is on basic research (although MAWA prefers the term fundamental) to improve the understanding of human illnesses and disabilities, their causes, progression, and the underlying features to facilitate prevention, early diagnosis and effective treatment of a wide variety of afflictions. The Trust has supported research into a vast range of diseases, disorders and disabilities. Examples are: cancer; cardiovascular diseases; diabetes; stroke; dementia; obesity; multiple sclerosis; neurological disorders; eye diseases, psychiatric disorders; malaria; acute and chronic pain studies; kidney diseases; gastrointestinal diseases; wound healing; epilepsy; and respiratory diseases including, more recently, COVID-19.

## MAWA Research Streams

MAWA does not limit its support to any particular research stream, but encourages research proposals from a broad range of disciplines within, for example: biological sciences; medical sciences; computer sciences; mathematical sciences; and bioengineering. MAWA also fosters transdisciplinary and collaborative approaches both within and across institutions and encourages the emergence of areas of research strength.

## MAWA Funding

Funding support is provided through direct funding by MAWA and by channelling third party funding for the award of: research grants; development grants; equipment grants; fellowships; a range of scholarships; and travel bursaries. The Trust also provides funding assistance for: distinguished scholar tours; the development of training programs in alternatives; sponsorship of significant symposiums, seminars and conferences; open access for pertinent scientific journal articles; and for individuals to travel for training and to attend relevant Australian and international conferences.

MAWA has supported a broad range of research projects in universities and research institutions throughout Australia including all the leading universities (Group of Eight Australia), and some of the most prestigious research institutions including the Walter and Eliza Hall Institute (WEHI), Australia's oldest medical research institution (see Appendix A).

The Trust has granted over 130 awards to 76 Australian universities and research institutions during its period of operation including funding for additional initiatives with the potential to promote animal replacement such as human tissue banks (see Appendix B).

ANU-MAWA Partnership

MAWA works in partnership with the Australian National University (ANU) and with the intention to establish The Australian Centre for Alternatives to Animal Research (ACAAR) to be hosted by the ANU when sufficient funding becomes available.

The ANU based research program began by establishing a research group within the John Curtin School of Medical Research (JCSMR), Australia's national medical research institution, and later by supporting researchers and scholars in ANU's Medical School, the Research Schools of Biology, Chemistry, Physics and Engineering, and ANU's Mathematical Sciences Institute.

ACAAR, when established, will provide a focal point for alternatives research, act as a knowledge and technical resource, and develop and implement strategies to facilitate a broad adoption of replacement methods.

As a first step MAWA awarded funds to ANU for the appointment of an Associate Professor in Alternatives to provide scientific leadership in replacement research, and subsequently MAWA introduced its Fellowship Programme. To date MAWA has awarded funds for fifteen MAWA Fellows. Five of the Fellowship awards have been made to ANU researchers, with the remaining ten awards going to institutions in other states including the University of Sydney, the University of Western Sydney, and the Victor Chang Cardiac Research Institute in NSW.

The work at ANU both complements and contributes to a broad range of research projects which MAWA supports in other Australian universities and research institutions.

ANU Replacing Animals in Medical Research Fund (RAMR)

MAWA has also provided funding to the Australian National University for the establishment of the ANU Replacing Animals in Medical Research Fund (RAMR) as a precursor to ACAAR. RAMR awarded a variety of grants, scholarships, fellowships and conference bursaries in 2019, 2020 and 2021.

## PRELIMINARY COMMENTS

1. It is clear to MAWA that there is valuable expertise across a range of alternative approaches to animal research methods and technologies throughout Australia, but that a coordinated national approach is required for widespread implementation. In the absence of such an approach, MAWA welcomes this inquiry and hopes that NSW will lead the way in Australia to support the development and uptake of alternatives, since past Commonwealth government initiatives have resulted in very disappointing outcomes.

2. In 1983, societal concerns regarding animal protection prompted the establishment of a federal Senate Select Committee into Animal Welfare. In 1989 an Australian Senate report recommended *"That the Commonwealth Government establish a separate fund for research into the use of alternatives to the use of animal experimentation",* but this was never implemented (1).

3. The current National Health and Medical Research Council (NHMRC) (2013) Australian Code for the Care and Use of Animals for Scientific Purposes includes a requirement that "*Methods that replace the use of animals or partially replace the use of animals must be investigated, considered and, where applicable, implemented"* (2). However, it is generally recognised that there have been no government incentives for the development of replacement alternatives in biomedical research in Australia, and that partnerships between government, academia, industry and other stakeholders to stimulate growth in this area have not been established as they have in the UK, US, EU, and several other countries in Europe and Asia.

4. In its Information paper: *The implementation of the 3Rs in Australia*, published in 2019, the NHMRC stated that "*Despite the importance of the 3Rs there is limited documented evidence about the use of the 3Rs in Australia*". To address this gap the NHMRC's Animal Welfare Committee initiated a project to obtain information about "*how the 3Rs are being implemented in Australia and factors that enable or hinder their development and adoption*". While the paper did provide valuable information, the

project's scope "*did not include funding of projects for the development of the 3Rs, identification of prospective research areas for the 3Rs, and the benefits or otherwise of specific 3R methods or techniques*". Rather it was limited to the conduct of a literature review and a survey of those involved with the use of animals for scientific purposes in Australia (the 3Rs Survey (3).

5. In 2019, Australia passed legislation to ban animal testing for cosmetics ingredients. However, in Australia there has only been very limited animal testing for cosmetics, and not for some time, so this ban is considered tokenistic by many. At the time, Senator Bridget McKenzie promised to support the development and adoption of animal replacement methods. She acknowledged the progressive international trend for the uptake of alternatives and committed 2.1 million AUD to implement the ban on cosmetic testing. It would be useful to know what happened to those funds and whether there is any left to spend.

6. Minister McKenzie also announced 11 government commitments at this time. MAWA was particularly interested in commitments 8, 9 and 11, that is: (*8) to facilitate rapid uptake of new non-animal approaches; (9) to include representatives and stakeholders in a governance arrangement to guide the implementation of the ban; (11) to explore the ability to use a portion of the funding to support the development and uptake of new approach methods to replace animal use in regulatory testing, and explore further funding in future budget contexts*. These are, of course, questions for the federal government, but may also be of interest and benefit to this Committee (4).

7. In 2021, MAWA was invited by the Commonwealth Department of Health to join a stakeholder group to assist with a *Review to identify Alternative Methods to Animal Testing*. The Department's introduction stated that the Australian Government remains committed to exploring alternatives to animal test data for chemical safety testing and that the review will aim to:
   - *analyse domestic and international evidence around non-animal testing methods to identify alternate viable approaches;*
   - *identify opportunities for collaboration domestically and internationally, and the potential for Australia to leverage activities and research occurring both nationally and overseas; and*
   - *investigate data accessibility and develop advice on practical steps to support innovation and information sharing.*

   MAWA was disappointed that the review would not encompass medical testing, but committee members may find the consultants' report of interest when it is available later this year.

<u>Evidence at Hearing</u>

Engaging in the debate about the advantages and disadvantages of animal research is outside MAWA's remit, however MAWA believes that the Portfolio Committee would greatly benefit from evidence provided by Professor Alastair Sloan and Professor Wojciech Chrzanowski. Both professors are MAWA grant recipients and act as MAWA Science Advisors.

MAWA is delighted to have recently welcomed Professor Sloan to MAWA's Scientific Advisory Panel. He is Professor of Tissue Engineering and Dental Biology, and Head of Melbourne Dental School, Faculty of Medicine, University of Melbourne. Professor Sloan moved to Australia from the UK two years ago and has extensive experience and expertise in alternatives. Professor Sloan has spent many years developing non-animal model systems for biomedical research/tissue repair research and has been funded by the UK National Centre for the 3Rs (NC3Rs) and the Dr Hadwen Trust (now renamed as Animal Free Research UK). Professor Sloan also sat as a grant panel member for the NC3Rs for 6 years. The NC3Rs not only supports research and skills development in alternatives, but also funds and works with academic institutions and industry. It has a key role in providing commentary, guidance and advice to government and other bodies and has strong relationships with industry.

MAWA has been working with Professor Chrzanowski since 2018. He is Professor of Nanomedicine, Faculty of Medicine and Health, and Sydney Pharmacy School, University of Sydney. MAWA's Trustees and Board recognise Professor Chrzanowski's leadership in the use of organ-on-chip technology in Australia. In late 2018, MAWA formed a research partnership with the charitable arm of Australian Ethical, a major fund management company that specializes in environmentally and socially responsible investments. From a

range of research proposals submitted by MAWA to the Australian Ethical Foundation (AEF), Professor Chrzanowski's organ-on-chip project was the first chosen by AEF for co-funding with MAWA.

Both professors would be pleased to provide evidence at a hearing, and/or ongoing advice to the NSW government to assist with the implementation of alternatives.

## COMMENTS ON THE TERMS OF REFERENCE FOR THIS INQUIRY

Some of the terms of reference (TOR) are beyond MAWA's remit so only brief comments will be made in regard to those. However, MAWA is aware that other organisations and relevant experts will be providing comprehensive responses to these TORs.

MAWA's submission will be focused on Replacement in basic research and will mainly concentrate on:

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

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

**TOR (g)** *any other related matters* - MAWA would like to focus on the barriers to the implementation of the 3Rs, with emphasis on Replacement in fundamental biomedical research.

### TOR (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

1. MAWA acknowledges that animal research has resulted in significant medical advances for human health and that our society has benefitted as a result. However, it is clear that not all animal research translates well to humans, and that adverse outcomes can sometimes occur putting human health and lives at risk. MAWA is not aware of any Australian government reviews at federal or state level regarding the effectiveness of medical research being conducted on animals in NSW. Scientific reviews could be conducted on the efficacy of animal-based methods used in NSW and a cost-benefit analysis system could be implemented as is used in the UK.

2. While MAWA's approach is based on replacing animal-based methods with human-relevant alternatives, when reflecting on the nature and purpose of medical research, comments made by overseas colleagues may be worth considering. For example, Dr Katy Taylor from the UK points out that conducting medical research without animals will not always rely on replacement, that it is not simply a case of looking for a direct replacement for an animal model:

   "*In the area of basic research in particular where the majority of animals are actually used, there is much more of an element of choice in conducting an animal experiment. In a world with infinite questions about human biology, there are equally important questions that can be tackled that do not require resorting to animal experiments. Some scientists choose to use animals, but they could choose to study humans, or cells, or computer models and still contribute to the pool of medical knowledge. If we change the goal to one of improving the humanity and quality of medical knowledge, rather than replacing like for like, then, in my opinion, a significant proportion of animal research could end today*." (5)

### TOR (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

MAWA is not in a position to comment on this term of reference other than to say that it is generally accepted in the medical research community that alternative non-animal methods are less expensive, that results can often be obtained more rapidly and in many cases can more reliably be translated to the clinic. It is also recognised that in some cases, the discovery of treatments and cures for humans have been held back because they have either not worked well in the animal model, or have worked well in the animal model but not in humans, or have caused harm to humans due to species differences. It is important that these costs also be considered.

## TOR (c) The availability, effectiveness and funding for alternative approaches to animal research methods and technologies, and the ability of researchers to meet the 3Rs of Replacement, Reduction and Refinement

1. NSW Department of Primary Industries' and NSW Animal Research Review Panel's initiative in establishing the Animal Ethics Infolink is commendable (6). However, despite the availability of these valuable resources as well as those from the National Health and Medical Research Council (NHMRC), the Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART) and other bodies, it is apparent that there is still insufficient knowledge of animal replacement alternatives in fundamental biomedical research in Australia.

2. It is also quite apparent through MAWA's extensive contact with researchers and scholars within the medical research community that compliance with the NHMRC Code of Practice on the Care and Use of Animals for Scientific Purposes, and adherence to the Guidelines, falls short of what should be expected regarding the replacement of animals in medical research.

3. MAWA is aware of, and has participated in, some excellent training programs throughout Australia and especially in NSW. Nonetheless, it appears that there are many universities and research institutions that are not providing sufficient training or resources in alternatives for their researchers and scholars which is disappointing.

4. MAWA is constantly being approached by organisations, animal ethics committee (AEC) members, and individual researchers and scholars for guidance and resources regarding alternatives. In response MAWA provides examples of animal replacement research and information on: international 3Rs centres; journals; websites; search engines; databases; step-by-step guides on how to search for alternatives; and international organisations promoting alternatives and funding animal replacement research.

5. However, MAWA does not have the resources to provide these materials in the best possible format. Given many countries provide such resources through government funded bodies, it would bring Australia into line with current advances if the states and territories could also assist and encourage researchers by providing similar support and guidance.

6. Furthermore, many AEC members have advised MAWA that very little evidence, if any, is provided by researchers seeking ethics approval to demonstrate that animal replacement alternatives have been investigated. Experts in the field recommend that researchers should list the biomedical bibliographic databases searched, and search strategies and terms used, to ensure their searches for alternatives have been thorough, and that research is not duplicative. It is also recommended that a literature review of previous animal experiments be requested to help assess whether the proposed animal experiments are needed. Such a pre-experimental exercise would enhance experimental design, produce higher quality results and ultimately save funds and time.

7. MAWA recognises that it is difficult for both researchers and AEC members to fully investigate alternatives given the speed with which replacement methods and technologies are emerging, and the fact that possible alternatives will often be developed outside of the researchers' discipline. However, the provision of a well-designed step-by-step guide on how to search for alternatives and accompanying worksheets could make it much easier for researchers to adhere to both the NHMRC Code and the Guidelines, and for AECs to properly assess and ensure compliance (7).

8. AEC members also advise that timing can be important as once a proposal is presented to an AEC, it often has funding approval and that issues regarding animal ethics are among the last to be considered. In other countries there is ethical screening before funding decisions are made which avoids the problem of researchers, faculties and institutions having so much invested by the time the AEC is required to assess whether alternatives have truly been investigated. AEC members have said that they feel immense institutional pressure at times to approve projects despite their reservations.

9. Another concern continually expressed by researchers and scholars is that project reviewers favour animal-based research for the allocation of funding, and furthermore that they consider that the use of animals will increase their chances of publishing their research. This may not be the case in fact, but it is most certainly the perception of many in the medical research community, and it is indeed concerning to MAWA that many students are advised that their chances of attracting funding, and publishing their research, are increased if they work with an animal model. To really give animal replacement methods equal opportunity, this situation needs to be addressed.

10. Both the University of Wollongong (UoW), and the University of NSW (UNSW), are to be commended for their efforts towards supporting the 3Rs. UoW was the first Australian university to provide funding specifically for 3Rs research, and MAWA has entered into an agreement with UoW to co-fund research projects that meet MAWA's criteria for animal replacement research. More recently, with the encouragement of the Director of Animal Services, Dr Malcolm France, UNSW has provided a significant budget for 3Rs funding, and the University is currently developing initiatives to further the 3Rs. MAWA has made a similar offer to UNSW for co-sponsorship of animal replacement projects.

11. Researchers and scholars from NSW have attracted approximately 25% of MAWA's national funding through various initiatives since the MAWA's inception. MAWA's awards to institutions in NSW alone include:

    University of Sydney
    University of New South Wales
    University of Technology Sydney
    Macquarie University
    Western Sydney University
    Australian Catholic University
    University of Wollongong
    University of Newcastle
    University of New England
    Charles Sturt University
    Victor Chang Cardiac Research Institute
    Lowy Cancer Research Centre
    Prince of Wales Medical Research Institute
    Kolling Institute
    Bosch Institute
    Nano Institute
    ANZAC Research Institute
    Charles Perkins Centre
    Neuroscience Research Australia
    MS Research Australia
    MS Brain Bank
    St Vincent's Hospital
    Royal Prince Alfred Hospital
    Concord Hospital
    Illawarra Health and Medical Research Institute

(See Appendix C for coverage of animal replacement research conducted in NSW with MAWA funding.)

12. Researchers and scholars funded by MAWA have developed and/or utilised a range of alternative approaches to replace animal use or animal products in their research including: organ-on-chips; organoids; human cell and tissue cultures; stem cell research; plant tissue cultures; biobanking; bioprinting; genomics; proteomics; virtual reality and physical model-based simulators; imaging; computer simulations; mathematical models and analytical technology; ethical clinical research with volunteer patients and healthy subjects; microdosing; bioinformatics; population studies (epidemiology); and post-mortem studies. It is accepted that it is difficult to replace a whole living system, but researchers also use multiple alternative methods in combination taking advantage of the strengths of each to achieve experimental objectives and to decrease animal use.

13. MAWA's Board and Scientific Advisory Panel have been delighted with the outstanding results achieved by MAWA scholars, and impressed by outcomes achieved by researchers from early career scientists, through to world leading senior researchers, who have been funded by MAWA's Grants and Fellowships Programme.

14. MAWA also recommends the establishment of more human tissue banks, and that support and resources are made available to overcome some of the obstacles currently causing concern regarding sourcing and using human tissue for research purposes. MAWA has provided funding support to the MS Brain Bank in Sydney and the Sydney Heart Bank.

15. The Sydney Heart Bank (SHB) was initiated and established by MAWA Board member Professor Cris dos Remedios over thirty years ago. It is one of the largest human heart banks in existence and is known to be a key experimental resource for those studying the biochemistry, genetics, physiology and anatomy of hearts. Many years ago, Professor dos Remedios developed alternative methods to reduce and replace the use of animals in his research as a protein chemist/biophysicist. The SHB operates as an open-source heart bank with no fees, international researchers simply apply to obtain tissue, and tissue samples have been used by more than 90 research teams around the world.

16. MAWA has also committed, but not yet awarded, funding to the newly established St Vincent's Hospital Tissue Bank in Sydney which was initiated and then progressed by Professor Anne Keogh while she served as a MAWA Trustee and Board member. Professor Keogh expressed frustration that it took many years to establish this tissue bank despite all her efforts, those of many others from St Vincent's Hospital and more recently with the assistance of Professor dos Remedios. Professor Keogh and Professor dos Remedios believe that the use of human tissue in research can substantially reduce the use of animal models. In 2017 MAWA awarded a research grant to a team of Australian researchers for their work in developing experimental alternatives to animal models using human heart tissue from the SHB.

17. Internationally, the development of animal replacement alternatives in fundamental research has really accelerated over the past decade and MAWA would particularly like to draw the committee's attention to the organ-on-chip and organoid work which MAWA is currently supporting, for example at the University of Sydney, as well as other state universities and research institutions. These technologies are some of the most powerful non-animal methods and represent a rapidly expanding (although not yet coordinated) field in Australia.

18. It would be hugely beneficial if Australia would follow the example of other countries which offer incentives by providing a proportion of available and proposed funding to encourage alternative approaches, and by setting targets to increase animal replacement research and decrease animal use.

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

MAWA does not support the use of animals in medical research, but the ethical and animal welfare issues are outside MAWA's remit.

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

MAWA is supportive of all measures to strengthen regulatory regimes and to increase transparency and accountability, but this does not fall within MAWA's remit.

However, MAWA commends NSW for having specific legislation to govern animal research and for publishing annual reports which include animal use statistics on numbers, purpose and procedures as well as general examples of strategies and methods used to implement the 3Rs (8). MAWA also acknowledges the important role that the Animal Research Review Panel (ARRP) plays (10). MAWA has appreciated participating in ARRP seminars and the opportunity for MAWA funded researchers to showcase their animal replacement research.

Nevertheless, it is clear to MAWA that current national and state regulatory regimes are inadequate despite a number of reviews of the NHMRC Code 2013. MAWA, along with many other stakeholders and interested parties, has spent considerable time providing submissions over many years but changes are needed, especially regarding the replacement of animals which is MAWA's area of involvement and expertise.

## TOR (f) Overseas developments regarding the regulation and use of animals in medical research

In the UK, US, Canada, the EU and other European and Asian countries, partnerships between government, academia, industry and a range of other stakeholders have been established to phase out animal testing and to develop alternative methods and technologies. Many countries have established centres for alternative methods and similar initiatives recognising both the scientific and economic value of more human-relevant, animal-free approaches and their investment potential. However, Australia lags behind with no government commitment or significant plan to phase out animal testing, or to develop alternatives to the use of animals in medical research.

There are Centres for Alternatives in the EU, UK, US, Canada, Netherlands, Norway, Denmark, Switzerland, Germany, Italy, Poland, Brazil, Romania, Japan and Korea (Appendix D) plus various programmes and initiatives for the implementation and commercialisation of non-animal methods.

Netherlands

The Netherlands has an established centre, the National Knowledge Centre on Alternatives to Animal Experiments (NKCA), but what is most notable is that the Dutch government (with the involvement of several different Ministries) has also initiated the Transition Programme for Innovation Without the Use of Animals (TPI) and the Netherlands is recognised as the international frontrunner with its plan to phase out animal testing by 2025. The government has partnered with various stakeholders including scientists, industry, regulators, transition experts, patients, animal protection organisations and the general public to encourage alternatives and innovations, and to accelerate the transition through open dialogue and collaborations.

TPI's mission is *"to develop alternative models and tests that better predict the effectiveness and safety of medicines and substances, thus making animal procedures increasingly redundant."* At the outset, the TPI partners "*deliberately chose to shift the focus from reducing animal procedures to building up alternatives. This allowed animal-free innovation in a broad sense to be discussed, as well as enabling cooperation between stakeholders with different interests and focus areas from very different research domains, target sectors, technologies and policy dossiers"* (10).

The TPI partners have formed a powerful and diverse network and are working effectively on innovative projects and initiatives leading to an exchange and pooling of knowledge. During their 2020 review of the programme the TPI partners decided to shift from an open search to a focused search by "*going in-depth with regard to current alternative and innovative practices*" and by "*embedding existing animal-free possibilities in policies and guidelines*" (10).

United Kingdom

The UK Government provides funding for the National Centre for the 3Rs (NC3Rs) which supports the discovery and adoption of predictive, reproducible and cost-effective alternatives to the use of animals. The NC3Rs collaborates with scientists and organisations from across the life sciences sector, nationally and internationally, including universities, industry, other research funders and regulatory authorities.

The NC3Rs has established an innovation platform Crackit, "*a challenge-led competition that funds collaborations between industry, academics and small and medium-sized businesses to solve business and scientific challenges which will deliver 3Rs benefits, either by improving business processes or developing a commercial product"* (11).

The UK conducted a series of consultations and workshops involving the NC3Rs plus academia, public bodies, government and industry to develop a strategy and vision for non-animal technologies and to draw up a non-animal technologies roadmap for advancing predictive biology to guide the efforts of all those working in this area.

Another important development in the UK is the formation of a new partnership between the NC3Rs (with funding from the Gates Foundation) and the World Health Organization (WHO) *to "review the animal testing requirements described in WHO guidance documents for biologics to identify opportunities for the integration of the 3Rs. The aim is to enable vaccines manufacturers and regulators to apply the latest non-animal testing approaches and strategies to support faster access to cheaper vaccines by the global communities who need them most urgently"* (12).

Another new collaboration between the NC3Rs and the Biotechnology and Biological Sciences Research Council (BBSRC), part of UK Research and Innovation, will focus on supporting the development and use of next generation non-animal technologies in bioscience research as alternatives to *in vivo* models. The overall aim is to support proposals that:

***"1. Develop the next generation of non-animal technologies that mimic the physiological environment enabling a whole system/multi-system approach for discovery and translational science:***

*Proposals should build upon existing knowledge to develop non-animal technologies that offer advanced solutions for modelling human and animal biology and predicting interactions to external challenge. This next generation of non-animal technology should incorporate a systems approach, that enables the study of intra-organ interactions, microenvironmental factors, or whole systems approaches. This could include addressing biological questions by integrating complex in vitro experiments with computational modelling."*

***"2. Enhance the capacity and confidence in non-animal technologies:***

*Proposals should support a step-change in current non-animal technologies in aspects such as physiological relevance and predictivity, throughput, and breadth of application to facilitate new research discoveries and translational approaches. Applications that include comparative analyses of different models/technologies and/or validation and feasibility or reproducibility studies are in scope."*

***"3. Establish partnerships between academia, the small and medium-sized business sector, and industry:***

*Proposals with an industrial partner are strongly encouraged to foster collaborations, improve understanding of cross-sector requirements, and bridge the gap between development, proof-of- concept and scale-up and help drive the development and commercialisation of non-animal technologies. It is envisaged that there will be substantial in-kind and/or financial contribution from a business partner"* (13).

An additional UK initiative of note is the formation of the Alliance for Human Relevant Science, an inclusive collaboration of companies, non-profit organisations and charities. The Alliance is working "*to accelerate innovation in human relevant research methods, known as new approach methodologies (NAMs) to create positive change. NAMs do not use animals and so avoid the problem of animal-human species differences that can result in misleading data"* (14). The alliance calls for supportive infrastructure, strategic funding, education, collaboration between industries and regulatory engagement.

United States

In response to recommendations from the National Academies of Science, Engineering and Medicine in 2018, the US developed a strategic roadmap for establishing new animal-free approaches to evaluate the safety of chemicals and medical products. "*This roadmap is a resource to guide U.S. federal agencies and stakeholders seeking to adopt new approaches to safety and risk assessment that improve human relevance and replace or reduce the use of animals. This document was developed with input from members of sixteen federal agencies, multiple interagency workgroups, and input from the public"* (15).

In 2019 the Environmental Protection Agency (EPA) stated it would reduce the use of animals in toxicity testing, with a goal of eliminating all routine safety tests on mammals by 2035. Chemicals such as pesticides

typically get tested for safety on animals like mice and rats. Researchers have long been trying to instead increase the use of alternative safety tests that rely on lab-grown cells or computer modelling. The EPA's then Chief directed the agency "*to reduce all requests for, and funding of, studies with live mammals by 30 percent by 2025 and to essentially eliminate all mammal study requests and funding by 2035, with the use of live mammals only allowed after that with special permission"* (16). Since the announcement, the EPA has held annual conferences on the development of new methods and has awarded substantial funding to universities for development and innovation.

In late 2020, the US Food and Drugs Administration (FDA) launched the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program to support the development and use of novel drug development tools. This pilot created a pathway for developers to submit proposals for novel technologies and scientific approaches for regulatory review, and ultimately for accelerating new therapeutics to patients (17).

The US FDA Modernisation Act was introduced in 2021 to end animal testing mandates. This legislation was designed to end an FDA mandate that experimental drugs must be tested on animals before they are used on humans in clinical trials. The bill does not ban animal testing outright, but does allow the option for drug sponsors to use alternative methods where they are suitable. This will accelerate innovation and can get safe effective drugs to market more quickly by cutting red tape that is no longer required (18).

<u>European Union</u>

In 2005, the European Partnership for Alternative Approaches to Animal Testing (EPAA) was established with aims "*to replace animal testing by innovative, non-animal testing methods, to reduce the number of animals used and to refine procedures where no alternatives exist or are not sufficient to ensure the safety of substances"* (19). EPAA is a voluntary collaboration between the European Commission, European trade associations, and companies from seven industry sectors. The partners are committed to pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches at national, European and global levels.

In 2010, the European Parliament and the Council of the European Union adopted a Directive for the protection of animals used for scientific purposes to come into effect in 2013. *"The Directive represented an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so"* (20). This Directive was amended in 2019, to incorporate ambitious goals for reporting and transparency to help progress towards the ultimate goal of total replacement of animal use.

In 2020, a review of advanced non-animal models in biomedical research was undertaken by the European Union Reference Library (EURL), of the European Centre for the Validation of Alternative Methods (ECVAM), to identify and describe available and emerging alternatives in basic, translational and applied research. EURL ECVAM carried out a series of studies in a selected number of disease areas based on "*disease incidence and prevalence, the reliance of related research on animal models, and the amount of animal procedures conducted"* (21).

*"The aim was to identify and describe specific research contexts where animal models have been put aside in favour of novel non-animal techniques that use, for example, in vitro methods based on human cells and engineered tissues or in silico approaches employing computer modelling and simulation. By understanding and sharing information on successful alternative models in biomedical research, EURL ECVAM expects that the transition towards non-animal approaches will be facilitated and potentially accelerated. Moreover, since complex human-relevant non-animal methods offer the promise of recapitulating human physiology more effectively than many animal models, shifting to new animal-free methodologies and research strategies can in fact enhance the understanding of human-specific biology and disease"* (21).

In 2021, EURL ECVAM pursued its work in the biosciences, analysing current approaches to health-related research, publishing new reviews of advanced non-animal models in different fields of disease research, assessing ways of building bridges within biomedical domains and evaluating the output and impact of biomedical EU-funded research.

In September 2021, the European Parliament adopted a resolution calling on the European Commission to establish an EU-wide Action Plan for the active phase out of the use of animals in experiments by defining milestones and targets to incentivise progress in the replacement of animals with non-animal human-relevant methods (22).

## TOR (g) Any other related matters

Barriers to the implementation of animal replacement alternatives:

From working with Australian researchers and listening to their views over many years MAWA has identified a number of impediments and perceived barriers regarding the development and uptake of animal replacement methods and technologies for fundamental biomedical research in Australia:

1. Lack of political will, government leadership and action
2. Inadequate policies, lack of targets and a roadmap to guide efforts to implement alternatives
3. Lack of funding, research support and other incentives
4. No commitment for a centre for alternatives to the use of animals
5. Weak legislation, regulation, guidelines and standards regarding the use of animals in medical research
6. Insufficient monitoring of compliance to current regulations and standards, and lack of enforcement measures
7. Entrenched vested interests
8. Insufficient education and training for researchers and Animal Ethics Committee (AEC) members, and therefore insufficient knowledge of alternative animal replacement methods
9. Australian government failure to bring policy makers, researchers, industry and regulators together for effective collaborations for the implementation of alternatives
10. Lack of coordinating cross disciplinary mechanisms for research groups using alternatives
11. Limited collaboration for the validation of alternative methods and technologies for medical research
12. No coordinated effort to facilitate the commercialization of alternative methods
13. Insufficient data and information sharing
14. Concerns about the comparability of data
15. Complicated bureaucratic processes for regulatory acceptance of alternative test methods after the scientific processes of development and validation.
16. Shortage of human tissue and difficulties in gaining access to existing sources
17. The position of many scientists that they could not achieve their research objectives without using a whole animal system, and that there is still a lack of scientific and technological innovation for the replacement of animals in fundamental research. MAWA recognises that this is the case in many areas of biomedical research.
18. Career concerns - some researchers and scholars believe it is safer to stay with traditional practices and use animals for successful career progression
19. Some researchers and scholars believe that there is bias on grant review panels for animal models and that there are publication biases in favour of animal research
20. Lack of transparency and insufficient reporting of experiments

## SUMMARY AND RECOMMENDATIONS

For alternatives to be implemented, cultural change and government leadership is essential, but to date the federal government has not shown interest in, or a commitment to, encouraging or incentivising animal-free methods. This is despite the fact that societal concern about animal experiments has increased in recent years and that many other countries are making significant efforts. The lack of a plan or any government funding for the replacement of animals in medical research in Australia is disappointing.

NSW has made genuine efforts to support the 3Rs and there have been successes in refinement and reduction, as well as some progress in replacing animals in teaching, however these initiatives have been insufficient to make significant progress towards the replacement of animals in fundamental biomedical research.

## Recommendations

That the NSW Government will:

1. Provide leadership and action, including an allocation of sufficient funding, research support and other incentives, to shift away from animal research as the dominant paradigm. Unlike other countries, Australia does not have a federally funded specific grant category for developing and commercializing non-animal methods.
2. Develop a strategy and vision for decreasing animal usage and for implementing alternatives, as well as a roadmap with established targets and a guide for action.
3. Facilitate systematic reviews and the implementation of a cost-benefit analysis system for research involving animals, such as is used in the UK.
4. Increase monitoring of compliance to current codes and standards and institute stronger enforcement measures.
5. Develop policy for alternatives, new legislation and stronger regulation.
6. Fund education and training in alternatives for students, researchers and AEC members to increase awareness, knowledge and expertise in animal-free methods and technologies.
7. Facilitate partnerships between government, academia, industry, regulators and other stakeholders to stimulate innovation and growth and in this area, and to accelerate the transition through open dialogue and collaborations between multiple sectors.
8. Recognise the economic value of developing alternatives in the medical technology and pharmaceutical sector given Australia's world class universities and research institutions, and achievements in medical research.
9. Create opportunities to showcase new alternative models and highlight work that can drive innovation and facilitate commercialization.
10. Facilitate information exchange among stakeholders and the pooling of knowledge and data from different models and test methods to help innovation.
11. Facilitate connections between policy makers, researchers, industry and regulators for effective collaborations for the validation of new methods and technologies.
12. Encourage coordination of cross disciplinary mechanisms for research groups using alternatives.
13. Review complicated bureaucratic processes for regulatory acceptance of alternative test methods after the scientific processes of development and validation.
14. Support the establishment of an Australian alternatives centre with a focus on replacement. Professor Michael Balls*, eminent biomedical scientist and a champion of animal replacement science for over 40 years, has stated that Replacement has been the neglected R of the 3Rs in biomedical research and this has been acknowledged internationally. While recent developments in animal replacement science have accelerated and shown great promise, it is recognised that there is still a long way to go in this field. Alternative centres and platforms serve as important points of contact and play an essential role not only to develop novel methods, but also for the widespread dissemination of knowledge, and for promoting and facilitating the implementation of alternatives.
15. Recognise that upscaling what MAWA provides in Australia, that is research, development and equipment grants, research fellowships, a range of scholarships, travel bursaries and sponsorships plus prizes for excellence in emerging fields, is urgently needed (see appendix E for examples of MAWA's national funding 2019-2021). MAWA's Board and Scientific Advisory Panel members are disappointed that promising animal replacement research proposals from first class investigators and institutions cannot be supported due to lack of funding in Australia.

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*Professor Michael Balls CBE was Chair of the Trustees for the Fund for the Replacement of Animals in Medical Experiments (FRAME) in the UK for 30 years, and served as Editor-in-Chief of the scientific journal, Alternatives to Laboratory Animals (ATLA) for 36 years. He was also an adviser to the UK government during the passage of the *Animals (Scientific Procedures) Act 1986* and a founding member of the Animal Procedures Committee. In 1993, he became the first head of the European Centre for the Validation of Alternative Methods (ECVAM). He is respected internationally as a very important figure in alternatives who has made an outstanding contribution to the field and has won a number of awards related to his work. Prof Balls recently stated that *"Ending the over-reliance of so much of biomedical research and testing on animal procedures will not only be of benefit to animals in laboratories, the development and use of human-focused replacement alternative methods will help us to understand more about human diseases and how to avoid or treat them more effectively"* (23).

16. Provide additional funding to support the development, adoption and commercialization of alternative methods, along with the Federal government where possible.
17. Encourage NSW universities and research institutions to follow the example of the University of Wollongong, and the University of NSW, which have committed funding specifically for the 3Rs.
18. Provide information on international organisations funding animal replacement research which accept applications from Australia.
19. Require researchers seeking ethics approval to demonstrate that animal replacement alternatives have been fully investigated.
20. Provide resources and information on alternatives journals, websites, 3Rs Centres, search engines, databases, and step-by-step guides on how to search for alternatives with accompanying work sheets to make it easier for researchers to adhere to both the NHMRC Code and the Guidelines, and for AECs to properly assess and ensure compliance. It is difficult for both researchers and AEC members to fully investigate alternatives given the speed with which replacement methods and technologies are emerging, and the fact that possible alternatives will often be developed outside of the researchers' discipline.
21. Support the pre-registration of all animal experiments and establishment of a national database of all research on animals that fails to achieve expected results, and/or lead to publication, and a requirement that researchers must consult this database before submitting a protocol to reduce animal usage and duplicative research, and free up funds for other research.
22. Require researchers to list the biomedical bibliographic databases searched, and search strategies and terms used, to ensure their searches for alternatives have been thorough, and that research is not duplicative. A literature review of previous animal experiments should be provided to assist AEC members to assess whether the proposed animal experiments are truly needed. Such a pre-experimental exercise would enhance experimental design, produce higher quality results and ultimately save funds and time.
23. Require ethics screening be conducted before funding decisions are made to avoid the problem of researchers, faculties and institutions having so much invested by the time proposals reach Animal Ethics Committees. AEC members have reported that they feel immense institutional pressure at times to approve projects despite their reservations.
24. Require action to ensure that animal replacement methods are given equal opportunity. Currently there is a common perception that reviewers favour animal-based research in regard to the allocation of funding, and that the use of animals will increase the chances of publishing research. Training in alternatives and resources should be provided for grant and journal reviewers.
25. Encourage the establishment of more human tissue banks and resources to overcome some of the obstacles regarding sourcing and using human tissue for research purposes.
26. With other Australian governments, work with world leaders in alternatives to contribute to, and promote, international acceptance of high-tech non-animal replacement methods based on human biology for biomedical research.

MAWA has established relationships with the research community developing and utilising alternative methods and technologies. MAWA funding is much sort after so MAWA can testify to the interest of researchers, and that there are many scientists in Australia who would like to make non-animal model development a key focus of their research portfolio and to be a part of a community of like-minded researchers.

A common goal within the scientific community is *"to develop predictive non-animal models and to better integrate all available data from in vitro, in silico and omics technologies into regulatory decision-making processes regarding, for example, the toxicity of chemicals, drugs or food ingredients. In addition, it is a general concern to implement (human) non-animal methods in basic research"* (24).

It is clear to MAWA that there is valuable expertise across a range of alternative approaches to animal research methods and technologies throughout Australia, but that a coordinated national approach is required for widespread implementation.

It is hoped, therefore, that more effort and resources could be dedicated to stimulating interest in animal-free alternative methods, facilitating the development and utilisation of replacement techniques, and providing training for researchers, scholars, AEC members and animal management officers.

In addition to providing the necessary resources and infrastructure that will be required to implement animal replacement alternatives, government support would also go a long way to address the issue of public accountability. Interest in animal welfare issues and animal protection has increased and societal concerns about animal experimentation could be somewhat assuaged if the public was assured that the government was offering support for initiatives designed to replace animal-based research.

MAWA calls for supportive infrastructure, strategic funding, education, collaboration between industries and regulatory engagement in line with our overseas colleagues. It would be hugely beneficial if the NSW government could take the lead in this endeavour as it has with other animal protection issues.

Thank you for the opportunity to make a submission to this most worthwhile inquiry.

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