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viewpoint

Towards responsible animal research

Addressing the ethical dimension of animal experimentation and implementing the 'Three Rs' principle in biomedical research

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Biomedical and basic biological research are fundamental tools used to address the numerous public health problems that challenge sufferers both in developing countries and in the industrialized world. However, they have not been without their share of criticism from other parts of society. Over the past few decades the use of animals in basic research and in the testing of potential new therapeutics has become a hotly debated issue, with the scientists who perform animal experimentation and patient organizations hoping for new treatments on one side and animal welfare groups on the other. In both Europe and the USA, militant activists have freed animals from research institutions or even destroyed whole research laboratories and the years of biomedical research that they contained. Nevertheless, other animal welfare groups have contributed to a constructive and informed debate which has led to an increased awareness of our responsibility towards animals. Although most people can see the benefits of animal experimentation and only the most ardent and militant groups demand a complete ban on their use, the question of how to protect animals from being used for unnecessary experiments and of how to alleviate their suffering remains a valid, sensitive and controversial issue for science, society and politics.

Particularly now that many people are feeling increasingly unhappy about the way we treat animals in general, not just in research, animal welfare in Europe and the relevant legislation and regulations have become an important priority for the European Commission (EC). To address the needs of scientists, patients and industry, as well as the demands of animal welfare groups and society at large, the EC is promoting a continuous debate with all interested parties (see the EC website at: http://europa.eu.int/comm/research/rrr.html). Here we explain the rationale behind the EC's policy on the use of animals in research and its proposed actions to decrease the number of animals involved.

The main goal of the EU legislation is to accomplish a uniformly high standard for the use and care of animals in experimental research. Its policies aim to replace the use of animals with other methods and, whenever this is not possible, to make sure that such experiments are undertaken only with the greatest attention to animal welfare. The principal instrument is a Council Directive (Directive 86/609/EEC) from 1986 "on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes." In this respect, the implementation of the 'Three Rs' principle—Replacement, Reduction and Refinement (Russell & Burch, 1959)—has become an important objective of EU legislation. Article seven of Directive 86/609/EEC clearly both expresses support for and outlines the practical application of the Three Rs. It specifies that "experiments may not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practically available. The choice of species shall be carefully considered. In a choice between experiments, those which use the minimum number of animals, involve animals with the lowest degree of neuro-physiological sensitivity, cause the least pain, suffering, distress or lasting harm and which are most likely to provide satisfactory results shall be selected.

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All experiments shall be designed to avoid distress and unnecessary pain and suffering to the experimental animals."

More recently, animal welfare and the protection of animals from excessive and unnecessary suffering have also found their way into EC legislation concerning the legal protection of biotechnological inventions. The 1998 Directive 98/84/EEC states that "processes for modifying the genetic identity of animals, which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes" are not patentable.

Even more important than these directives is the Treaty of Amsterdam that came into force in May 1999. The treaty's protocol on animal welfare introduces for the first time legal stipulations in favour of animal welfare in both law and politics. As a consequence, European institutions and Member States now have to pay full regard to the welfare of animals when drawing up new agriculture, transport, research and single-market policies. So far this can be considered as the greatest contribution to the protection and respect for the welfare of animals as sentient beings, raising their status from 'goods' or 'agricultural products' as they were previously considered.

However, regarding Directive 86/609/EEC on the use of animals in experimentation, the scientific basis is at least 15 years old and several provisions are clearly out of date. Realizing that the directive does not meet all current demands, the EC is preparing a revision and, through discussions with the member states, representatives from industry and non-governmental animal welfare organizations, has begun to identify areas for further attention and controls.

The Fifth Framework Programme for Research (FP5) (1998–2002) incorporated concrete measures both to implement the Three Rs in research and to consider further the ethical dimension of animal experimentation, with the 'Quality of Life and Management of Living Resources' programme (http://www.cordis.lu/life/) playing an important role. On the basis of provisions set out in Directive 86/609 and on the opinions of the European Group on Ethics—in particular those regarding the ethical aspects of FP5, the genetic modification of animals and cloning techniques—the Council and the European Parliament have laid down restrictive provisions for animal experimentation and tests performed on animals in all EC-funded research projects. They specify that "animal experiments and tests on animals should, whenever possible, be replaced by *in vitro* or other alternative methods" and that "the modification of the genetic heritage of animals and animal cloning can only be envisaged for objectives which are justified on ethical grounds…with respect for the well-being of animals and the principles of genetic diversity".

Of more practical consequence for researchers, five actions have been initiated under the Quality of Life programme to ensure that the provisions included in this ethical framework are implemented for EC-funded research. First, applicants are obliged to describe the potential ethical implications of their research proposal regarding its objectives, its methodology and the possible implications of the expected results (see sidebar). The application should justify the research design and in particular describe the procedures used to respect the Three Rs principle and to protect the welfare of animals. Furthermore, the applicants need to explain how ethical requirements will be fulfilled and to indicate the relevant legal and/or regulatory requirements of the Member State or countries where the research will take place.

A second action—actually closely related to the first—consists of assessing the level of awareness among the applicants about the ethical implications of their research, including ethical aspects of animal experimentation, and their responsibility to address these issues. In practice, the assessment is made during the scientific evaluation of a proposal. Proposals that deal with sensitive issues and, in particular, if the legislation in the Member States involved differs, such as regarding the use of human embryonic cells and fetal tissue or the use of non-human primates, undergo a specific ethical review. However, differences between Member States' national legislation are not necessarily a reason for excluding such research from funding within the Framework Programme, but are a reason for greater vigilance, transparency and accountability.

The proposals are examined by an ethics panel of independent experts that the EC establishes for each call for proposals. These

Information requested from the applicants regarding animal experimentation:
Proposers should provide details of the species (and strains where appropriate) of animals to be used and explain why these have been chosen. They should explain why the anticipated benefits justify the use of animals and why methods avoiding the use of living animals cannot be used. They should also justify the numbers of animals proposed with reference to statistical advice if applicable.

Proposers should provide a summary of the main adverse effects for the animals, including any adverse effects due to methods of husbandry and supply of animals as well as the effects of the scientific procedures themselves. They should state what will happen to the animals at the end of the procedures (e.g. rehoming)

They should also indicate what steps have been taken to comply with the principles of reduction, refinement and replacement. In particular they should describe the procedures adopted to ensure that the amount of suffering to the animals is minimized and their welfare is protected as far as possible (e.g. improvements in technique, application of humane end-points, environmental enrichment).

Transgenic animals
Proposers should be aware that the issues and questions relating to the use of animals in general (as above) apply equally to transgenic animals and the same information should be provided. In addition proposers should state what the possible phenotypic effects of transgenesis are and how this may effect animal welfare.

Non-human primates
In the case of non-human primates the proposers must, in addition to the information above, specify not only which species are used, but also their origin. It should state which partner is in charge of the importation or breeding of animals, where the primates are to be housed and which partner is performing the experiments.

Additional information and justification on any likely restrictions to the animal husbandry and care (e.g. single housing) and on the numbers of animals to be sacrificed should also be provided.

experts represent different disciplines such as biology, medicine, genetics, neuroscience, psychology, law, philosophy and theology, and also include representatives of animal welfare groups. The panels assess whether the applicants have identified all potential ethical questions and whether they have taken appropriate measures to fulfil ethical and legal requirements at the national and European levels, including approval of local ethics committees. They also assess whether the principle of the Three Rs has been applied, including the overall benefit of the research proposal as compared with the possible costs in terms of animal suffering.

During the period from October 1999 to January 2001, the panels examined a total of 121 proposals—13% of the total number of proposals retained for funding after scientific evaluation under the Quality of Life programme. Thirty-three proposals came under such special ethical review as they involved the use of non-human primates, dogs, cats or transgenic animals. In two cases, the panels, in agreement with the scientific evaluation panel, questioned the justification regarding the use of non-human primates, and the research protocols were subsequently modified during the contract negotiations. In the remaining 31 proposals, the experts saw opportunities for improving the presentation and disclosure of information on how to implement the Three Rs. For these proposals, additional information or clarifications were requested. The funding of any project was suspended until the applicants had satisfactorily answered all questions regarding ethical implications. The ethical review at the EC level does not replace the need for evaluation and authorization by local ethics committees where this is required by national legislation.

The implementation of the 'Three Rs' principle has become an important objective of EU legislation

These measures, which are now being applied in other EC research programmes, ensure that all ethical questions raised by the research proposal have been adequately addressed before the project starts. But they also serve to increase the awareness among applicants and among scientific peer reviewers. Ultimately, a Europe-wide dialogue between scientists, industry, experts in ethics and animal welfare and patient organizations should be established so that a consensus can be reached on more responsible behaviour regarding animal experimentation in research.

A third more general action to increase the overall welfare of animals is the EC's support for research in bioethics (http://biosociety.cordis.lu/Home_Bioethics.cfm). The European institutions (the European Parliament, the Council of Ministers and the European Commission) recognized as early as the 1980s that innovative research programmes in the life sciences cannot be responsibly implemented without also analysing the potential ethical, social and legal implications of the research and its applications. Currently, 22 bioethics research projects are funded under the Quality of Life programme. One of these projects, coordinated by Dr Flavia Zucco from the Instituto di Neurobiologia at the Consiglio Nazionale delle Ricerche in Rome, Italy, assesses developments that have been made over the past 10 years to implement the Three Rs concept at the scientific, institutional and regulatory levels. Its ultimate goal is to come up with an updated concept of alternative methods and of the Three Rs concept that could be used in research.

Over the past two decades, the development of alternatives to animal experimentation to reduce the use of animals in research and in toxicity testing has been an increasingly important priority for the various Framework programmes. From an initial funding of €2 million under the Biotechnology Action Programme (1984–1988) the EC is currently supporting more than 43 research projects to develop *in vitro* or *in silico* alternatives, with an overall contribution of about €65 million. Such alternatives to animal experimentation are not only important in relation to the implementation of the Three Rs, but they may also offer more reliable and economical alternatives for industry and for academia.

The development of alternative methods is specifically promoted under the 'Food, Nutrition and Health', 'The Cell Factory' and 'Environment and Health' key actions of the Quality of Life programme. These actions cover a wide variety of fields, such as cell culture research, pharmacotoxicology, ecotoxicology and mathematical modelling. In addition, relevant research projects, workshops, conferences, training programmes and activities to stimulate awareness in small and medium-sized enterprises are other ventures that are funded, demonstrating the growing importance of finding suitable alternatives to animal testing and of raising the awareness of these alternatives within the scientific community.

The Treaty of Amsterdam introduces for the first time legal stipulations in favour of animal welfare in both law and politics

Furthermore, in response to Article 23 of directive 86/609/EEC, which highlights that the Commission and the Member States should actively support the development, validation and acceptance of methods which could reduce, refine or replace the use of laboratory animals, the EC created the European Centre for Validation of Alternative Methods (ECVAM) in 1991, which is a unit of the Institute for Health and Consumer Protection within the EC's Joint Research Centre. ECVAM coordinates the validation of alternative test methods at the EU level and manages databases on these procedures. In addition, the centre acts as a focal point for the exchange of information on the development of alternative test methods while promoting dialogue between legislators, industries, biomedical scientists, consumer and patient organizations and animal welfare groups.

Finally, research on animal welfare, in particular in the context of farming, has been and continues to be a research priority. So far the EC has contributed €11.5 million to such research. Current research funded under the action 'Sustainable agriculture, fisheries and forestry, and integrated development of rural areas including mountain areas' focuses directly on welfare-related research, such as the transport of cattle over long distances, animal welfare in organic farming, poultry genetics and feather pecking in chickens, as well as including a study on public attitudes to welfare issues (http://europa.eu.int/comm/research/quality-of-life/animal-welfare/seminars/index_en.html).

The EC is committed to continuing these activities in the future. Under the 6th Framework Programme for Research (FP6) (2002–2006) (http://www.cordis.lu/rtd2002/), it will take further responsibility for promoting the ethical debate, addressing animal welfare issues, and ensuring that the principle of the Three Rs becomes an integral part of all research projects that are funded.

The new integrated projects and networks of excellence are particularly adapted to these needs. It is expected that consulting with a wider range of groups will allow the integration of the views of all interested parties—academia, industry, non-governmental animal-welfare groups, patient organizations, regulatory bodies, consumer organizations and society as a whole.

An essential element of FP6 is the integration of activities that address the ethical and social aspects of the life sciences and biotechnology, including public dialogue during the early research phase and before technologies are ready for use by society. Special attention will be given to animal welfare issues and the Three Rs concept. In addition to raising awareness among life scientists about the ethical implications of their work, the EC will also encourage experts in ethics and law and social scientists to participate actively in research projects. This integration should allow for mutual education and dialogue, as well as suggesting mechanisms to integrate ethics into the training of scientists and their subsequent research activities. Trans-disciplinary collaboration between all relevant groups should ensure that ethicists have the means to continuously assess the social relevance and adequacy of evaluation procedures and recommendations.

The development of new *in vitro* tests to replace animal experimentation will be continued with funding from the 'Life Sciences, genomics and biotechnology for health' priority. Although it takes into account the fact that the development of some alternative methods requires a medium- or long-term perspective, the policy-oriented research in the 'Supporting policies and anticipating science and technological needs' activity will deal with short-term research, thus helping to cope with European Union-specific requirements to use, wherever possible, alternative methods such as those included in the White Paper on the Strategy for a future Chemicals Policy and in the Seventh Amendment to the Cosmetics Directive (Directive 76/768/EEC).

The need for a commitment from all the different parties involved (the EC, the Council of Ministers, the European Parliament, governments, non-governmental organizations, science professionals, and so on) has been highlighted in the EC's Communication (COM 2002) on 'Life sciences and biotechnology—a strategy for Europe', published on 27 January 2002 (http://europa.eu.int/comm/biotechnology). This plan of action, now being discussed within the European Parliament and EU Member States, stresses the need to identify the ethical issues at an early stage of research and the importance of public participation early in the process of developing applications of biotechnology. It also highlights the EC's willingness to work with public and private partners in order to establish a consensus on ethical guidelines, standards or best practice, such as those applicable to the use of animals in research.

The EC will also encourage experts in ethics and law and social scientists to participate actively in research projects

The need for coordination is also stressed in the EC's 'Action Plan on Science and Society' (http://www.cordis.lu/science-society). It proposes, among others things, to establish a network of animal welfare committees in order to exchange information and develop best practice for the ethical review of animal experiments. It also proposes to promote the training of young scientists in animal welfare issues, thus improving the awareness of the Three Rs.

Given the growing concern of society in general regarding the treatment of animals not only in research, but also in farming and agriculture, it is becoming increasingly important to address the ethical issues involved and to find a solution that will both benefit society and address the needs of the scientific community. The European Commission is committed to continuing the debate on animal welfare issues and to the implementation of the principle of the Three Rs so that it becomes an integral part of research and development in life sciences and biotechnology.

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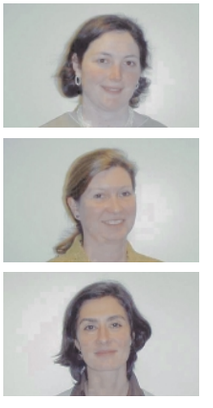

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