

# Optimising Resources by Reduction: The FRAME Reduction Committee

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**Summary** — The Fund for the Replacement of Animals in Medical Experiments (FRAME) Reduction Committee, formed in 1998, comprises experienced professionals in the fields of statistics, experimental design, animal welfare and alternatives. The committee undertakes projects designed to contribute to reduction by addressing the implementation of recommendations made at an European Centre for the Validation of Alternative Methods (ECVAM) workshop on reducing the use of laboratory animals. The use of improved experimental design and statistical analysis techniques are key means of achieving reduction. Literature surveys have shown that there is scope for improvement in these areas. Projects include organising workshops that explain how these techniques can be used to achieve reduction, the creation of guidelines for journal editors and the compilation of a directory of training material on experimental design and statistical analysis. The first FRAME Reduction Committee international symposium will be held in October 2002.<sup>1</sup>

**Key words:** *experimental design, FRAME Reduction Committee, reduction, statistical analysis.*

## What is Reduction?

The Fund for the Replacement of Animals in Medical Experiments (FRAME) is a scientific charity, founded in 1969, that is dedicated to developing alternatives to the use of live animals in medical research and toxicity testing. FRAME promotes the Three Rs — the *reduction, refinement and replacement* of laboratory animal experiments.

What are reduction alternatives? One of the most appropriate definitions of reduction techniques is:

*... methods for obtaining comparable levels of information from the use of fewer animals in scientific procedures, or for obtaining more information from the same number of animals (1).*

## The FRAME Reduction Committee

Soon after the 29th European Centre for the Validation of Alternative Methods (ECVAM) workshop was held, the report of the workshop, *Reducing the Use of Laboratory Animals in Biomedical Research: Problems and Possible Solutions* (2), was published. One of the recommendations made in the report was that a committee should be established to progress the recommendations made in this and other reports. Following this recommendation and before publication of the final

report, the FRAME Reduction Committee was formed in 1998.

The members of the committee are from industry and academia and have expertise in statistics, experimental design, animal welfare and alternatives. Members attend committee meetings in an individual capacity and not as official representatives of the organisations for which they work.

## Aims

The Reduction Committee's main aim is to reduce the number of animals used in research, education and testing, but without compromising the scientific quality of research and without disrupting scientific progress. Russell & Burch (3) stated that, "... reduction remains of great importance, and of all modes of progress it is the one most obviously, immediately and universally advantageous in terms of efficiency". It is possible to achieve reduction without disrupting scientific progress. This was shown by Guaitani *et al.* (4), who examined the use of animals at a research institute in Italy. In 1980, the Institute used 130,000 animals — 16 years later, this number had dropped to 25,000. And yet, within this period, the total number of scientists working with animals increased, as did the number of scientific papers generated. The reasons for this impressive reduction included the use of improved analytical and statisti-

<sup>1</sup>The proceedings of this workshop will be published in ATLA.

cal methods, combined with the involvement of an Institutional Committee for Animal Care and Welfare, and a policy of self-regulation.

### **Achieving reduction — but at what cost?**

Despite the obvious benefits of achieving reduction, there is an important caveat whenever reduction strategies are under consideration, and that is that reduction should be considered in combination with refinement. When considering the use of techniques to reduce the number of animals in an experiment, the likely impact on the welfare of the individual animals must be considered. Provided that this cost is taken into account, there are many ways of achieving reduction, and the committee is focusing on a number of key areas.

### **How to achieve reduction — better experimental design and the use of the correct statistical methods**

The first of these is ensuring the use of improved experimental designs and correct statistical analysis. Russell & Burch (3) highlighted the fundamental importance of this with their affirmation that “Every time any particle of statistical method is properly used, fewer animals are employed than would otherwise have been necessary”. It is also essential to ensure that a sufficient number of animals are used in an experiment, so that the data generated can be analysed statistically. Experiments should be designed so that biologically important effects can be detected. It is within these situations that the accurate use of statistical methodology becomes essential.

Unfortunately, evidence suggests that some experiments are badly designed and that the results are analysed incorrectly. This results in unnecessary animal use. A study by Festing (5) on 48 animal experiments found that 35 (73%) had obvious statistical errors. This suggests that there is a need for better training in experimental design and statistics. When scientists attending UK Module 5 courses were asked about their knowledge of statistics, 62% rated their knowledge as “basic”, and only 5% considered their level of knowledge to be “good” (6). To respond to this need for better training, a directory of training material on experimental design and statistics has been compiled, and committee members are reviewing self-teach computer software packages.

### **Other means of achieving reduction**

There are many other ways to achieve reduction. For example, at the international level, the harmonisation of regulatory requirements for toxicity

testing can have spectacular effects. Lumley & Van Cauteren (7) stated in 1997 that “. . . international harmonisation of the regulations controlling the testing of pharmaceuticals will, if fully realised, lead to a reduction of nearly 50% in the number of animals used in toxicity testing of these products . . .”.

At a local level, methods include:

- the use of pilot studies before undertaking large-scale experiments;
- the use of specific pathogen-free animals (8);
- the use of inbred strains (8, 9) as a means of controlling variation; and
- the use of *in vitro* systems where possible.

### **Projects undertaken**

The committee has undertaken a number of projects, some of which will be highlighted. A survey of 46 scientific journals revealed that only half have a policy on animal care and use (10). The committee, with Professor van Zutphen of Utrecht University, has written a set of guidelines for journal editors on the humane use of animals and the application of the Three Rs. The guidelines have been distributed to over one hundred journal editors and were highlighted in an editorial in *The Veterinary Journal* (11) on animal research and publication ethics. The guidelines are now on the FRAME website at <http://www.frame.org.uk/Guidelines.htm>.

The evidence that the results of some experiments are analysed incorrectly, suggests that the production of a set of statistical guidelines for authors could contribute to reduction. In one study of 133 papers published by one journal (12), in 26% of the papers, the authors reached conclusions that were not supported by the results of statistical analysis. Almost half of the papers (45%) included mistakes in the statistical analysis techniques used; 30% had deficiencies in the experimental design used — one of the main problems was the size of the experiment. Dr Michael Festing, Chairman of the Reduction Committee, is currently co-authoring a set of statistical guidelines, adapted from the guidelines that he wrote for *ATLA* (13), and guidelines contained in *Statistics with Confidence* (14), with one of the authors of this book, Professor Douglas Altman. These statistical guidelines will be distributed to journal editors.

There appears to be a tendency to use fewer numbers of larger animals than smaller ones, such as rodents. However, ECVAM workshop 11 (15) concluded that, “In cases where a choice between species is possible, there is generally no scientific justification for using more of the smaller species

than of the larger one". The committee will identify the areas where this occurs and why. The reasons may match those that Wilson (16) suggested for why the group sizes of rodents and non-rodents differ in toxicity testing — ". . . expense, expediency and convention".

A book, entitled *The Design of Animal Experiments — Reducing the Use of Animals in Research Through Better Experimental Design* (17), has recently been published. The book was written by two members of the committee, Michael Festing and Philip Overend, as well as by others from the University of Oxford and the British Region of the International Biometric Society.

Members have organised many talks and workshops on how to use experimental design and statistical analysis techniques to reduce animal use. This aspect of the work of the committee has been particularly successful and has resulted in the receipt of extremely positive feedback.

A CD-ROM (18) has been produced, in conjunction with Dr David Dewhurst and Jake Broadhurst of Edinburgh University. The software enables researchers who would like to learn more about how to reduce the number of animals used in experiments through the use of good experimental design techniques to do so.

The progress of the recommendations made at the ECVAM workshop on *The Three Rs: The Way Forward* (15) has been followed up by the committee. The committee has recommended ways of improving the information presented in the UK *Statistics of Scientific Procedures on Living Animals* (19) and is also currently examining the trends in animal use since the implementation of the UK *Animals (Scientific Procedures) Act 1986*.

### Future projects and activities — the road ahead

Several research projects are planned for the future. The committee will continue to follow the progress of recommendations made at the ECVAM workshop on reduction (2). Since it is known that the use of inbred strains can lead to a substantial reduction in the number of animals used in an experiment, the number of outbred rats and mice in selected disciplines will be studied to determine the current extent of their use. The need to use both sexes in acute toxicity testing will be investigated. The acceptance process for scientific papers and the information contained within their methods section will be analysed to ascertain the level of consideration given to the Three Rs. Members of the committee will continue to present talks and training workshops on reduction strategies. For example, committee members are currently organising a talk and a workshop at a forthcoming meeting of the British Pharmacological Society.

The committee plans to set up a website on experimental design and statistical analysis. The aim of the website is to provide resources to scientists looking for information that will enable them to reduce the numbers of animals that they need, by designing their experiments more efficiently. The site will include information on how to determine sample sizes, as well as checklists on the design and statistical analysis of animal experiments. Researchers will also be able to use the site to find useful books, papers, software and links to other relevant sites.

The first Reduction Committee symposium is being held in London in October. The meeting will serve several purposes. It will be an opportunity for the Reduction Committee to identify researchers' needs, in order to prioritise future activities. Furthermore, as with the Fourth World Congress, the symposium will enable scientists working in different fields to meet and exchange ideas of useful reduction techniques. The meeting has been designed to ensure that a broad range of topics will be discussed — from opportunities for reduction in the genetic modification of animals (which is particularly relevant, given the rapid ongoing rise in the use of these animals) — to a pharmacological approach in cancer research. Consequently, speakers are from a wide range of organisations. By the time that the proceedings are published in FRAME's journal *Alternatives To Laboratory Animals (ATLA)*, the FRAME Reduction Committee hopes to have made substantial progress in contributing toward reduction.

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