



# Revision of the EC directive on the welfare of research animals

## An advance briefing

Updated version, December 2005\*

♥ The European Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes is currently under review.

♥ Many proposed changes aim to promote the “3Rs” of experimental animal use – reduction, refinement and replacement. It is vital that careful thought is also given to the limitations that these changes could place on existing and future biomedical research, and the extra administrative and practical burden to researchers and animal breeders that could result.

♥ This document arises from a focus meeting of stakeholders and commentators from academia, industry, and the realms of accreditation and research defence, convened by EMBO<sup>1</sup>. It serves mainly as a briefing for academic researchers, with the aim of encouraging them to become more involved in the political process surrounding the Directive revision.

### Background on the Directive and its revision

The Directive sets minimum standards for animal housing and care, training of animal handling personnel and supervision of experiments. It also promotes the reduction in numbers of research animals by encouraging the development and validation of alternative methods. However, its wording leaves it open to different interpretations, and it does not explicitly mention the 3Rs and ethical review processes, or require the compulsory authorisation of all experiments.

Many countries in Europe already apply stricter regulations than the current Directive stipulates, but there is much variation. Updating the directive will help to standardise national legislation and harmonise the conditions applying to animal research across the European Union.

The revision is expected to focus strongly on improvements in animal welfare provisions and the promotion of alternative techniques. It will probably specifically address conditions for animal use in new research methods post-dating the original Directive (e.g. transgenics, xenotransplantation and cloning research) and experiments on highly sentient animals, e.g. non-human primates.

### The revision process

A first draft of the revised Directive is likely to appear in 2007 or 2008. It will be based on answers given to a “thought starter” issued to a Technical Expert Working Group in 2003. The process will progress as follows:



\* Revised timetable reflects new information

### How the revision should be seen

The revision presents researchers with opportunities as well as challenges. It provides a fresh stimulus for considering current practices, the superiority of self-regulation over external regulation and the value of communicating research and its methods proactively.

Many aims of the revision are achievable through existing regulations. These require experiments to be done in accordance with the best current scientific knowledge – an area already addressed by independent training and accreditation organisations (e.g. FELASA and AAALAC Intl.). Nevertheless, the Directive will be revised, and national laws must implement it. It therefore pays to examine some possible changes that urgently deserve the attention and input of researchers in particular fields.

<sup>1</sup>The meeting was held under the auspices of EMBO. This document reflects discussions at that meeting, and is not a policy statement from EMBO or individual participants.

## Possible changes and likely consequences

It is unlikely that a European database for compulsory submission of animal experiments will be proposed, but bans on certain animal uses that are currently permitted may well be seriously considered in the process of revision. Such moves could considerably hinder progress in biomedical research. Even minor incremental changes could conceal land mines:

- ❖ Severe restrictions on the re-use of animals would slow down much research and cause an additional rise in numbers of experimental animals (in conflict with the 3Rs). If “repeat experiment” is defined to include even minor interventions, that increase could be huge. Furthermore, certain important experiments could be made impossible.
- ❖ Compulsory cost-benefit analyses of experiments – weighing the suffering of the animals against the benefit derived – would substantially increase the workload on research institutes. Furthermore, they can be highly subjective, and therefore of doubtful significance.
- ❖ Inclusion of foetal and embryonic forms, and certain invertebrates in the new Directive would greatly increase the administrative burden of some researchers, hence slowing down their work.
- ❖ Unrealistic restrictions on transportation of research animals could severely hinder international collaboration.
- ❖ Limits on research use of non-human primates to the F2 generation would almost stop primate research, because existing breeding facilities would not be able to supply more than a small fraction of the resulting demand.
- ❖ Legislation against higher grades of suffering *per se* could encourage further pressure from activist groups and gradually work downwards to affect lower grade interventions (so-called “Step-by-Step-to-Stop”).

## What to do

This is about communication and the integration of academic stakeholders into the political process. Keeping one’s head down does not work. Researchers have a lot to gain by being open about what they do. As well as stressing contributions to improved healthcare, it is important to communicate that scientific research has some of the strictest quality control mechanisms of any profession (in funding and publication).

Though all experiments involve some inconvenience or suffering to the animals concerned, most involve minor procedures –

e.g. injections – contrary to public perceptions. It is also not widely appreciated that researchers put effort into improving the lives of experimental animals, and that animal health in general has been vastly improved by the same experimentation that has advanced human health. The public is receptive to such communication and largely supports – with conditions – the use of animals in research. Researchers must reassure the public that those conditions are overwhelmingly met.

The research community needs to get involved in the debate – contributing proactively through increased openness and the involvement of academic institutions in the political process. Researchers and politicians must engage at European level for constructive exchanges on the Directive revision. Both are busy professionals, so it helps if messages are kept simple, and hard facts – rather than elaborate arguments – are presented.

## Where to start

EBRA, the European Biomedical Research Association, acts as a focal point for co-ordinating the participation of academic stakeholders in the political process – see: <http://www.ebra.org> or e-mail [matfield@ebra.org](mailto:matfield@ebra.org)

## Animal research and welfare – present and future

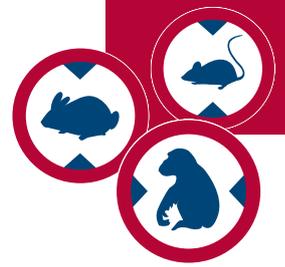
Changes to the Directive must address the 3Rs while improving the quality of science and taking into account the needs of biomedical research.

Current justifications for animal experimentation rest partly on numerous examples of its contribution to medical progress. The test of deletion suggests that without animal research, many advances would not have been made (or at least not so rapidly). Vaccines developed using animals have reduced the occurrence of nine global diseases – smallpox, poliomyelitis, diphtheria, measles, rubella, mumps, pertussis, H. influenzae and tetanus – by more than 98%. True though this may be, researchers should focus on better communication of present research, future prospects, and current reasons for using animals.

## ❖ Trends in animal use – some examples

### Mice

Genomics allows the study of thousands of genes and their interactions, which inevitably depends on studies using large numbers of animals, mainly mice. Most diseases are multifactorial (involving many genes) and even genes that do not cause a disease can be involved in determining the susceptibility to and course of a disease. Multiple tests on individual mice often lead to the fast and efficient identification of many new phenotypes (expressed characteristics) in one line.



## Non-human primates

The faster development of better vaccines for human and animal diseases is increasingly necessary. Researchers agree that some important work on vaccines for human diseases is impossible without using non-human primates (NHPs), particular in the study of cellular responses to new vaccines. It is scientifically demonstrated that NHPs are essential for the development of vaccines against Hepatitis viruses and HIV. The immune system of NHPs mimics that of humans in critically important ways that other animals, even “humanised” mice, cannot. Some other diseases are also best modelled in NHPs (e.g. multiple sclerosis).

Research using NHPs represents a small but important part of all animal research, with its own special requirements. Many researchers see the need for a European primate breeding centre. Bans on certain primate research – as enacted in the Netherlands – could cause it (and the researchers) to move elsewhere, possibly to places where animals are less well protected.

## Humanised animals

A growing demand for transplant organs has necessitated research into “humanising” animals. In pigs highly efficient and refined transgenesis can now be achieved with lentiviral vectors, requiring fewer animals and less time and money than conventional DNA-microinjection followed by reproductive cloning. This, and research in other mammals, increasingly offers a hope of providing urgently needed transplant organs and optimised animal models of human diseases.

## ♥ Welfare of research animals

### Monitoring and promotion of good care

Both global (AAALAC Intl.) and European (FELASA) organisations issue certifications and provide training courses, ensuring the highest standards in animal treatment. Staff who handle animals legally require such certification in the EU. Research projects (e.g. COST) are constantly increasing the knowledge necessary for ethically and scientifically defensible use of animals.

### Better scientific understanding

The better a species is understood, the better its welfare can be catered for. The need for better phenotyping (description of expressed characteristics) of genetically modified mice is already being addressed via large scientific networks across Europe (Eumorphia).

Phenotype/welfare relationships can thus be defined and made available to other researchers. Large research projects promote improvements in standardisation, validation and data sharing, all of which promote the 3Rs.

## Research on cage environments

Cage enrichment may allow certain species to demonstrate “luxury” behaviour. Changes in such behaviour might be useful as more sensitive indicators of an animal’s wellbeing than those normally used. Cage enrichment appears to have an effect on phenotype, and hence experimental results. It is a complex subject, requiring more research.

## Improved technology and techniques

New, on balance less invasive, technologies (e.g. magnetic resonance imaging markers and telemetry for remote monitoring) can increasingly refine experiments, as can better definition of humane end-points and better knowledge of normal and pathological physiological values. Minimising suffering, furthermore, improves the quality of experimental data, a phenomenon generally appreciated by researchers.

Genetic modification of animals (producing specific characteristics in potentially highly reproducible ways) is usually both a reduction and a refinement. It can often replace more harmful methods that produce less consistent results. Conditional mutants even allow the expression of a particular defect to be switched on and off.

## Institutional and self-regulation

Funding bodies and scientific publications can help by requiring scientists to explain in detail the suffering caused to experimental animals, and the action taken to minimise it. Ultimately, however, nothing improves the credibility of scientists more than being seen to ensure animal welfare by self-regulation.

High standards of animal treatment can only be ensured, however, if staff are properly trained. While the revision of the EC Directive may be felt necessary to establish better standards, there is no legislative substitute for in-house enforcement of good practice.

## Conclusion

Everyone who benefits from the results of biomedical research is faced with a dilemma: experimental animals undergo procedures – often harmful – without consenting, and without individually benefiting. Still, humans have a moral imperative to alleviate human suffering. Animals should be respected and used, but never abused. That means making efficient use of them for necessary applications, and regarding them as a precious resource. They must be used in a manner that promotes rapid progress in science and medicine, while continually reassessing their treatment in light of the latest knowledge and methods. This future relies on the harmonisation of societal expectations with regulations.

## NOTES

The focus meeting "The importance of animal use in scientific research" was held under the auspices of the European Molecular Biology Organization (EMBO) in Madrid, Spain, on 18–19 March, 2005, and organised by the EMBO Science & Society Programme. The following stakeholders attended:

**Ronald Bontrop**, Biomedical Primate Research Centre (BPRC), The Netherlands

**Steve Brown**, MRC Mammalian Genetics Unit, United Kingdom

**Anne-Dominique Degryse**, AAALAC Intl., and Centre de Recherche Pierre Fabre, France

**Simon Festing**, Research Defence Society, United Kingdom

**Oretta Finco**, Research Center, Chiron Vaccines, Italy

**Martin Hrabe de Angelis**, National Research Center for Environment and Health, GSF, Germany

**Alastair Kent**, Genetic Interest Group, United Kingdom

**Gabriele Küsters**, EFPIA Animal Research and Welfare working group and Research and Technology, Sanofi-Aventis group, France

**Mark Matfield**, European Biomedical Research Association EBRA, United Kingdom

**Silvia Matile-Steiner**, F. Hoffmann-La Roche Ltd & EFPIA, Switzerland

**Adrian Morrison**, University of Pennsylvania, United States

**Anna Olsson**, Institute for Molecular and Cell Biology – IBMC, Portugal

**Rami Rahamimoff**, The Hebrew University, Israel

**Merel Ritskes-Hoitinga**, FELASA, and University of Southern Denmark, Denmark

**Tilli Tansey**, Wellcome Trust Centre for the History of Medicine, United Kingdom

**Glauco Tocchini-Valentini**, Istituto di Biologia Cellulare, CNR, Italy

**Björn Vennström**, Department of Cell and Molecular Biology, Karolinska Institute, Sweden

**Eckhard Wolf**, Institute of Molecular Animal Breeding and Biotechnology, Gene Center of the University of Munich – LMU, Germany

**Wolfgang Wurst**, Institute of Developmental Genetics, GSF, Germany

## FURTHER INFORMATION AND FOLLOW-UP

For links to the current Directive, and the reports of the Technical Expert Working Group, see: [http://europa.eu.int/comm/environment/chemicals/lab\\_animals/revision\\_en.htm](http://europa.eu.int/comm/environment/chemicals/lab_animals/revision_en.htm)

To become more involved in the process, visit: <http://www.ebra.org> or e-mail [matfield@ebra.org](mailto:matfield@ebra.org)

## GLOSSARY

### 3Rs

Reduction, Refinement and Replacement of experimental animal use (Russell WMS and Burch RL, 1959, The Principles of Humane Experimental Technique)

### AAALAC Intl.

Association for the Assessment and Accreditation of Laboratory Animal Care International ([www.aaalac.org](http://www.aaalac.org))

### COST

Intergovernmental framework for European Co-operation in the field of Scientific and Technical Research, allowing the co-ordination of nationally funded research on a European level ([www.cordis.lu/cost/](http://www.cordis.lu/cost/))

### Eumorphia

EU-funded integrated research programme involving the development of new approaches in phenotyping, mutagenesis and informatics leading to improved characterisation of mouse models for the understanding of human physiology and disease ([www.eumorphia.org](http://www.eumorphia.org))

### F2

Second filial generation, resulting from self- or inter-crossing within the first generation, F1 (i.e. F2 is two generations away from the parents of the F1)

### FELASA

Federation of European Laboratory Animal Science Associations ([www.felasa.org](http://www.felasa.org))

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