

Alternatives to the Use of Animals for Scientific Purposes

In 1959 Russell and Burch introduced the concepts of replacement, reduction and refinement as a starting point for the humane treatment of laboratory animals. The 3R's are:

- **Replacement**
To replace the use of animals by lower organisms, or non-biological methods.
- **Refinement**
To refine scientific procedures so that any suffering, discomfort or pain endured by the animals is minimal, consistent with the scientific objective.
- **Reduction**
To reduce the number of animals used to the minimum consistent with statistical and scientific validity.

The need to consider these principles is encapsulated in the Australian Code of practice for the care and use of animals: [NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes](#).

Planning Projects

The consideration of possible use of alternatives starts at the planning stage and FRAME has produced an excellent chart on strategies to consider the 3R's when planning projects, which may involve the use of animals. This Poster can be downloaded from: <http://www.frame.org.uk/images/EarlyPlanningPosterCompressed.pdf>

FRAME is the Fund for the Replacement of Animals in Medical Experiments. It is an influential body in animal based research in the UK, has been involved in a major way in the concept of 5 World Congresses on Alternatives and Animal Use in the Life Sciences and as its name suggests it is a charitable body that funds research into methods that may replace animals in medical experimentation. It acted as an adviser to the UK Government during the preparation and passage through Parliament of the Animals (Scientific Procedures) Act 1986.

A really good recently installed (2008) search engine regarding alternatives can be found at <http://www.go3r.org/>.

Alternatives in Education and Training

In recent years there has been considerable evolution of alternatives in education and training and the realization that animal use is not essential to many components of the teaching of science, of veterinary medicine and of medicine. The emerging range of alternatives is impressive and examples of this range are detailed below.

InterNICHE

InterNICHE (www.interniche.org) is an international network for humane education. It aims for a high quality, fully humane education in biological science, veterinary and human medicine. It supports progressive science teaching and the replacement of animal experiments by working with teachers to introduce alternatives, and with students to support freedom of conscience. The types of alternatives offered by InterNICHE include:

- Models and simulators
- Film and video
- Multimedia computer simulation

The InterNICHE Alternatives Loan System

The InterNICHE Alternatives Loan System is an evolving library of multimedia CD-ROMs, videos, models and mannequins. It covers fields such as anatomy, physiology and surgery. Teachers and students from anywhere in the world can borrow items from the Loan System to trial them. This gives user the opportunity to familiarise themselves with some of the best products available.

All items in the Loan System have been chosen with reference to meeting teaching objectives for practical classes to shift the emphasis away from the invasive animal lab towards alternative approaches.

The NORINA Database

The Norwegian Reference Centre for Laboratory Animal Science and Alternatives (Laboratory Animal Unit, Norwegian School of Veterinary Science) has maintained a website featuring the NORINA database (www.norinadatabase.org). NORINA is an English language database and contains information on nearly 4,000

audiovisual aids and other material that can be used as alternatives or supplements to animal use in teaching and training. The website also includes TextBase, a database with information on 1100 textbooks of relevance to the three R's. The site includes information on guidelines for animal research, the care and use of fish, and links to databases with the 3 R's.

Film and Video

Film and video can give good background and provide a quality visual alternative. Videos of professionally-performed dissections, for example, can often impart much more information to students than dissections performed by the students themselves, and can be used to train those students who need such skills in their careers before they do real dissections on ethically-sourced cadavers.

Models and simulators

These range from inexpensive models and surgical training devices, right up to computerised mannequins. Basic models can contribute to the study of anatomy or facilitate the learning of good animal handling without animal stress and student anxiety. The diversity of surgical training devices available include models of skin, internal organs and limbs which can provide opportunities for students to master basic skills such as eye-hand co-ordination, the use of instruments, and techniques such as suturing. Waste organ training devices allow for the use of real tissue in the process. More complex products include mannequins used to train IV skills, intubation and catheterisation of animals, and critical care from resuscitation to thoracentesis. Computerised mannequins add another level of complexity and support to the effective training of students.

Multimedia computer simulation

The opportunities associated with the development of computer software in contributing to effective life science education have grown exponentially within the last few years. From virtual dissections that students can perform on-screen, to full virtual reality simulations of clinical technique with 3-D and tactile facilities, the possibilities are limited only by technical and imaginative boundaries. Computer-assisted learning can also offer much greater depth and breadth to the learning experience. For example, morphology between species can be compared at the click of the computer mouse, or histology and other fields introduced to the practical lesson. An image can be easily magnified or reduced, circulatory or nervous systems dissolved away or highlighted in 3-D, muscles activated, and even qualities such as the opacity of organs controlled in order to more fully appreciate structure and structural relationship. The increased sensory experience and level of control in new software supports effective, quality learning. Some programmes include virtual laboratories with options for working through different experiments, and others can be customised by teachers to adapt them to the location and to specific teaching objectives. Students can also work at their own pace, repeat parts of the exercise and use the support material until they are confident with knowledge and technique, and be as self-directed as the structure of the course allows. The innovative nature of new technological developments can be exciting, which adds to the learning experience for students and is an important part of their informal training for professions where IT and computer skills will continue to play a major role. Wherever possible, however, computer simulation should be used in tandem with experience of living people or non-human animals so that technology is kept as a powerful tool, not an alternative to reality.

Alternatives to the Use of Animals for Toxicity Testing

Increasingly validated alternatives to sentient animals are being used in the field of toxicity testing. Validation is defined as the process whereby the reliability and relevance of a procedure are established for a particular purpose (Fentem and Balls 1997). With reference to the Australian veterinary situation the Australian Pesticides and Veterinary Medicines Authority websites states that experiments involving animals should be conducted with the minimum number of animals necessary to allow valid conclusions to be drawn. Applicants are encouraged to submit data obtained in *in-vitro* assay systems, or from alternative methods which use fewer animals, as a means of facilitating validation of alternate methodologies and reducing the number of animals used in toxicity testing (APVMA 2005)

Before commencement of toxicology studies, and with regard to possible alternatives to animals reference to relevant data bases should be made. Roi (2005) discussed the ECVAM Data Base service on Alternative Methods (DB-ALM). DB-ALM provides its information as evaluated data sheets and is based on extensive literature reviews including ECVAM in-house information. The current on-line version can refer to 3000 registered users from 65 countries. There are a number of web sites that may be similarly referred to. In 1997 the John Hopkins Center for Alternatives to Animal Testing (CAAT) launched Altweb, the Alternatives to Animal Testing Web Site (<http://altweb.jhsp.edu>). Altweb was created to serve as a central reference point or gateway to alternatives information, resources and news. It is international in scope and freely available to all users (Howard 2005).

Langley (2000) felt that replacement alternatives in toxicology had evolved rapidly in the previous decade and that the process of method development, pre-validation, and validation had reached the level of international consensus.

Alternatives to the Use of Animals for Biomedical Research Purposes

Animal Ethics Committees and investigators are required by the Code to consider the principle of replacement of animals where possible. Applicants have responsibility to inform AEC's about the suitability of alternatives. Replacement alternatives in toxicology have evolved rapidly in recent times. The processes of method development, pre-validation and validation have reached a level of international consensus. When it comes to replacement methods, biomedical research presents different challenges and opportunities and investigations are more open ended. The techniques used to explore such questions are not controlled by regulatory bodies, but instead are influenced mainly by peer review (Langley 2000).

The Netherlands Centre for Alternatives to Animal Use identifies two groups of replacement alternatives: relative and absolute replacement models. Relative replacement alternatives still require an animal for the donation of organs tissues or cells. Absolute replacement models have no vertebrate animal involvement.

There are several non-animal methods currently used in biomedical research (Combes 2004):

- a) prior information (databases)
- b) computer modelling
- c) biokinetic modelling
- d) the use of new molecular biology technologies (genomics, proteomics, metabonomics)
- e) in vitro models (cells, tissues, organs)
- f) human studies

As an example of computer modelling offering opportunities to replace animals, Buchanan (1999) reports on a heart model representing heart cells with more than 30 types of ion pumps and membrane channels joined with connective tissue and supplied with blood vessels. Oxygen consumption, carbon dioxide production, changes in acidity and the ATP cycle are included and feedback between electrical and mechanical activities of the heart is also simulated. The model is enabling studies of the underlying causes of heart problems.

As an example of biokinetic modelling Helma (2005) described a lazar prediction system and its application for the prediction of carcinogenicity. He found in cross-validation experiments lazar is capable of predicting rodent carcinogenicity for the Carcinogenic Potency Database (1376 compounds) with more than 70% accuracy.

Human cells can be used in tissue culture, providing both scientific and welfare benefits, compared with tests using the whole animal surrogate species (Combes 2004). Species extrapolation is obviated, human cells being better models for the human condition than animal cells.

It is also possible to replace technologies used in animals by in-vitro alternatives. As an example of replacement of a technology that can provide pain and distress in animals, the ascites fluid method of monoclonal antibody production is no longer acceptable, and must be replaced by in-vitro methods, except in rare cases where in vitro methods are shown to be unsuitable.

Alternatives in toxicology research for humans

The assessment of the efficacy and safety of products for use in humans requires the provision of suitable data that is compliant with international standards. Australian regulatory approval of products for use in humans is controlled by the Therapeutic Goods Administration (<http://www.tga.gov.au/index.htm>). The technical data requirements for the registration of medicines evaluated by the Drug Safety Evaluation Branch of the TGA have been aligned with those required for applications for marketing authorisation by the European Union. A list of EU guidelines adopted in Australia is available from the TGA website (<http://www.tga.gov.au/docs/html/euguideh.htm>).

The European Medicines Agency (EMA, <http://www.emea.eu.int/>) is a decentralised body of the European Union responsible for the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The Committee for Medicinal Products for Human Use (CHMP) has prepared a document reviewing the use of alternative, genetically modified animal models for carcinogenicity testing (<http://www.emea.eu.int/pdfs/human/swp/259202en.pdf>). The European Centre for the Validation of Alternative Methods (ECVAM, <http://ecvam.jrc.it/index.htm>) is responsible for coordinating the validation of

alternative test methods in the EU. Its web site can be searched for validated alternative tests and information on alternatives for scientific and regulatory purposes.

A comparable organisation in the USA is the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) (<http://iccvam.niehs.nih.gov/>). The National Institute of Environmental Health Sciences (NIEHS) established the ICCVAM to develop and validate new test methods, and to establish criteria and processes for the validation and regulatory acceptance of toxicological testing methods. The National Toxicology Program (NTP, <http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=7182FF48-BDB7-CEBA-F8980E5DD01A1E2D>) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) was established to provide operational support for ICCVAM. The ICCVAM web site can be searched for alternative test methods and information.

Other Websites and Links

A very good reference site re alternatives and the three R's is that of FRAME (Fund for the Replacement of Animals in Experiments): frame@frame.org.uk

FRAME is responsible for the publication of the journal ATLA: atla@frame.org.uk

Based in Australia and providing excellent information re the 3R's is the Australian and New Zealand Council for the Care of Animals in Research and Teaching web-site: anzccart@adelaide.edu.au You should make use of the Helpful Links facility.

Animal Ethics Infolink: Developed by the NSW Animal Research Review Panel provides ready access to web-based publications: www.animaletics.org.au

The John Hopkins Center for Alternatives to Animal Testing (CAAT): www.altweb.jhsph.edu provides a central reference point to alternatives information, resources and news.

Another good reference site is the NC3R's national Centre for Replacement, Refinement and Reduction in Research: www.nc3rs.org.uk/

The Netherlands Centre for Alternatives to Animal Use: www.nca-nl.org The Dutch have set a good example to the rest of the World re their pro-activity re the 3R's.

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