



## Session 3.5

# Ethical review – good practice and outputs

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## The Role and Evolution of Independent Government Advisory Committees: The New Zealand Experience from 1985 to 2005

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### Summary

*In the New Zealand national animal welfare infrastructure, the National Animal Ethics Advisory Committee (NAEAC), the National Animal Welfare Advisory Committee (NAWAC) and the Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART) all play important and discrete roles in ensuring that the New Zealand government receives independent, broadly-based advice regarding the use of animals in science, in agriculture and for other purposes. This paper covers the genesis, legal status and management disciplines associated with the New Zealand NAEAC/NAWAC system, including the role of the scientific community, Government and NGOs.*

*Keywords: government advisory committees, animal welfare, animal ethics, New Zealand*

### Introduction

Over the last two decades, animal welfare has received increasing attention in New Zealand as a complex, multi-faceted public policy issue with important scientific, ethical, economic, cultural and social dimensions. Over this same period, New Zealand has developed a cohesive national animal welfare infrastructure, animal welfare science and ethics capability and has introduced contemporary animal welfare legislation (Bayvel, 2000; Mellor, 1999; Ministry of Agriculture and Forestry, 1999; Ministry of Agriculture and Forestry, 2000; Mellor and Bayvel, 2004). The latter takes note of both the concepts of the Three Rs of Russell and Burch (1959) and the five freedoms originally developed by the UK Farm Animal Welfare Council (Farm Animal Welfare Council, 1993).

Two independent ministerial advisory committees play a vital role in the national infrastructure, with their functions, responsibilities and membership prescribed by the Animal Welfare Act 1999. The National Animal Ethics Advisory Committee (NAEAC) deals with the use of live animals in research, testing

and teaching, while the National Animal Welfare Advisory Committee (NAWAC) covers all other uses of animals, including in agriculture and in entertainment.

In the development of animal welfare policy and the setting of regulatory standards, the consultative requirements of the Animal Welfare Act provide extensive opportunity for input from both the public at large and affected and interested stakeholders. This input is complemented by high level independent advice to Government from two committees, whose membership reflects the broad spectrum of opinion which exists within any society on animal use in science, agriculture and for other purposes.

### Discussion

#### History and background

Reid (1989) provided a very valuable account of the historical developments leading up to the establishment in New Zealand of Animal Ethics Committees (AECs) and the National Animal



Ethics Advisory Committee (NAEAC). In the 1970s and 1980s, the New Zealand scientific community had recognised the need for legislation covering the use of live animals in research, testing and teaching and, through the Royal Society of New Zealand, had worked closely with Government in formulating appropriate policy and legislation. AECs were, to an extent, modelled on existing human ethics committees and also took note of the experience gained in countries such as Sweden and Canada. In spite of some opposition, it was decided that NAEAC should be located within, and serviced by, the Ministry of Agriculture as a core Government department.

NAEAC was established in 1984 and the complementary National Animal Welfare Advisory Committee (NAWAC) held its first meeting in 1989. A third significant development, in the early 1990s, was the establishment of the Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART). Unlike the two ministerial advisory committees, ANZCCART has no statutory status and is constituted as a committee of the Royal Society of New Zealand. It does, however, play an important role in encouraging informed debate on the ethical use of animals in science, promoting humane science and sponsoring valuable conferences in conjunction with ANZCCART Australia.

### Roles and Responsibilities

Part 4 of the New Zealand Animal Welfare Act 1999 is devoted to advisory committees and covers in detail the purpose, functions, membership, terms of office and annual reporting requirements for both NAEAC and NAWAC.

The functions of NAEAC are:

- (a) To advise the Minister on ethical issues and animal welfare issues arising from research, testing, and teaching
- (b) To make recommendations to the Minister under section 3(3) (which relates to manipulation)
- (c) To make recommendations to the Director-General under section 85 (which relates to restrictions on use of non-human hominids)
- (d) To provide advice and information on the development and review of codes of ethical conduct
- (e) To make recommendations to the Director-General concerning the approval, amendment, suspension, or revocation of any code of ethical conduct
- (f) To make recommendations to the Minister concerning the setting of standards and policies for codes of ethical conduct
- (g) To provide information and advice to Animal Ethics Committees
- (h) To recommend, for approval by the Director-General under section 109, such persons as are, in the opinion of the committee, suitable for appointment as accredited reviewers
- (i) To consider the reports of independent reviews of code holders and Animal Ethics Committees:
- (j) To make recommendations to the Minister under section 118(3) (which relates to the power of the Minister to approve research or testing).

The membership of NAEAC reflects the need for the committee to possess knowledge and experience in the following areas:

- (i) Veterinary science
- (ii) Medical science
- (iii) Biological science
- (iv) The commercial use of animals in research and testing
- (v) Ethical standards and conduct in respect of animals
- (vi) Education issues, including the use of animals in schools
- (vii) The manipulation of animals in research, testing, and teaching
- (viii) Environmental and conservation management
- (ix) Animal welfare advocacy
- (x) Any other area the Minister considers relevant; and

The membership recognises the need for a balance between those members who are currently involved in research, testing, and teaching and those members who are not so involved.

- (a) To advise the Minister on any matter relating to the welfare of animals in New Zealand, including (without limitation)
    - (i) Areas where research into the welfare of animals is required; and
    - (ii) Legislative proposals concerning the welfare of animals
  - (b) To make recommendations to the Minister
    - (i) Under section 3(3) (which relates to manipulation); and
    - (ii) Under sections 6 and 16 (which relate to surgical procedures)
  - (c) To discharge its functions under section 32 in relation to the making of Orders in Council declaring traps or devices to be prohibited or restricted traps or devices
  - (d) To discharge its functions under section 32 in relation to the conditions that should be attached to the sale or use of any restricted trap or restricted device
  - (e) To make recommendations to the Minister concerning the issue, amendment, suspension, revocation, and review of codes of welfare
  - (f) To promote, and to assist other persons to promote, the development of guidelines in relation to
    - (i) The use of traps or devices or both;
    - (ii) The hunting or killing of animals in a wild state
- The membership of NAWAC reflects the need for the committee to possess knowledge and experience in the following areas:

- (i) Veterinary science
- (ii) Agricultural science
- (iii) Animal science
- (iv) The commercial use of animals
- (v) The care, breeding, and management of companion animals
- (vi) Ethical standards and conduct in respect of animals
- (vii) Animal welfare advocacy
- (viii) The public interest in respect of animals
- (ix) Environmental and conservation management
- (x) Any other area the Minister considers relevant

Schedules to the Act cover a range of administrative matters and also describe in detail the provisions applying to accreditation of independent reviewers of AECs and associated code holders. In all cases, members are appointed to committees in a personal capacity recognising their individual experience and expertise and do not play a representational or advocacy role on behalf of nominating organisations.



## Policies and procedures

Initially, appointments to both committees were not time-bounded. Fixed terms of three years were, however, introduced during the 1990s for both committee members and chairs. In most cases, two terms is the maximum period served by committee members and chairs but, in exceptional cases, this can and has been extended. This policy ensures a balance of committee experience and knowledge with the introduction of “new blood” but requires careful planning in relation to succession management and committee member and chair induction and hand-over. In the case of NAEAC, the independent committee chair has historically had no involvement with the use of animals in science, while in the case of NAWAC a detailed familiarity with animal agriculture and animal welfare science has been seen as an important attribute.

Formal strategic planning was introduced for both committees in the early 1990s. The strategic plan is reviewed in detail every three years and updated annually. The agreed strategic plan gives direction to the annual operational plan which, in turn, defines specific responsibilities for individual committee members and associated resource requirements.

Annual performance reviews are conducted for each committee. These involve completion of a standard questionnaire regarding committee performance and have proved to be a useful and valued tool in identifying issues and improving committee effectiveness. Policy manuals have also been prepared for both committees to record committee policies and decisions, to assist with the induction of new members and chairs and ensure consistency of decision making.

## Communications

In addition to such committees generating quality advice and recommendations and effectively managing and discharging their statutory responsibilities, it is vital that they also communicate effectively with Government and all interested stakeholders. Communication with Government is assured by annual meetings of chairs with the relevant Minister, occasional attendance by the Minister at committee meetings and the preparation of an annual report which is a legislative requirement. This annual report is a major communication vehicle to all stakeholders and is complemented by annual or bi-annual newsletters from each committee.

Other strategic communication initiatives are included in an annually updated communications plan, which includes specific activities such as workshops, conferences, press conferences and press releases.

## International and domestic relationships

It is in New Zealand’s strategic interest to keep abreast of international trends in the area of animal welfare and ethics and to liaise closely with organisations, institutions and other Government agencies to foster exchange of information and to undertake collaborative initiatives. In the area of animal use in research, testing and teaching, New Zealand has thus developed

important relationships with ANZCCART in Australia, the United Kingdom Home Office, the International Council for Laboratory Animal Science (ICLAS), the Canadian Council for Animal Care (CCAC), Three Rs centres in Europe and North America, the European Commission and the UK Research Defence Society (RDS).

In the case of animal use in agriculture, similar important relationships exist with the UK Farm Animal Welfare Council (FAWC), the UK Department for the Environment, Food and Rural Affairs (DEFRA), the European Commission, university research groups and non-governmental organisations in Europe and North America and the USDA Animal Welfare Information Center.

Formal Government to Government interaction also takes place between New Zealand and Australia via the Trans-Tasman Animal Welfare Working Group (TTAWWG), and between New Zealand, Australia, Canada and the USA via the Quadrilateral Animal Welfare Working Group (QAWWG). The World Organisation for Animal Health (OIE) involvement in animal welfare is an important recent development on the world stage and New Zealand has participated actively in this strategically important international initiative. Such international communication has been dramatically facilitated by electronic communication and the availability of information on web sites.

On the domestic front, both NAEAC and NAWAC have established close links with the New Zealand Bioethics Council (Toi te Taiao). The purpose of the Bioethics Council is to:

- Enhance New Zealand’s understanding of the cultural, ethical and spiritual aspects of biotechnology
- Ensure that the use of biotechnology has regard for the values of New Zealanders.

The New Zealand Government established the Bioethics Council in December 2002 following a recommendation by the Royal Commission on Genetic Modification. The Royal Commission wished to address public concern that decision-making was not adequately considering the cultural, ethical and spiritual dimensions of biotechnology. Submissions to the Royal Commission had highlighted the need for high-level advice to Government with community input on overarching cultural, ethical and spiritual concerns that had wider implications for society. The Bioethics Council has been set up as a ministerial advisory council that sets its own work programme and priorities. It reports to the Government through the Minister for the Environment.

To promote dialogue between politicians and key stakeholders involved in the animal welfare and ethics debate, an All Party Animal Welfare Group (APAWG) was established in 1994. This group was modelled on similar groups existing in the UK and European Union and is sponsored by the Royal Society of New Zealand (via ANZCCART), the New Zealand Veterinary Association (NZVA), the Royal New Zealand Society for the Prevention of Cruelty to Animals (RNZSPCA) and Federated Farmers of New Zealand (FFNZ).

## Operational research

Research funding is made available, on a contestable basis, by the New Zealand Ministry of Agriculture and Forestry for



research studies to support policy formulation and standard setting in the area of animal welfare. As indicated in the NAWAC Annual Report (National Animal Welfare Advisory Committee, 2005), over the period 1993 to 2004, 88 studies have been completed with the majority published in peer reviewed journals and the internationally recognised MAF publication "Surveillance". Such research findings have proved extremely valuable to support both committees in their independent advisory roles and to ensure that recommendations are supported, or at least informed, by relevant science.

## Conclusion

Both NAEAC and NAWAC have evolved over the last 20 years in terms of core functions and supporting management and administrative disciplines. The relationship between the two committees is formalised by the NAEAC chair also being a NAWAC member. This ensures that areas of common interest and policy parallels are addressed efficiently and effectively. Ethical debate, which has been a key element of NAEAC discussions, is now also receiving increasing attention in relation to the use of animals in (particularly intensive) agriculture. The minimisation of pain and distress will continue to be a key priority for both committees.

In the case of NAEAC, genetic modification research presents a particular challenge. The Three Rs of Russell and Burch (1959) have played a critical role over the past fifty years but the opportunity to expand the Three Rs, as described by Schuppli (Schuppli et al., 2004), will assist in addressing the challenges of the future. Schuppli proposes that "Some of the concerns that fall outside the Three Rs framework might be captured by adding a fourth "R" for responsibility. Responsibility, as proposed by the International Foundation for Ethical Research, could be elaborated to include responsibility to not violate community standards, responsibility to enhance the quality of life of animals in human care, and responsibility to reflect real costs in analyses of costs and benefits." (Schuppli et al., 2004).

In a recent paper Balls (2004) emphasises the importance of the "middle ground" i.e. "the only way forward to co-operation between people of goodwill and common sense – in the middle ground – is to secure the development and use of reliable and scientifically sound alternatives. This means rejecting the extremism on both sides." Goldberg (2004) also refers to the "troubled middle" as reflecting a societal "understanding of the need for animal-based research but a desire to ensure that pain and distress are eliminated or, at least, minimised" and the "silent middle" i.e. scientists who practise humane science, who would prefer not to use animals but who do not publicly articulate their position or commitment. (Goldberg, 2004).

Goldberg further emphasises that extreme positions reject both societal expectations and scientific need and that "the issues for the general public are transparency, accountability and humaneness". In the New Zealand context, NAEAC, NAWAC and ANZCCART are essential elements of a cohesive national infrastructure and make important and unique contributions to addressing these issues.

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# Processes and Policies for Ethical Evaluation in Nordic Countries and Europe

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## Summary

*In ethical evaluation of animal studies both costs and benefits are broken down to smaller elements in order to attach an ethical value judgment to each, and look for improvements in areas of concern. Ethical evaluation must focus on the refinement and reduction alternatives. Evaluation of the 6th Framework Programme applications is a truly European process: Benefits are assessed first by scientific evaluators, and applications with high scores go to ethical panel. A similar assessment of benefits should be done in local ethics committees, but they may lack the needed expertise. The Nordic Forum suggested a Cost-Benefit-Means approach for evaluation.*

*Keywords: ethical evaluation, policy, cost benefit assessment*

## Background

Special attention has been paid in European regulations and policies to the 3Rs alternatives. The European Commission Directive on the protection of animals used for experimental and other scientific purposes (86/609/EEC) (1986) states that the EU Member States must actively encourage and support the development, validation and acceptance of methods which could Replace, Reduce and Refine the use of laboratory animals (3Rs). The same is true for the Treaty of Amsterdam and the policy paper of the European Science Foundation (ESF). The same approach and policy are presented in the Commission's White Paper to the New Chemicals Directive (REACH) (2001).

The Report on Directive 86/609 (2001) by the Committee on the Environment, Public Health and Consumer Policy (2001/2259(INI)) states more specifically that an ethical and animal-welfare assessment must be carried setting limits to the level of suffering and distress to which the animals may be subjected.

Revised Directive (86/609/EEC) shall require detailed and harmonised ethical evaluation of animal studies, and will be based on cost-benefit analysis. In this analysis the likely benefits of the study are weighed against the cost – i.e. harms like pain, suffering and distress – to the animal. It can be foreseen that both commodities to be weighed have to be broken down to smaller elements in order to weigh or attach an ethical value judgment to each and then these elements can be used in the overall assessment of an animal study.

What is perhaps even more important is improving all relevant areas of concern, but particularly so that both animal welfare and good science are promoted. Whenever replacement alternatives cannot be used, ethical evaluation can and must focus on the two other alternatives, refinement and reduction and these are also fundamental elements of any harm in a cost/harm-benefit analysis. Processes and policies of ethical evaluation vary considerably in Europe, and need in many cases to be modified.

## The EU Framework Programmes

The Ethical Rules for the 6th Framework Programmes (FP) proposals reiterate the application of the 3Rs principles and entail a description of the procedures adopted to ensure that the amount of suffering imposed on the animals is minimised and their welfare is guaranteed as far as possible (e.g. through improvements in experimental technique, application of humane endpoints, environmental enrichment, etc.).

According to the Ethical Rules for the 6th FP proposals, applicants should provide – at the end of the application – a summary of the main adverse effects for the animals, including those due to methods of husbandry and supply of the animals as well as the harmful effects of the scientific procedures themselves.

Evaluation of the 6th Framework Programme applications is an example of truly European process: Benefit assessment is carried out first by scientific evaluators, and applications with high scores go to ethical review panel. The ethical review panel is composed of independent experts of law, sociology, psychology, philosophy and ethics, medicine, molecular biology and veterinary science. It has a parity of scientific and non scientific members. Once the application is discussed in the ethical panel, the panel can ask for more information, require or recommend changes and modifications before negotiations between the consortium and the Commission can commence.

Limited experience from ethical panels indicates that many applicant consortia do not really know what the 3Rs are. Perhaps this is due to the fact that by the end of the application they are tired by other questions to be addressed, regard other ethical issues more important or do not care to find out. It is simply not enough to state that the consortium is committed to the three Rs principles while the question is how to implement them in their own study.

A similar assessment of benefits should be done in all cost-benefit analyses, but the local ethics committees may often lack the



needed expertise for detailed scientific scrutiny. Perhaps local ethics committees should ask for evaluations received with applications for funding from major national or European sources. This approach would leave benefit assessment of only small or new groups to the local ethics committees.

### The Nordic Forum

The Nordic Forum for Ethical Evaluation of Animal Experiments, held in Helsinki 2003, was arranged to see whether a suitable scoring system for a cost-benefit analysis are available, and if any evaluation scheme could be agreed among the Nordic participants (Voipio et al., 2004). The workshop introduced the terms “Cost modifiers” or “means” which can be used to decrease the costs for the animals, or to improve the benefits from the study. The use of scoring systems for ethical assessment did not receive support since they were considered to give a false impression of objectivity. A classification of costs versus benefits into three degrees (low, medium and high) was considered the most suitable approach. Example protocols were evaluated by the workshop participants; the result revealed a large variation in scoring the degree of costs, the importance of the benefits, and the possibilities of modifying the means. Clearly, further and continuing interaction between all of the interest parties is necessary for the creation of more precise tools for ethical assessment of animal studies.

### The two Rs initiative

Until now the replacement alternative has received far more attention and EU funding opportunities than the other Two Rs – reduction and refinement. An initiative – called the Two Rs Initiative – to be included into the 7th Framework Programme (2007-2013) has been submitted by the COST Action B24 “Laboratory Animal Science and Welfare” to the Commission and was endorsed by 50 European institutions and scientific associations.

Since replacement is not always possible, the animals still used should not be neglected. To help the animals and science more research on the Two Rs methods should be encouraged leading to better quality animals and to a reduction of the numbers used. The COST Action believes that even better science evolves from the application of the Two Rs.

The application of the Two Rs will also be instrumental when practising cost-benefit analysis, as will be the quality of use, care and housing of laboratory animals. They should be regarded as the

means to either increase the benefits or decrease the costs in a study. This is particularly true with GM-animals and some new research methods.

The welfare and number of animals used can be regarded as essential elements in assessment of costs/harms, incurred to the animals in the study. This approach can only be successful if tackled by multidisciplinary teams, i.e. by both the study groups themselves and laboratory animal scientists. Involvement of both parties is necessary for attainment of critical mass, a prerequisite to large scale outcome. And the Two Rs means will be creditable only if they have proven ‘efficacy’ to animal welfare and proven ‘safety’ to the study.

European consortia and European funding are needed to coordinate national research activities and studies on the Two Rs, to attain European added value through implementation of the Two Rs methods and to show that the European research community practices good ethics in their daily work. By high quality research, improving animal welfare and avoiding unnecessary duplication of animal studies, a valuable contribution to sustainable economic growth is attained within the EU.

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# Revision of a Scale for Assessing the Severity of Live Animal Manipulations

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## Summary

*In 1997, a severity scale to assess and record the level of welfare compromise to animals used in research, testing and teaching was introduced in New Zealand. Under this scale, the severity of procedures was expressed in terms of different categories of suffering based on numerous examples at the five levels outlined in a paper by Mellor and Reid (1994). This paper reports on a review into the operation and effectiveness of that scale and the extent to which it fulfils the purposes for which it was devised. Key features of the scale are described, including its strengths and limitations, and comparisons with other scales operating internationally are made. Recommendations regarding modification of the scale based on this evaluation are outlined, and key steps in its implementation are described.*

*Keywords: animal welfare, research, testing and teaching, impact scale, severity scale, adverse effects in animal research, animal suffering*

## Introduction

The New Zealand Animal Welfare Act (1999) requires that any person or institution wishing to manipulate live animals for the purposes of research, testing or teaching must operate under an approved Code of Ethical Conduct (CEC). The code requires that an Animal Ethics Committee (AEC) be set up so that all projects can be scrutinised, and only approved projects may proceed. Although the Animal Welfare Act itself is relatively recent, this system has in fact been in operation since 1987 as a result of the process used to implement the Animals Protection (Codes of Ethical Conduct) Regulations 1987.

One of the functions of the AEC is to carry out a cost-benefit analysis of projects, with more “invasive” or “severe” manipulations requiring greater justification for the work in terms of the anticipated benefits that accrue from it. Applicants presenting protocols to AECs must therefore predict the level of animal welfare compromise expected as a result of the proposed manipulations, although that assessment may be corrected once the manipulation has taken place if the actual degree of compromise is found to have varied from that expected.

As detailed by Bayvel (2004), the data from such assessments are collected for each approved study, accumulated on an institutional basis and, after submission to the Ministry of Agriculture and Forestry (MAF), collated as annual national figures. These provide published details of the number of animals of different types exposed in New Zealand to manipulations of different severity levels on the specified scale. Thus, a more detailed picture of annual animal use in New Zealand is provided than would be from a grand total for animal use.

In assessing welfare compromise, New Zealand uses a five-point scale devised by Mellor and Reid (1994), which was intro-

duced in 1997. Concerns have been raised, however, about a probable lack of consistency across institutions in the way the scale has been applied. This could have resulted in both under- and over-assessment of the impact of manipulations. A tendency for the collected statistics to be misrepresented has been dealt with in part by a new requirement in the collection of statistics by MAF, which differentiates animal use according to whether it is for research, testing or teaching. Thus the relatively large numbers of animals that are used in testing required by legislation, some of which have a high degree of welfare compromise, are separated out within the total number of animals used. This confirms, for the concerned public, that experimental research or teaching rarely involves animals at high levels of “suffering”, contrary to the charge that is often levelled at researchers by animal rights protestors.

It has also become apparent that the purposes of the scale are not well understood by some of those using it, with the result that it has, in a few cases, been applied by simply using the minimal definitions (no suffering, little suffering, moderate suffering, severe suffering and very severe suffering) found on the MAF statistics collection form. Others have merely used the examples given in the full explanation provided by MAF (Anon (b), 2001) in a way that prevents the greater flexibility and judgement allowed under the five domains as intended in the original paper (Mellor and Reid, 1994).

Concerns have also been raised about whether the use of animals in biotechnology is adequately covered within the current system, with the suggestion that separate categories might be more appropriate.

Accordingly, as part of a process of continuing improvement followed since the system was first introduced in 1987, MAF commissioned research to review the rationale, terminology and



explanation of the scale and to compare it with others now used overseas, with the aim of ensuring clarity and minimising ambiguity in definitions and descriptions of purposes and differences between categories.

### Purpose of grading the impact of manipulations

A severity scale for animal-based scientific manipulations is of significance to four interested parties: animal-based scientists, animal ethics committees, regulators and the public.

- *Animal-based scientists* need to assess the invasiveness of their manipulations as an integral part of seeking approval to undertake them. Evaluating invasiveness gives an indication of the harm that may be done to the animals. Conducting a harm-benefit analysis is a pivotal part of achieving approval for a proposed manipulation. This ensures that the potential adverse effects on the animals used are greatly outweighed by the benefits accrued from the work. This way of justifying the work is in compliance with the utilitarian ethical basis for using animals in research, testing and teaching.
- *Animal ethics committees* are required by the Animal Welfare Act and their institution's Code of Ethical Conduct to undertake a harm-benefit analysis for each application to manipulate animals in research, teaching and testing. This too relates to the utilitarian ethical mode of assessing the justification for such animal use as proposed in applications to each committee. It also allows members of the AEC to help to ensure that the principle of refinement, or minimisation of harm, is fulfilled.
- *Regulators* require it because it confirms that such assessments are indeed being undertaken in compliance with the Animal Welfare Act, and this can be demonstrated by the public release of annual statistics showing the range of invasiveness of approved manipulations.
- *Interested members of the public* desire knowledge of this kind in order to be reassured that (1) excessively invasive manipulations are not being conducted in a high proportion of the animals, (2) very invasive manipulations are properly justified, and (3) within the full range of severity, the majority of manipulations have been at the bottom end of the range where the impacts are very low (benign) with few negative consequences.

### Key features of the current scale

- *Five levels of severity are defined.* They are O, A, B, C and X, and range from no, or virtually no, impact (Grade O) to the most severe impact that one could imagine would ever be approved (Grade X). They are currently expressed in the Animal Welfare (Records and Statistics) Regulations 1999 in terms of severity of suffering, although this was not the mode of expression employed by Mellor and Reid (1994) in their original description of the scale. They referred to different levels of "ethical cost", not suffering.
- *The predicted severity of welfare impacts is assessed comprehensively.* This is achieved by reference to *five domains of potential welfare compromise*, which relate to the nutritional,

environmental, health maintenance, behavioural and mental needs of animals. The final assessment of the severity of welfare compromise refers mainly to the *mental domain*, because the overall welfare status of an animal is directly reflected in its affective or mental state. Nevertheless, consideration of the other four domains is imperative, as it helps to ensure that the welfare status of the animals to be manipulated has been assessed thoroughly in all of its dimensions.

- The predicted severity of impact determines the required level of justification. The different levels of justification were characterised by Mellor and Reid (1994). The greater the impact, i.e. the more severe the manipulation, the greater is the justification that is required for animal ethics committee approval to be given. Those justifications range from no requirement to demonstrate immediate or even long-term benefits for people or animals for Grade O manipulations, to the most exceptionally strong justifications in terms of benefits to people and/or animals for Grade X manipulations. Grade X should contribute to resolving a pressing need of great significance.

### International comparisons

A paper that considered the possibility of international harmonisation of "pain and distress" classification systems (Purves, 2000) highlighted the considerable international variation in the way such systems are used.

In the present critical review, the New Zealand system was compared with nine other current scales (tab. 1), all of which were included in the Purves paper (2000), except one developed by New South Wales Agriculture in Australia (Anon (c), 2003). The Swedish system, which was legally abandoned in 1989 and only recently reinstated, was omitted.

Seven of the ten systems used classifications based only on the effect on the animal, with descriptors including discomfort, stress, pain, sorrow, harm, fear, suffering, severity degree and constraint. In addition, some of these included consideration of the duration of manipulation.

Of the other three, the Australian scale alone classifies types of procedures rather than effects on the animal, while the other two combine features of both systems: the New South Wales system outlines broad categories of intervention, differentiating between minor and major surgical and physiological challenges, while the US system, having separated out procedures causing little or no pain and distress, simply divides the remainder according to whether or not pain relief is given.

### The Impact Scale

The demands for transparency made by interested members of the public will not be met if, for whatever reason, the categorisation within the scale is not accurate or meaningful, the scale does not give a balanced view of overall animal use or the scale does not support the production of meaningful statistics. The present critical review confirmed the sound basis for categorisation set in the original paper by Mellor and Reid (1994), thus

**Tab. 1: Comparison of available “impact” scales**

Comparison of international impact scales						
Country	Year of adoption	No. categories	No. manipulated* categories	Severity-based Classification	Other Classification	Duration acknowledged
New Zealand <sup>1</sup>	1997	5	5	Yes		Yes
Australia <sup>2</sup>		13	12		Yes (manipulation type)	
Canada <sup>3</sup>	1987	5	4	Yes		
Finland <sup>4</sup>	1986	3	3	Yes		
Germany <sup>5</sup>		4	4	Yes		Yes
Netherlands <sup>6</sup>	1979	3	3	Yes		Yes
NSW <sup>7</sup>	2003	9	9	Mainly	Phys v surgery, GM	
Switzerland <sup>8</sup>	1994	4	4	Yes		
UK <sup>9</sup>	1986	3	3	Yes		Mild band only
USA <sup>10</sup>		3	3		Yes (+/-pain relief)	

\*A manipulation is:

- (a) subjecting an animal to a procedure which is unusual or abnormal when compared with that to which animals of that type would be subjected under normal management or practice and which involves
- (i) Exposing the animal to any parasite, microorganism, drug, chemical, biological product, radiation, electrical stimulation, or environmental condition; or
- (ii) Enforced activity, restraint, nutrition, or surgical intervention; or
- (b) Depriving the animal of usual care (New Zealand Animal Welfare Act, 1999).

<sup>1</sup> New Zealand (Mellor and Reid, 1994)

<sup>2</sup> Australian (Purves, 2000)

<sup>3</sup> CCAC – Categories of Invasiveness in Animal Experiments (Anon [a], 1991)

<sup>4</sup> Finland (Purves, 2000)

<sup>5</sup> Germany (Purves, 2000)

<sup>6</sup> Netherlands (Anon [a], 2004)

<sup>7</sup> NSW Agriculture (Anon [c], 2003)

<sup>8</sup> Swiss Federal Veterinary Office (Anon [d], 2004)

<sup>9</sup> U.K. (Purves, 2000)

<sup>10</sup> USDA – APHIS (Anon [e], 2004)

recognising that the total impact on an animal depends on more than the specific manipulation being carried out, e.g. the competence of those carrying out the manipulation. However, the review also identified areas where greater clarity of purpose and more effective practical implementation could be achieved.

These included:

- Use of more appropriate and balanced descriptors of steps on the scale;
- Ensuring that the scale categories collectively cover the whole range of possible manipulations;
- Ensuring greater accuracy in categorisation by predicting impact on individual animals or groups within an experiment rather than giving one grade to a whole experiment;
- Ensuring greater accuracy of statistics by requiring that grading reported to MAF reflect actual rather than predicted impact;
- Ensuring that category descriptors and examples are seen as guidelines rather than as prescriptive requirements, thus emphasising the importance of judgement when assessing individual cases;
- Determining whether the scale will adequately cover new developments such as those used in biotechnology;
- Ensuring that all factors with the potential to impact on ani-

mals are taken into consideration, for example the provision of enrichment, special nursing techniques, and the use of analgesia.

Given the role of the classification system in following statistical trends in the distribution of manipulations from year to year, as well as the need to ease transition to a modified scale, there would be value in ensuring that any changes to the system are compatible with the previous scale.

### **The influence of terminology – “impact” vs. “severity” and “suffering”**

The Mellor and Reid (1994) paper discusses potential welfare compromise, ethical cost and the impact of procedures on animals. It outlines a rigorous method, based on functional criteria and informed judgement, to rank the severity of manipulations and assign them to specified categories. This has commonly become known as the “severity scale”. In practical terms, on animal ethics application forms and on the statistics forms required to be sent back annually by institutions using animals to MAF, the five grades, each of which is explained in some complexity within the body of the Mellor and Reid (1994) paper, have been



reduced to the following simple definitions – no suffering or virtually no suffering (O), little suffering (A), moderate suffering (B), severe suffering (C) and very severe suffering (X) (Anon (b), 2001).

Given that one of the reasons for reviewing the scale was to assess whether it best meets the needs of all those who use it and the interested public, it was important to determine if misconceptions can arise simply from the naming of the categories. Both “severity” and “suffering” are words with negative connotations. While they may be appropriate when the degree of welfare compromise is high, it is perhaps misleading to label the whole grading system in this way. For instance, in the New Zealand context at least, animals which may be manipulated simply by a change in diet, thus falling into the minimal impact “0” category, are still categorised in terms of “suffering”, albeit “little or no suffering”. The concept of suffering has a particular meaning when used in the assessment of welfare, including as it does varying degrees and combinations of anxiety, fear, pain and distress. In a wider “lay” context, however, it is an emotive word and one that can have very different meanings to different people. The word “severity” in relation to the grading scale likewise sets a negative context.

The recommendation to replace both “severity” and “suffering” with the more neutral word “impact” is not in any way meant to imply that some animals do not suffer when used for research, testing and teaching. One of the impacts on animals may indeed be suffering, but having the words “severity” and “suffering” to describe the scale is clearly not precise when they are already used as descriptors for categories *within* the scale. Rather, the change is an acknowledgement that while there is always an impact, suffering does not always occur. “Impact” covers all effects that any procedure may have on an animal, while “suffering” does not. Thus the words “suffering” and “severity” may be used within categories of the “impact” scale, but do not define them.

### Number of categories

The need to classify the wide range and diverse characteristics of manipulations in animal-based research, teaching and testing into categories has been well established. The present system aims to cover all possible procedures that might be carried out on animals used in research, testing and teaching, but it is suggested here that classification systems should also include manipulations, referred to by Banner et al. (1995), which would not be allowed under any circumstances.

The comparison of scales used internationally showed that most used between three and five categories, and reviews have raised suggestions that overcomplication may result from too many categories (Smith and Jennings, 2004). While New Zealand’s current 5-category scale starts at the lowest level, where the manipulations involve no or very little invasiveness or severity, and progresses to the highest such severity rating that would only very rarely, and for the most compelling of reasons, be approved, it is recommended that a sixth category of manipulations be added to include manipulations, which, while quite possible, are of a severity that is unacceptable. It is proposed that this grading be designated Z. Modified thus, the impact scale

would then encompass the full range of possible manipulations. This puts the range in true perspective as it indicates that the small number of manipulations that are graded X, while of high impact, are not as high as is possible. Without this extra grading, the impression is conveyed that X manipulations are “as bad as it gets”. If this were to be adopted, the annual national score for this sixth category (Z) would therefore always be zero.

### Segregation of manipulation categories within an experiment

The Animal Welfare Act 1999 lacks some clarity in how different animals used in a single experiment are categorised. Quite frequently there is a marked difference between groups within an experiment. For example, severe impact groups may be compared with negative controls. This can, and has been, interpreted in two ways. Either the whole experiment is categorised according to the most severe category or groups are segregated and individual groups are categorised separately. In collecting statistics, it is essential to be as accurate as possible, but it is as important to be consistent.

Greater accuracy is obtained if scoring is carried out separately on segregated groups or even individuals. Untreated controls, for example, would not be counted with other groups of treated animals, which would inflate the number of animals receiving high impact treatments. This is particularly important in experiments in which large numbers of animals are compared in groups, but also, for example, where a series of groups of animals may be set up in which the effect of a substance is measured as a dose response. The groups may vary as a graded series from nil to high impact, requiring a measure of judgement on behalf of both researchers and animal ethics committees.

### Reporting of actual, rather than predicted, impacts

The prediction of impact is necessarily part of an application for ethics approval prior to animal manipulations taking place. In many cases, particularly those where the researcher has extensive experience with a particular manipulation, those predictions will be accurate. However, this is not always the case. There may be instances where a manipulation results in a lesser or indeed a greater impact than predicted.

It is important in terms of accuracy of the statistics that the grading listed in the annual returns to MAF reflects not the predicted impact but the actual impact. This requires that those manipulating animals keep accurate records of the actual impact during the experimental or testing period for subsequent reporting, a practice that is not universally carried out at present. This practice not only enables greater accuracy of reported statistics, but should also allow more accurate predictions for similar manipulations in subsequent experiments. This is important for both the applicants and the AEC members, for whom such information informs the monitoring process, which is part of their remit.

### Category descriptors as guidelines

It is important that the grading system is not seen as inflexible. It is not possible to produce a workable scale that specifically takes account of all possible manipulations in all possible



species. This necessitates the use of various qualitative magnitude terms such as “short term”, “rapid”, “protracted”, etc., where what is meant very much depends on a number of factors, such as species and type of manipulation. This means that any assessment or prediction of impact will require a measure of judgement on the part of both applicant and AEC. It also underlines the importance of regrading manipulations upon completion of the study (as noted above), not only to provide accurate statistics, but also to widen the knowledge base on the effect of such interventions.

### Animal manipulations in biotechnology

There is a public perception that the accelerating development of biotechnology has provided completely new challenges with respect to the ethics of using animals in research. As a result there has been an active societal debate on the acceptability of biotechnology, particularly in relation to specific processes such as genetic manipulation.

In the context of this discussion, biotechnology can be defined as the use of techniques such as those of “molecular biology” to effect functional changes at the tissue and/ or whole-animal level. Changes may be temporary or may become a heritable trait.

Leaving aside the wider ethical question of the acceptability of biotechnological applications in general, the concern here is with the more specific question of whether such manipulations are acceptable in animal welfare terms. That is, whether they meet currently appropriate and generally accepted ethical criteria for animal use in research and can be assessed with the expertise currently available on ethics committees as set up in New Zealand.

Examples of such manipulations include:

- (i) Manipulating the gamete (ovum, spermatozoon) or embryo;
- (ii) Addition to or deletion from the genome;
- (iii) The cloning of animals;
- (iv) The repopulation of tissues or creation of whole animals with stem cells;
- (v) The secretion of proteins originating from other organisms;
- (vi) Xenotransplantation.

The following observations on some of these examples can be made:

- At the present time, manipulating the ovum, during cloning for example, does not require ethical approval in New Zealand, because an ovum is not considered to be an “animal” under the Animal Welfare Act 1999. Moreover, the associated whole-animal manipulations are identical to, and standard for, *in vitro* reproductive manipulations, which are now routine and have received AEC approval for some time. However, the potential for such manipulations to affect the phenotype of resultant offspring has led to a review currently being conducted by the National Animal Ethics Advisory Committee of the exclusion of ova manipulation from the need for ethical approval. (See final bullet point below for monitoring of animals with new phenotypes).

- Changing the genome of animals with the use of mutagens has been a process carried out for many years, although now largely replaced by biotechnology. Screening for mutations is already carried out in investigations of unwanted side effects with candidate anti-cancer drugs under AEC approval.
- Stem cell biology has been studied for many years. Altering stem cells prior to transfer is carried out *in vitro* and therefore presents no novel ethical considerations for AECs, which focus on the welfare implications of the introduction of such cells into whole animals.
- The xenotransplantation debate mainly involves animal-to-human transfers. Notwithstanding this, and acknowledging that obtaining pathogen-free supply animals does have special welfare considerations, any associated consequences can be well managed by current AEC procedures that have applied to animal-to-animal transfers conducted for many years.
- Breeding offspring from founder animals may appear to be novel, but the processes have been long carried out in mice in producing inbred lines and recombinant inbred lines. Clearly, the presence of new genes, for example, may produce different phenotypes depending on the gene background and on whether the animal is heterozygous or homozygous with respect to the new gene, which may have negative animal welfare impacts. Again, these can be well managed by current AEC procedures.

In summary, whether animals used in biotechnology are the providers or carriers of manipulated genetic material, the resulting offspring and even the subsequent generations, related animal welfare considerations can provide some new challenges in terms of rate and scale of change. The vast majority of the manipulations involved are variations on current technologies which have provided few problems during AEC assessment. Although extra care will be needed to monitor the welfare of animals having phenotypes with unknown welfare implications, this requirement falls within the current remit of animal ethics committees. This is supported by a paper (de Cock Buning, 2004) which concluded that, as long as the welfare of animals at all stages of a biotechnological procedure is assessed by an animal ethics committee, the wider discussion surrounding these processes should be addressed in a different forum.

### Factors impacting on animals in research, teaching and testing

The five domains of compromise, which relate to the nutritional, environmental, health (injury, disease), behavioural and mental needs of animals as suggested by Mellor and Reid (1994), provide an appropriate basis for classification, as they allow an holistic approach to assessing impact – an approach that has been endorsed by other reviews of such categorisations (Orlans, 2000; Smith and Jennings, 2004). The current scale goes through physical impacts first and then addresses the mental state of the animal. However, it is now suggested that a provisional score with respect to mental state be established first as the ultimate measure of impact, with the other four as contributors to that ultimate measure being double-checked to ensure no



factor has been missed, nor the impact with regard to mental state over or underestimated.

Alongside and contributing to the “domain” assessment, both intrinsic (animal) and extrinsic (environmental, procedural) factors that will influence the impact on the animal need to be taken into account. These include:

#### Animal factors

- Species/type/breed differences – marked variation between and within species can occur in terms of, for example, responses to human presence, fear responses and temperament. A detailed understanding of unique and common features of the biology and behaviour of each species studied, including life stage differences, is essential in assessing welfare impact. Moreover, an adequate application of the scale may necessitate consultation with others with greater expertise in the species of interest.
- Size – the impact of factors such as needle gauge, injection volumes and extent and complexity of surgical manipulations relative to the size of the manipulated animal needs to be accommodated.

#### Environment

- Provision for social and behavioural needs, including the enrichment of environments, should be taken into account in the categorisation of procedures. Likewise, the influence of physical environmental features, including temperature, light, sound, air quality, vibration, space, comfort of ground/floor surfaces, safety and other aspects need to be assessed. Also, the impact of animal attendants and investigators who are part of the animals’ environment should be considered.

#### Procedures

- Types of manipulation – the welfare impact of each manipulation relates to both the magnitude of negative effects and their duration, as well as to the interval between successive manipulation, e.g. for recovery. The five domains of potential welfare compromise (Mellor and Reid, 1994) provide a comprehensive way of assessing impact. Any guidelines relating to specific procedures should be indicative, not prescriptive, requiring the exercise of good judgement when being applied.

The final grading will depend on other factors as well, including:

- Operator skill – there may be a need to grade skilled operators and trainees differently, for example. This emphasises the need for some flexibility in grading procedures.
- Harm minimisation – the extent of application of the 3Rs to proposed manipulations will affect the final grading.

#### Summary

1. The basis of the system in the Mellor and Reid (1994) paper remains appropriate.
2. The name of the categorisation system should be the “impact scale”.
3. The current 5-point system should be enlarged by the addition of a sixth category which includes procedures that must not be

carried out under any circumstances. To minimise confusion in the transition from one scale to another, it is suggested that the original categories retain their symbols of 0, A, B, C and X, while the sixth should be labelled Z.

4. To ensure greater accuracy where individuals or groups within an experiment are likely to experience significantly different impacts, they should be graded on an individual or group basis, rather than a whole experiment basis as originally suggested by Mellor and Reid (1994).

5. Animal manipulations in biotechnology are adequately covered by the present system and the addition of special categories is not necessary.

6. An exhaustive list of manipulations with recommended gradings is not advisable, both because it will inevitably be incomplete and because it tends to be viewed in a rigid manner. Implementation of all the recommended features will require judgement to be exercised by scientists and AEC members alike.

7. A requirement should be made for the predicted impacts of manipulations to be reconsidered at the end of each study to ensure that the actual impacts, as assessed by researchers, animal-care staff, animal welfare officers and AECs, are supplied in the annual statistical returns to MAF.

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# A Wider Interpretation of the Three Rs Model

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## Summary

*The project Anim.Al.See, which aims to update the 3Rs model, has explored in detail, both from the philosophical and the scientific point of view, the issue of alternatives to animal experimentation. Concepts and language involved in specific case studies related to each R have been analysed. On this basis, new definitions, among others of replacement, reduction, and refinement, have been coined in order to implement a more advanced version of the Russell and Burch model. This has been achieved by widening the framework of reference and thus offering a wider range of approaches.*

**Keywords:** alternatives, three Rs, scientific procedure, sentiency

“Indulge your passion for science, but let your science be human, and such as may have direct reference to action and society.”

D. Hume (1711-1776)

Enquiry concerning human understanding. Introduction, 9.

## Introduction

About 50 years have gone by since the publication of “The Principles of Humane Experimental Technique” in 1959 by the British scientists Russell and Burch. In this book they challenged the scientific community to take the proposal to improve the treatment of animals used in scientific procedures seriously, and to this purpose they introduced the concept of the 3Rs: replacement, reduction and refinement.

Even if this book has produced efforts by some scientists to improve animal experiments and to search for alternatives (mainly defined as *in vitro* methods), after so many years the debate between proponents and opponents of animal use in scientific procedures seems to have stalemated. A number of aspects, most of them existing since the 1980’s, have led to this standby.

The most relevant aspect has been the slow advancement of *in vitro* models in the area of toxicology and pharmacology. While in all areas of biomedicine, *in vitro* cellular models were widely and successfully adopted, toxicology has remained almost impermeable to their adoption for many years, due also to the strict limitations of international regulations requiring testing of chemical substances on animal models before they can be introduced on the market (Council Directive 67/548/CEE and subsequent amendments, 1967). However, it should also be admitted that the prevailing culture among scientists in the field was that of “*in vivo veritas*”. This statement was surprisingly contradictory, because, at the same time, it was clear also to toxicologists that basic toxicity mechanisms can be better investigated in isolated systems, which avoid the complexity of the whole organism. Thus, toxicology appeared a very conservative discipline,

poorly amenable to novelty (Paganuzzi-Stammati et al., 1981; Zucco et al., 2004).

The second aspect was that the Russell and Burch model (3Rs) was subsequently defined as the “3Rs alternative model” by Smyth, and thus the focus has been mainly on replacement. Indeed, in the original Russell and Burch proposal non-animal approaches were only one part of the story (replacement). Reduction and refinement, which should ameliorate the situation of animals in the labs, were also addressed.

The third point was that Smyth’s definition (1978) of the 3Rs as “alternatives” has created confusion, giving rise to an endless discussion about whether they should be called alternatives or (better) complementary or adjunct strategies. When Smyth referred to the 3Rs as alternatives, he was probably not simply referring to possible options but, according to the Webster Dictionary, to “an option existing or functioning outside the established cultural, social or economic system”. However this choice of word has been misleading the debate, which became biased by exceeding expectations.

The final aspect was that the 3Rs model mainly addressed the scientific community, so that it was of no help in the public debate on animal experimentation, where pro and contra stakeholders, including the society at large, were confronting each other with opposite positions without any progress.

Moreover, it should be taken into account that from that time, much scientific advancement has been reached, both in terms of knowledge as well as of technology, so that the 3Rs can be discussed with a more solid background than before, but also with more challenges to be faced (Schuppli et al., 2004). In the meantime, the culture of the society has changed, and those changes regard science as well as the position of humankind in the natural environment and its relationship with all living species.

For all the above-mentioned reasons, the issue of animal experiments and their possible alternatives needs to be investigated more deeply from the theoretical and ethical point of view in connection with intrinsic aspects of scientific research and the present social culture. Theoretical and ethical aspects, indeed, deserve to receive as much study and elaboration as practical



and scientific aspects in terms of research into, and implementation of, alternatives.

In 1999, the project “Alternative methods in animal experimentation: evaluating scientific, ethical and social issues in the 3Rs context” (Anim.AI.See: *Animal Alternative: Scientific and Ethical Evaluation*) was proposed to the European Commission under the Bio-ethics activity of the Quality of Life Programme (FP 5).

### **The Anim.AI.See project**

The aim of Anim.AI.See was to assess scientific and philosophical aspects together to update language and concepts. It was clear that too many years had passed since the 3Rs model had been proposed and that too many changes had happened in many different fields related to the issue of animal experiments. The major issue was that technological progress had not been followed by adequate philosophical and ethical analysis. The need for a more advanced ethical inquiry was justified by impressive changes in the societal culture. For this reason the project was carried out by both scientists and philosophers.

### **The Science**

Science is no longer seen at the core of the progress: different tools are needed to cope with the technological advancement in order to translate it into progress in civilisation.

The criticism to which science has been submitted in the last decades, not only by the public but also by experts and scientists themselves, has been relevant in revealing the changes that science has undergone in the most recent decades: no longer authoritative, often raising uncertainty by controversial viewpoints, insufficiently transparent, intrinsically bound to technology and thus to market. The practice of science should thus be reconsidered, and since technology is continuously offering new opportunities but also opening new questions of a scientific and ethical nature, the scientific world is invested with a wider responsibility (Kelley, 1998; Ziman, 2000; Novotny et al., 2001).

### **The Society**

The general societal culture is moving from the historical animism and anthropocentrism to a global concept of a more equilibrated relationship between humankind and the natural world. The new relevant societal subjects are often the movements and NGO, while the national states are losing their identity. We are thus facing a transition in approaching and solving problems, searching for alternatives in science and technology. The reference to values and personal, as well as collective, responsibilities expresses the need to direct science towards different ways and goals. One of these is the change from the historical view of discontinuity between animals and humans (rational beings) to a more holistic view of life forms, suggesting a sort of reconciliation between the human species and the natural system.

Recent research has shown that animals are closer to us than thought before, both from genetic and physiological points of view. At the same time, differences between animals and

humans have also been highlighted. This brings us to the problem of considering them worthy of moral consideration, and less reliable as models for humans. Our analysis should specifically take into account the new moral concern for animals, which not only rejects their instrumental use, but points at their relationships with humans, based on ethical concerns and our new knowledge on animal sentience.

### **The semantics**

The issue of bridging the gap between the humanistic and scientific cultures seemed a relevant aspect to be taken into account in this research area (see also Fraser, 1999; Porter, 1992). This debate indeed dates back to the 1950's, particularly to a book published by C. P. Snow in 1959. The essence of this debate is that science can no longer be considered the only engine of progress: it must be accompanied by humanistic approaches to readdress the question of progress in civilisation. Technological progress (application of science) needs to be combined with responsible ethical analysis, grounded in humanistic approaches (sociology, history, psychology, philosophy).

It was thus clear that the work should also focus on the revision of the semantics, i.e. the language, definitions and the concepts behind them. This is indeed a current topic in science at large. Scientific language is becoming less and less appropriate to address new concepts and theories emerging from the advancement of knowledge. Several disciplines have been dealing with this aspect, which not only gives rise to problems in communication with society, contributing to a lack of transparency, but also affects scientific disciplines (Appleby, 1999; Bensaude-Vincent, 2001; Kiessling, 2001; Sloviter, 2002; Wallace, 2002; Wilczek, 2001). It is increasingly admitted that the analysis of theoretical concepts (and assumptions of the framework of reference) and of the language used is indispensable to progress in specific fields of science. This is certainly the case for the 3Rs and their definition as alternatives.

Confrontation with the above-mentioned aspects has led to a broadening of the meaning of the 3Rs model and to provision of new definitions of replacement, reduction and refinement, as well as of alternatives. Thus, while the model still mainly addresses the scientific community, it now also considers the issue of responsibility towards other subjects, such as public and private institutions, regulatory boards and the public at large, and includes ethical evaluation as a factor with the same weight as scientific evaluation in areas where multiple interests are involved.

### **Methodology**

The project was developed in three phases

#### **1. Phase One**

Each partner obtained an updated background of current practices in the 3Rs as alternatives to animal experiments. The preliminary step was to define key concepts of the different aspects involved.

A questionnaire (in electronic format) was then formulated, assisted by an expert in social surveys, in an endeavour to



enquire into the conceptual background. The mailing list was carefully drawn up in order to cover the main experts in the different fields, i.e. scientists, regulatory boards, industry, consumers, animal associations and ethicists, but, at the same time, was targeted to avoid dispersion.

The responses were analysed and the results compared to the definition of the key concepts on which the questionnaire had been formulated (Pollo et al., 2004).

## 2. Phase Two

Three different interdisciplinary groups challenged the outcomes of the first phase against case studies chosen as relevant for each “R”. Thus, the extent to which the framework, developed during Phase One, reflected the reality of the problems raised by practical approaches to alternatives to animal experiments was verified. Two case studies were analysed as being relevant to the concept refinement: experimental protocols involving non-human primates, and housing of non-human primates in biomedical research. In both cases, a philosopher analysed the appropriateness of the criteria used to define the ethical aspects of the research when these criteria were applied to the welfare of non-human primates in biomedical laboratories, whereas primatologists focussed on the possibility of applying non-invasive procedures in experimental protocols and environmental enrichment in housing conditions.

From this analysis the following definition of refinement was elaborated:

*Refinement refers to any approach which avoids or minimises the actual or potential pain, distress and other adverse effects suffered at any time during the life of the animals involved, and which enhances their well-being.*

Regarding reduction, the “single-dose” test alternatives to the multi-dilution test in vaccine quality control and the case of telemetry were analysed. These examples are of interest for various reasons: traditional testing uses large numbers of animals, a high level of distress is involved, and the tests are required within a regulatory framework. Telemetry is interesting due to its recent widespread use as a possible means of reducing the numbers of animals used, but it can conflict with refinement.

The proposed definition of reduction is:

*Reduction refers to any approach in scientific research, product testing or education that leads, directly or indirectly, to a decrease in the number of animals used.*

The case study on replacement dealt with issues of *in vitro* methods as alternatives in cosmetic testing. This area has a high impact on public opinion and has produced a series of amendments to the legislation, mostly concerning postponing the European ban on animal testing for cosmetics. An evaluation has been performed of the interplay between the different aspects underlying new tests and their development, and how they comply with the existing conceptual framework. The relative importance of each aspect has been assessed in relation to the practicability and feasibility of possible innovations, as well as the ethical issues involved in the so-called alternatives. The following definition has been proposed:

*Absolute replacement refers to any approach in scientific research, product testing, and other technical procedures in which no animals are used.*

The *ex vivo* aspects of cell cultures – serum provision and primary cell cultures – are considered to fall under reduction and refinement practices.

## 3. Phase Three

In Phase Three, the work was concentrated on producing an updated version of the “3Rs” model, according to the outcome of the investigations of the case studies in relation to the current cultural context.

A short executive summary of the unified report and the drafted recommendations have been submitted to selected experts invited to a final conference scheduled shortly before the termination of the project, in order to obtain the opinion of representatives of the different stake holders. The outcome of the conference has been integrated in the final edition of the project report.

Beside the redefinition of the 3Rs, new definitions of “alternatives” have been elaborated: A narrow definition referring to the scientific practice is as follows:

*An alternative to an animal experiment is any procedure – i.e., any method or technique, proposal or approach – that is meant to replace a particular science-based procedure that may harm the interests of animals, to reduce the numbers of animals required, or to refine the procedure in such a way that the welfare of the animals in the procedure itself or in its context, is optimised.*

A wider definition offering wider possibilities of solution, also external to the scientific context, is the following:

*An alternative to animal experiments is any ethical, cultural, political choice, which is meant to abolish animal scientific procedure, on the basis of a responsible societal agreement supported by the awareness of the implication concerning science, policy etc.*

Moreover we proposed to adopt “scientific procedure” instead of “experiment” and defined it as follows:

*A combination of one or more acts carried out on an animal for an experimental or other scientific purpose, and which may cause that animal pain, suffering, distress or lasting harm.*

Finally we provided, following all the considerations emerging from the work done on animal care and welfare, a definition of “sentient animals”:

*Sentient, non-human vertebrates, and other species of animals that have interests and capacities that are comparable to those of vertebrates.*

## Conclusions

In summary, the main conclusions emphasise the need to:

- Acknowledge that the ethical dimension to animal experiments is as important as the scientific dimension.
- Clarify concepts underpinning current terminology concerning alternatives and animal experiments, methods, procedures, etc., to recognise the role played by semantics in this debate.
- Adopt a narrow and a wider definition of alternatives related to the socio-political context.
- Reinforce the “3Rs” model as a sound scientific approach to improve animal experimentation.

- Adopt the updated definitions of the principles of Replacement, Reduction and Refinement.

- Promote the application of alternative procedures to animal experiments, according to this new framework of reference.

Beside the specific aspects mentioned above, a more general feature should be pointed out: the theoretical approach and the practical methodology adopted in this project may be useful in other areas of conflict between science and society.

The most important aspects that can be transferred to other areas are:

- Honest, exhaustive and interdisciplinary analysis of the issue;
- A precise and commonly accepted use of language;
- Making scientific aspects more accessible, reducing technicalities and making explicit embedded concepts and values;
- The importance of an appropriate philosophical background to understand the relevance of ethical evaluation in technological implementation.

For more information (documents, recommendations, etc.) on the project Anim.AI.See, consult the website [www.inemm.cnr.it/animalsee](http://www.inemm.cnr.it/animalsee).

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