

Use of Animals in Research: A Science – Society Controversy? The European Perspective*

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Summary

The use of animals for research and testing purposes has decreased substantially during the last two decades but is now increasing again, mainly because of the increased use of transgenic animal models. Presently, 10-12 millions of vertebrate animals are used per year within EU Member States. Scientists who are using animals in research are frequently criticised by animal protection groups and blamed that they do not respect the integrity of an animal's life. The European Science Foundation (ESF) is recognising that legislation cannot be the only answer to those worries in society and that it is essential to take a stand and to clearly explain what the Foundation's position with regard to the use of animals is. In a recently published position paper, ESF has discussed its views and has adopted guidelines for the use of animals in research. The document explicitly states that laboratory animals have an intrinsic value, which must be respected. The consequences of recognising the intrinsic value have been elaborated in the position paper and include, among others, strong endorsement of the replacement, reduction, refinement principles. It is stated that, prior to the performance of an animal experiment, the protocol should be subjected to independent expert review including the weighing of the likely benefit versus the likely animal suffering. Also, the development and organisation of accredited courses on laboratory animal science, including information on animal alternatives, welfare and ethics are encouraged. The guidelines, as formulated in the position paper, can be seen as reinforcement of developments that have already been started in several countries, but have not always received full support from the scientific community. With this document, the association of 70 leading national science organisations in Europe has taken a position that, in several aspects, exceeds current European legislative regulations. For bridging the science – society controversy, it is essential to continue this initiative by promoting the implementation of the guidelines at all levels of the scientific community. This requires commitment and scientific leadership.

Zusammenfassung: Versuchstiere in der Forschung: Kontroverse zwischen Wissenschaft und Gesellschaft? Die europäische Perspektive

In den letzten zwei Jahrzehnten konnte im Forschungsbereich eine deutliche Abnahme der Anzahl Versuchstiere festgestellt werden. Aufgrund des vermehrten Einsatzes von transgenen Mausmodellen steigt diese Zahl jedoch wieder an. Innerhalb der EU-Mitgliedsstaaten werden zurzeit pro Jahr 10-12 Millionen Wirbeltiere in Versuchen eingesetzt. Forscher, die Tierversuche zu Forschungszwecken durchführen, werden von Tierschutzorganisationen häufig kritisiert und beschuldigt, das Leben der Tiere nicht zu respektieren. Die ESF (European Science Foundation) hat erkannt, dass durch die Gesetzgebung alleine die Vorbehalte in der Gesellschaft nicht ausgeräumt werden können und es erforderlich ist, in Bezug auf den Einsatz von Versuchstieren klar Stellung zu beziehen. In einem kürzlich veröffentlichten Positionspapier hat die ESF Richtlinien für den Einsatz von Tieren in der Forschung verabschiedet. Aus diesem Dokument geht klar hervor, dass Labortiere einen Eigenwert besitzen, welcher respektiert werden muss. Die Konsequenzen, die sich aus dieser Erkenntnis ergeben, wurden im Positionspapier herausgearbeitet und schliessen unter anderem den zwingenden Einbezug der 3R Prinzipien (Replacement, Reduction, Refinement) ein. Es wurde festgelegt, dass das Protokoll vor der Durchführung eines Tierversuchs von unabhängigen Experten geprüft werden soll, um den voraussichtlichen Nutzen gegenüber dem Leiden der Tiere abzuwägen. Des Weiteren wird die Durchführung und Organisation anerkannter Kurse in Labortierkunde, einschliesslich Informationen zu Alternativmethoden, Tierschutz und Ethik gefördert. Diese Richtlinien können als Verstärkung einer Entwicklung angesehen werden, welche bereits in verschiedenen Ländern eingesetzt hat, seitens der Forscher jedoch noch nicht voll unterstützt wird. Mit diesem Dokument hat die Vereinigung von 70 führenden nationalen Wissenschaftsorganisationen in Europa eine Position eingenommen, welche in mehreren Bereichen über die Europäische Gesetzgebung hinausgeht. Um den Meinungsstreit zwischen Wissenschaft und Gesellschaft zu entkräften, ist es notwendig, die Umsetzung dieser Richtlinien auf allen Ebenen der Wissenschaftsgemeinschaft voranzutreiben. Dies erfordert Engagement und wissenschaftliche Führung.

Keywords: European Science Foundation, DNA technologies, laboratory animals, alternatives

1 Developments on the use of animals in research

During the 20th century there has been a tremendous increase of activities in the biomedical sciences and, as a consequence, also in the use of animals as a model for man. In the first part of the century the number of animals used for research, testings and education increased gradually, but after World War II, when the biomedical field began to explore several new disciplines, an exponential growth occurred. In the late seventies, in the UK more than 5 million vertebrate animals were used each year, and in the Netherlands about 1.3 million. Since then, in most of the Western countries, animal use started to decrease. Improved quality of the animals and strict legislative regulations have contributed to this decrease. During the past five years this decrease tends to slow down, mainly because of the growing use of transgenic animals. In Figure 1a graphical representation is given on the development of the use of transgenic animals during the last decade in the UK. In the Netherlands, after an increased use of transgenic animals for several years, no further increase was observed in the last two years. It is uncertain how the total use of animals will develop in the next decades. In the future, it may be more effective to study dysfunctions of physiological pathways directly in the

human model. With the development of novel DNA technologies it is possible to capture variation in expression of many genes simultaneously in one microarray (Lander, 1999). With these microarrays it is possible to compare mRNA samples from diseased and healthy tissues and thus to analyse which genes are up-regulated or down-regulated in the diseased tissue. This, in combination with information from proteomic studies, is providing clues as to which genes are involved in the pathophysiology of a particular disease.

At present this development is still in an early stage, but it will soon become a common tool in research laboratories and clinics (Cheung et al., 1999; Somogyi, 1999). Human materials can then be used to study the causative factors for a human disease. There is a great potential here for the reduction of the use of animal as models for the study of the pathophysiological background of human diseases.

On the other hand, these developments will increase the insight into the genetic pathways and the gene-environment interactions that are involved in the etiology of a complex genetic human disorder. This knowledge can be applied to produce transgenic animals or knock-outs (gene targeting in ES cells) which can, better than the presently available models, mimic the physiological complexity of the human system. Therefore, they can serve as more precise models in

the search for new therapies. This would imply a shift in animal use: from models for the identification of causative genes to models for studying the effect of changes in genetic pathways.

The developments in the fields of genomics, proteomics, biotechnology and bioinformatics will drastically change the landscape of biomedical research in the next decades. It is hard to predict what the net results on animal use will be.

At present the world-wide use is estimated to be 100-150 million vertebrates per year. This estimate is based on the extrapolation of data obtained from countries with a long tradition of registering animal use, e.g. the UK, Canada and the Netherlands. In the USA the registration of animal use has been restricted to procedures on primates, dogs, cats, guinea pigs, hamsters, rabbits and some other species but, as yet, the most frequently used animal species, mice and rats, are not covered by the law.

2 Animal experiments and society

Animal experiments have been a subject of criticism as long as animals have been used for research purposes. The first anti-vivisection movement, The Victoria Street Society, was established in 1875 in London. In several other countries similar societies have been founded in the past. The publication of some influential books (Singer, 1975; Regan, 1983) has fueled this movement and some of the societies have become large organisations with international branches and substantial political influence.

The policy of these societies to achieve their goals may differ. Eurogroup for Animal Welfare has its emphasis in the political lobby, whereas RSPCA (Royal Society for the Prevention of Cruelty against Animals) also organises public campaigns and protest demonstrations. ALF (Animal Liberation Front) does not seem to shun raids on laboratories in order to get the issue of animal experimentation on the political agenda.

The activities of the animal protection/anti-vivisection movement have undoubtedly contributed to legislative regulations for the protection of animals

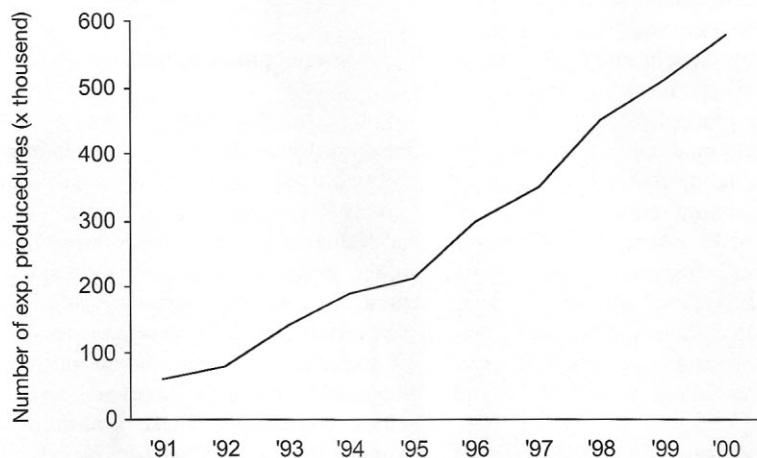


Fig. 1: Development of the use of transgenic animals during the last decade in the UK.

used for experimental purposes. The first law, the Cruelty to Animals Act, was adopted by the UK parliament in 1876. Since then other countries have included into their laws provisions to protect animals used for experimental purposes. However, it took more than a full century before laws specifically dealing with the protection of the experimental animals were adopted in other countries. In the Netherlands the Act on Animal Experiments was adopted by parliament in 1977. At the European level, an important decision was taken by the European Parliament in 1986, when the Council Directive 86/609 was adopted. Each of the EC (EU) Member States was obliged to implement the regulations of the Directive into their national legislative system.

These regulations provide a formal basis for the humane use of animals in research.

3 European Science Foundation

It is recognised by science organisations that it is essential to formulate guidelines for the ethical use of animals. In Europe such guidelines have recently been published by the European Science Foundation (ESF). ESF is an association of major national organisations for science in Europe. Member organisations of the Foundation are 70 leading science-funding agencies, research councils and academies of science, from 23 European countries. Its role is to advance science by stimulating co-operation between national organisations and individual scientists from different countries and to advise on science policy. ESF has published a position paper on the use of animals in research (<http://www.esf.org/articles/3/ESPB9.pdf>). The paper was intended to set out views on conditions that must be met to make the use of animals for research purposes morally acceptable. It is explicitly stated that the paper refers to all vertebrate species (and invertebrates with comparable neurophysiological development). ESF encourages member organisations and individuals involved in animal experimentation to follow the guidelines formulated in the position paper.

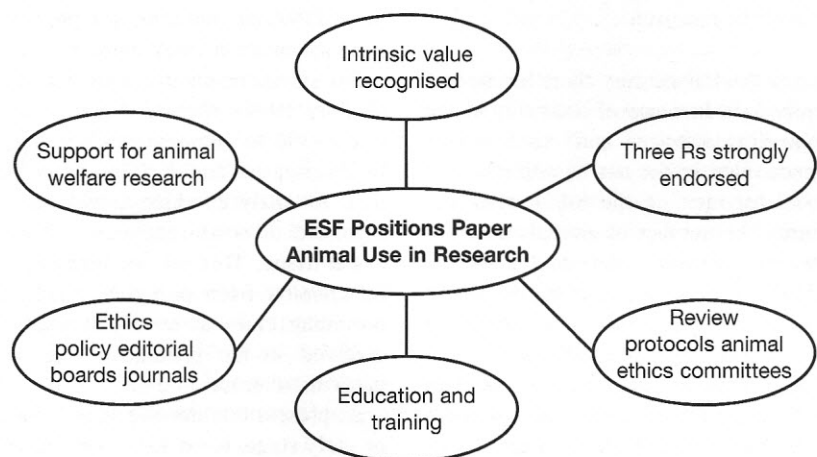


Fig. 2: Guidelines formulated by the ESF (European Science Foundation) in their position paper.

The guidelines can be summarised as follows (see Fig. 2):

- ESF recognises that laboratory animals not only have an instrumental value, but also an intrinsic value (value in themselves) which must be respected.
- While accepting the need for animals to be used to advance scientific knowledge and to promote human and animal health and well-being, ESF strongly endorses the *reduction, replacement and refinement* principles (Three Rs, Russell and Burch, 1959).
- Prior to the performance of a programme of research, the proposed animal use should be subjected to independent expert review, for both scientific and animal welfare considerations. The assessment and weighing of the likely benefit and likely animal suffering should be an essential part of the review process.
- Investigators and other personnel involved in the design and performance of animal-based experiments should be adequately educated and trained. ESF member organisations should encourage the development and organisation of accredited courses on laboratory animal science, including information on alternatives, animal welfare and ethics.
- ESF encourages the editorial board of journals publishing the results of animal-based research to include in the "instruction to authors" a policy state-

ment on the ethical use of animals.

- Research to improve the welfare of animals should be encouraged and actively supported by ESF member organisations.

It is, undoubtedly, a significant step forward, that the leading science organisations in Europe have agreed on these guidelines. For implementation, the evaluation of protocols by animal ethics committees and the education and training of persons involved in animal experiments are of particular importance.

In the following paragraphs information on the requirements and the developments regarding these issues in Europe will be presented.

4 Animal ethics committees

So far, only a limited number of European countries have included into their national law the requirement that protocols for animal experiments must be evaluated by an animal ethics committee prior to conducting the experiment. In Sweden, Germany and the Netherlands, it is not permitted to start an experiment if there is no positive judgement from a local/regional animal ethics committee. These committees evaluate the research protocol on ethical and animal welfare aspects. It is not permitted to perform the experiment if, according to the judgement of the

committee, the likely benefit does not outweigh the likely suffering of the animal(s).

In Finland, local committees on animal experimentation have the task to decide on the degree of suffering involved in the experiment. If it is estimated that the experiments might cause severe suffering, the committee is not allowed to give a license, but must send the application to the Provincial State Office that has the authority to grant a license for such experiments.

In Switzerland, any experiment with animals is subject to authorisation by the cantonal authorities. Each canton appoints a committee of specialists for animal experiments that examines the proposals and advises to the authority entitled to authorise the experiment. The advice should cover the supervision of the housing of the experimental animals and the experimental procedures.

In the UK, licenses are granted by the Home Office. The Secretary of State requires that all designated establishments have a viable ethical review process in place. There is no specific section in the law requiring that a protocol be submitted to a (local) animal ethics committee. This is also not the case in several other European countries, e.g., France, Italy, and Norway. This, however, does not mean that there is no ethical evaluation prior to the carrying out of experiments in those countries. In the UK, there are over 250 local animal ethics committees, whereas in France many institutions have also set up their own committees.

The main task of animal ethics committees is to evaluate whether the benefit of the research outweighs the suffering of the animals. But these committees also play an important role in the implementation of the Three Rs. In order to promote the implementation of the Three Rs through the ethical review of protocols, it is a prerequisite that the committee members are unbiased and competent. Most animal ethics committees are composed of persons with different expertise with respect to animal experimentation. Often laypersons or persons from outside the research institute are also members of the committee.

Other aspects that must be assessed are the origin of the animals and their housing and care, but also the competence of the persons involved in the experiment.

5 Education and training

Persons involved in the design and execution of animal experiments must be specifically educated and adequately trained. This is essential, both for the quality of experiments and for the welfare of animals. There are several sections dealing with competence in Directive 86/609/EEC:

- Art 7.1. Experiments shall be performed solely by competent authorised persons, or under the direct responsibility of such a person.
- Art 14. Persons who carry out experiments or take part in them, and persons who take care of animals used for experiments, including duties of supervisory nature, shall have appropriate education and training. In particular, persons carrying out or supervising the conduct of experiments shall have received instruction in a scientific discipline relevant to the experimental work being undertaken and be capable of handling and taking care of laboratory animals; they shall also have satisfied the authority that they have attained a level of training sufficient for carrying out their tasks.
- Art 19 b, d. In each user establishment sufficient trained staff shall be provided. A veterinarian or other competent person shall be charged with advisory duties in relation to the well being of the animals.

The provisions for education and training in national laws of EU Member States must be in line with Directive 86/609/EEC. There is, however, a problem here. Although the objectives of the provisions on competence, as formulated in the Directive, are clear, there is still much room for interpretation when it comes to practical implementation. In an attempt to harmonise the requirements for education and training at the European level, the Council of Europe (CoE, 1994), in collaboration with the Federation of European Laboratory Animal

Science Associations (FELASA, 1995), has worked out the provisions in more detail. Four categories of persons requiring appropriate education and training are distinguished: persons taking care of animals (Category A), persons carrying out procedures (Category B), persons responsible for directing or designing animal experiments (Category C) and laboratory animal specialists (Category D).

According to FELASA priority should be given to the education and training of persons in Category C, young scientist intending to continue a research career involving the use of animals.

In most EU countries, national laws on animal experimentation now contain a section on competence. Despite the programme outlines as recommended by CoE (1994) and FELASA (1995), specific requirements still differ between countries. For instance, for the persons belonging to Category C, most countries require an academic degree in biology, medicine or veterinary medicine, but in some countries (e.g. UK, Portugal, Ireland and Denmark) the degree is not specified. Also, the recommended basic course in laboratory animal science of at least 80 hours has not yet been implemented in all EU Member States. In Sweden, Denmark, Finland, France, the Netherlands and the UK, such a course has been made mandatory by law, but the length of the course varies (1-3 weeks). In other countries, like Belgium, Spain and Germany, courses are organised at several universities, although such a course has not been made mandatory by law (for details on the differences in legal requirements, see Van Zutphen, 1997).

There is a need for harmonisation in this respect, not only because the diversity that presently exists hampers the free exchange of scientists between Member States, but also because harmonisation with respect to the Council of Europe and FELASA guidelines, will have a positive effect on the welfare of animals (Van Zutphen and Blom, 2000).

6 Conclusions

After a sharp decrease during the last decades of the 20th century, the use of

animals for research purposes is increasing again, mainly due to the increased use of transgenic animals. It is, as yet, uncertain how animal use will develop in the future. But, whatever the numbers, it is of utmost importance that the scientific community be pro-active in implementing the ethical standards that must be met when the use of animals is inevitable. The Position Paper on the use of animals, as published by the European Science Foundation, provides the scientist with guidance. Adoption of the ESF guidelines should provide benefits for both animals and science and may contribute to overcome the science – society controversy.

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