

# Trends in Animal Use and Animal Alternatives

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**Summary** — The Third World Congress (1999, Bologna) celebrated the fortieth anniversary of the publication of Russell & Burch's *The Principles of Humane Experimental Technique*. There was the general notion that the Three Rs offer a unifying concept that contributes to a progressive reduction and refinement in animal use without compromising the quality of research, human health or the protection of the environment. The Bologna Three Rs Declaration was accepted unanimously, calling upon all parties involved to incorporate the Three Rs into animal-based research. The question is raised, what progress has been made and, in particular, what are the developments in animal use and in the implementation of validated alternative methods. For the present contribution, we requested colleagues from European countries, Canada and the United States to provide information on the numbers of animals currently used for scientific purposes, on the development and implementation of alternative methods and on future perspectives about the issues. Based on the results of this survey, the conclusion is reached that legislative regulations are widely implemented and have become rather strict during the last decade. An exception here is the legislative regulation for rats, mice and birds in the USA. These species are not (yet) protected by the US *Animal Welfare Act*. The number of animals used has decreased considerably, and the review of protocols by animal ethics committees has become a significant trend. In all countries, there is growing support for the Three Rs concept.

**Key words:** legislation, protocols, statistics, Three Rs.

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## Introduction

The Three Rs concept of Russell & Burch (1) has served as a guiding principle for each of the previous World Congresses on Alternatives and Animal Use in the Life Sciences (Baltimore, 1993; Utrecht, 1996; Bologna, 1999). At the Third World Congress, when celebrating the fortieth anniversary of Russell & Burch's book, *The Principles of Humane Experimental Technique*, the participants unanimously adopted a declaration on the Three Rs, and called upon all parties involved to fully support the Three Rs and to incorporate these principles, wherever possible, into daily practice of animal-based research.

In order to investigate the progress that has been made during the last decade, and to obtain information about trends on the use of animals and on the implementation of animal alternatives, we have contacted colleagues from several European countries, from Canada and from the USA, and have requested information on developments of legislation, animal use and ethical review of animal research, and on the implementation of animal alternatives. Based on the interviews, an overview of the developments in the fields is presented. In this overview, the emphasis is on the situation in

Europe and, where appropriate, some references are made to the situation in Canada and the USA.

## Legislation

The use of animals for experiments has always been a matter of great concern in society. From the eighteenth century onward, people have argued against the use of animals for experiments for ethical reasons. The general public in the United Kingdom took the lead; in 1875, the first anti-vivisection organisation (the Victoria Street Society) was established and, as a result of a long debate between scientists and animal protectionists, in 1876, the first law on the protection of animals, the *Cruelty to Animals Act*, was introduced. The 1876 Act required researchers to register the number of animals and the purposes for which animals were to be used. Thus, rather accurate data are available from the UK, as far as the development of animal use is concerned.

In the twentieth century, the development of several biomedical disciplines such as microbiology, toxicology, virology, immunology and, in particular, pharmacology, caused a rapid increase of animal usage. This increase, in particular after World War

II, has been the impetus for politicians to prepare legislation as to the use of animals in research.

In Europe, there are two main legislative documents controlling the use of animals for experimental purposes:

- the Convention for the Protection of Vertebrate Animals used for Experimental Purposes (*Convention ETS 123*), issued in 1986 by the Council of Europe (CoE; 2), and
- the Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, *Directive 86/609/EEC*, issued in 1986 by the European Commission (3). The aim of the Convention and the Directive is to protect animals by defining the legitimate purposes for which animal experiments are allowed to be performed, and by setting requirements for the welfare of the animals, including the competence of persons involved in animal experiments and the collection of statistical data.

The CoE (44 Member States) must be distinguished from the European Union (EU; 15 Member States), which was originally created in 1957, as the European Economic Community (EEC). The CoE was set up in 1949, to enable the governments of European States to achieve a greater unity between its Member States for the purpose of safeguarding and realising the ideals and principles that are their common heritage, whilst facilitating their economic and social progress. Among its tools for achieving its objectives are Conventions between Member States. These treaties become binding only if signed and ratified by a Member State.

The text of *Directive 86/609/EEC* is similar to that of CoE *Convention ETS 123*, although some of its regulations are stricter. Member States of the EU are bound to implement the provisions of the Directive via their national legislation. The Directive had to be implemented by 24 November 1989. Because of its strong legislative impact, in this contribution, reference will be made to the Directive.

The Treaty of Rome, which was the basis in 1957 for founding the EU, defines animals as agricultural goods. For a long time, animal welfare groups opposed this definition, but it lasted until 1997, when in the Treaty of Amsterdam, the leaders of the EU agreed upon the following text:

*The High Contracting Parties, desiring to ensure improved protection and respect for the welfare of animals as sentient beings, have agreed upon the following provision, which shall be annexed 'In formulating and implementing the Community's agriculture, transport, internal market and research policies, the Community and the Member States*

*shall pay full regard to the welfare requirements of animals, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage'.*

The impact of this protocol is that it created the legal obligation for Member States to pay full regard to the welfare of animals as *sentient beings*. This is entirely in line with the obligations of the Directive.

The Directive provides for minimum requirements: Member States may go further, depending on the national situation, such as:

- According to the Directive, *an animal . . . means any live non-human vertebrate . . .* However, in a few Member States, invertebrate animals can also be legally protected, if the neurophysiological development has reached the level that a similar protection is justified; e.g. in the UK, *Octopus vulgaris* is also covered by the *Animals (Scientific Procedures) Act 1986*.
- Animals maintained for experiments, but killed without any previous intervention for scientific purposes, are not considered to be experimental animals, and are therefore not covered by the Directive. However, in several Member States, these animals are also covered by the national legislation; e.g. in Sweden, all use of animals that have a scientific purpose must be recorded. Therefore, the statistical data include all animals used for behavioural studies or feeding trials or animals being euthanised for the use of their tissues and organs. During 2000, about 114,000 animals were reported according to this definition.
- In the UK and in The Netherlands, the use of great apes for experiments is not allowed.

In some countries, the legal standing of animals has been discussed extensively. Recently, Germany has incorporated the protection of animals into the German constitution, the so-called Basic Law for the Federal Republic of Germany:

*The state, also in its responsibility for future generations, protects the natural foundations of life and the animals in the framework of the constitutional order, by legislation and according to law and justice, by executive and judiciary.*

On 21 June 2002, after a debate, the Bundesrat adopted the bill.

The Directive was prepared and adopted in the 1980s. Since then, both science and views on animal welfare have progressed significantly. Therefore, several provisions should be adjusted on the basis of new insights and experiences.

In 2000, the EU Member States decided to start an in-depth revision of the Directive. The following topics are examples that are being considered:

- animals killed for tissue and organs;
- provisions concerning competence;
- the use of non-human primates, dogs and cats;
- the use of transgenic animals and cloning; and
- the ethical review of protocols.

Not only governmental agencies, but also scientific organisations, animal welfare groups and industry are involved in the revision process, resulting in a considerable increase of accountability. Indeed, the revised Directive will provide for a stricter legislative framework that will certainly benefit the welfare of experimental animals. It is anticipated that the revision of the Directive will be finished by the end of 2003.

In Canada, the protection of laboratory animals is a matter of provincial jurisdiction. Since 1968, the Canadian Council of Animal Care (CCAC) has been the national organisation overseeing the care and use of animals for research, testing and teaching.

Since there is no federal legislation, the CCAC adopted a multi-faceted strategy to ensure the universal implementation of its programme on the care and use of animals in science. Consistent efforts on the part of the CCAC and its allies resulted in reference now being made to CCAC standards in the regulations to the acts in five of the six provinces that have enacted provisions to the use of animals for experimental or other scientific purposes. The sixth province, Ontario, has its own inspectorate system and works in close collaboration with the CCAC.

The two major federal granting organisations, the Canadian Institutes of Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC), are among the founding members of the CCAC, and they have an explicit policy, enforced since 1982, making it mandatory for all applicants to participate in the CCAC programme to be eligible for the agencies' funding.

In addition, in January 2002, the agencies began asking all institutions to sign a Memorandum of Understanding as a necessary condition for eligibility for their funding. While participation in the CCAC programme is voluntary for governmental laboratories, the five federal departments using animals for regulatory testing are represented on the CCAC Council and enforce the participation of all their units in the programme.

In the USA, animals used for scientific purposes are protected by the 1985 Amendment of the *Animal Welfare Act* (AWA). The United States Department of Agriculture (USDA) is charged with enforcing the AWA. The laws governing animal use are federal,

and there are no state laws regarding animal research oversight. Some states, however, are beginning to adopt legislation that requires institutions to use available alternatives.

In addition, all research institutions that receive federal funding must follow National Institutes of Health (NIH) Public Health Service (PHS) policy on humane care and use of laboratory animals. The policy requires that institutions follow the *Guide for the Care and Use of Laboratory Animals* and that they establish an Institutional Animal Care and Use Committee (IACUC). These NIH guidelines apply to more than half of the facilities using laboratory animals.

In contrast to the NIH guidelines, rats, mice and birds are not covered by the AWA. The system of government oversight of animal research is largely one of self-regulation. However, those facilities that use only rats, mice and birds and do receive federal funding, have no obligation to register with the government, and therefore will have no oversight at all.

Animal welfare organisations are opposing this aspect of the existing legislation. The exclusion of rats, mice and birds is considered a serious deficiency, and in 2000, the Alternatives Research and Development Foundation (ARDF) filed a lawsuit against the US Department of Agriculture (USDA) to try to force it to regulate the use of rats, mice and birds. It could be expected that, in the event of a positive decision of the court, the USDA would have to immediately extend the coverage under existing standards to rats, mice and birds, with no opportunity for input of any kind from the research community and other interested parties. Because such a rapid change was considered as counter-productive, the ARDF and the USDA reached the agreement that the USDA would initiate and complete, in a reasonable time, a regulation on rats, mice and birds, and would keep the ARDF informed about the current procedural status of the rulemaking process.

However, in 2001, the biomedical research community, with the help of Senator Helms, successfully persuaded Congress to continue the exclusion of rats, mice and birds from the AWA. At the same time, however, the Institute of Laboratory Animal Research (ILAR) was asked to perform a study on the implications of including rats, mice and birds in the AWA. Topics such as regulatory burden and the possibility of shifting responsibility for laboratory animal protection from the USDA to the NIH are also part of the study. Although, as far as the research community is concerned, the discussion is closed, the animal welfare groups continue to pressure Congress for the inclusion of rats, mice and birds in the AWA.

## Numbers of Animals Used

Many scientists feel that collecting data on animal use for scientific purposes is not only time-consum-

ing, but is also a waste of money — money that could better be used for scientific purposes. However, statistics are essential, because they provide the basis for a sound discussion on the use of animals in experiments (e.g. what proportion is really used for cosmetics testing or for safety testing of chemicals). Statistical data not only assist in understanding where and how animals are used, but also give information on trends, e.g. in the field of development of alternatives. Furthermore, with the help of statistics, the effects of alternative methods can be monitored.

According to the Directive, EU Member States have to collect and, as far possible, make publicly available, the statistical information on the use of animals with respect to:

- the total number of animals of each species used in experiments;
- the number of animals, in selected categories, used for selected purposes; and
- the number of animals, in selected categories, used in tests that are required by legislation.

In 1995, the European Commission issued the first report to the European Parliament and to the Council of Europe on the numbers of animals used for experimental and other scientific purposes. For some of the Member States, nation-wide collection of the statistics was an unprecedented exercise; therefore, data from a few Member States were lacking. Further, among the data received, there was lack of uniformity. It was not possible to draw firm conclusions from the 1995 inventory. This first report should be considered as a very first step in the process of monitoring trends in animal use in Europe.

Reports on statistics must be made available to the Council of Europe and the European Parliament at intervals not exceeding three years. In 1999, the European Commission issued the second report. This report contained the statistics for the year 1996. It indicated that 11.6 million animals were used in that year. However, again, no firm conclusions could be drawn.

In 1997, after eight years of negotiations, the Member States had reached an agreement on the data to be collected. These so-called EU Tables provided insight into the species used, as well as into information on the purposes. For example, for safety testing of substances, it has to be indicated which tests have been used, such as LD50, LC50, acute and sub-acute toxicity testing, skin irritation, skin sensitisation, eye irritation, subchronic and chronic toxicity, developmental toxicity, mutagenicity or reproductive toxicity. Also, data on the number of animals that have been re-used have to be collected. With the help of the EU Tables, the Member States have collected the data on animal

experiments performed in 1999. The data show that, in total, 11.9 million animals were used for scientific purposes, which is close to the 11.6 million of 1996. However, the 1999 report includes more countries and more-accurate numbers. The main reason why the total numbers of 1996 and of 1999 are about the same is that animal use has been substantially decreased between 1996 and 1999.

In Belgium, Finland and Greece, since 1996, the number of animals used decreased by nearly 50%. In Spain, Italy, The Netherlands and Sweden, the reduction was 5–15%. Only in Ireland was there a slight increase of the number of animals used (7%).

Currently, the report is due to be adopted by the European Commission. One of the reasons why it takes a considerable time before such a report can be published is that it has to be translated into the 11 languages of the European Union. This time-consuming procedure is under discussion now, because in the near future, the EU will be expanded by more than ten Member States.

From the data so far available, it can be concluded that, in most European countries, the use of transgenic animals is still increasing. The information obtained from Sweden, however, indicates that the use of more-sophisticated biotechnological methods will subsequently lead to a decrease in animal use. This is in line with the latest data from the UK. The data for 2001, as recently published by the Home Office, show the smallest rise in ten years for the number of genetically defected or genetically modified animals, namely, 5%.

There is great concern among animal protection groups about the White Paper, *Strategy for a Future Chemicals Policy*, the basis for a new EU Chemicals Policy (4). The main objective of this policy is to ensure a high level of protection for human health and the environment, while ensuring the efficient functioning of the internal market and protecting the competitiveness of the EU chemical industry. However, this policy might cause a substantial increase of the number of animals to be used for the further testing of some 30,000 chemicals that are currently in use in the EU.

In an editorial in *ATLA*, Robert Combes (5) wrote:

*It is true that [the White Paper] is based on a logical policy that all chemicals (both new and existing) should be subjected to the same stringency of safety assessment. However, those who devised the strategy failed to take sufficient account of animal welfare considerations under current EU legislation. Many thousands of laboratory animals will be sacrificed to test chemicals that have proved to be safe in use over a considerable time.*

All parties involved have agreed that animal numbers should be minimised as far as possible. Although the need to use alternatives is promoted in the White Paper, the report does not define a

strategy to facilitate this process. It is the obligation and the duty of the European Commission to fund the research required to develop alternative methods.

The European Centre for the Validation of Alternative Methods (ECVAM) plays an advisory role in the formulation of the new policy. In order to help ECVAM in this role, a *Working Group on Chemicals* has been established, with the task of proposing a way forward for the application of existing alternative methods and to identify those methods that have potential for use, once they have been evaluated. In his editorial, Combes (5) expresses his hope that “the scheme being prepared by the ECVAM working group will provide an effective means of obtaining the required information by acting as a relevant and reliable alternative to unscientific, animal-based, check-box approaches to toxicity testing”.

Based on the information obtained from Canada and the USA, the major trend in both countries is a reduction in the total number of animals used. In Canada, between 1980 and 1999, a downward trend was observed in the use of dogs, cats, primates, rabbits, hamsters and rats, whereas an upward trend was observed for guinea-pigs, mice, fish and birds. The 1999 total number of animals used in Canada was reported to be 1,746,606.

In the USA, the data about animals used in research are collected by the USDA under the AWA. The 1999 total number of animals used in the USA was reported to be 1,217,998. However, since rats, mice and birds are not included, the figures reflect probably less than 10% of all the animals used for research. Although the total number of animals continues to decline, there are also exceptions: the use of transgenic animals continues to grow. Also the number of non-human primates being used for safety testing is not decreasing and may even increase in the years to come, due to the need to test new drugs and/or vaccines produced through biotechnological procedures.

## Review of Protocols and Implementation of the Three Rs

In Europe, the review of protocols on animal-based research is becoming the main trend, not as an absolute value, but as a way to improve enforcement of the Three Rs. A survey of the European Science Foundation, performed in 2000, showed that many European countries have now introduced a system for the ethical evaluation of protocols. Through this evaluation, the question of the purpose of an experiment and its justification are addressed. Either a governmental authority or an institutional committee is charged with the task of assessing the proposed benefits against the likely degree of animal suffering.

In Canada, the CCAC has provided guidelines for the review of protocols by the Animal Care Committees. According to the CCAC, the Animal Care Committees are in the best position to develop their own processes, so that the system is most appropriate for each of the individual institutions. In the USA, the PHS policy and the AWA require the existence of an IACUC. These committees review proposals for animal studies, to ensure the humane use and care of the animals.

Based on the information obtained from the interviews, we can conclude that there is growing support for the Three Rs concept. However, the question remains whether it is just verbal support. Indeed, there is little funding available when compared with the amount of money spent on animal research overall.

In the EU Directive, the Three Rs concept has been formulated in article 23:

*Member States are obliged to encourage research into the development and validation of alternative techniques that involve fewer animals or that entail less painful procedures. They shall take other steps as they consider appropriate to encourage work in this field and shall take all steps as they consider appropriate to encourage work in this field.*

In October 1991, the European Commission responded to this article by means of the establishment of ECVAM. The mission of ECVAM is to play a leading role, at the European level, in the in-depth evaluation of the relevance and reliability of proposed new tests for specific purposes, through research on these methods and through validation studies.

In the past decades, several EU Member States have also established a national institution dedicated to the development of alternative methods. At the moment, there is a network of centres in the EU, with ECVAM as the coordinating body. The achievements of ECVAM include:

- the establishment of guidelines for prevalidation and validation procedures in agreement with named experts;
- several successful prevalidation/validation studies;
- six ECVAM Scientific Advisory Committee (ESAC) statements in the area of biologicals and ten in the area of toxicology;
- three *in vitro* methods have been accepted at the OECD level;
- the organisation of more than 50 workshops on animal alternatives; the results of 46 of these

workshops have already been published in *ATLA*; and

- the organisation of the 3rd World Congress (Bologna, 1999).

It can be concluded that ECVAM has been successful in promoting the implementation of the Three Rs and, in particular, in the validation of non-animal alternatives. This has had a substantial impact on the use of laboratory animals. However, the activities have also made clear that the validation and implementation of animal alternatives can be tedious and time-consuming.

According to the Convention and the Directive, “An experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought not entailing the use of an animal, is reasonable and practicably available”. In 1997, ECVAM organised a workshop on alternatives to the *in vivo* production of monoclonal antibodies. The conclusions resulted in a guideline, which was published in ECVAM workshop report 23 (6). The guideline indicates that, since sophisticated *in vitro* techniques such as the Techno-mouse are available, the *in vivo* production of monoclonal antibodies should be replaced by the *in vitro* methods. However, some of the EU Member States do not accept the guideline, despite the fact that the ESAC has stated that, now that scientifically validated *in vitro* methods are reasonably and practicably available, the *in vivo* production can no longer be justified and should cease. Nonetheless, at present there are a few countries where the *in vivo* production of monoclonal antibodies is prohibited.

Recently, the initiative has been taken to establish the European Consensus Platform on Alternatives (ECOPA). Its aims are:

- to facilitate the exchange of scientific information, expertise and experience between national platforms;
- to enhance further development and implementation of Three R methods in the EU and worldwide; and
- to raise public, governmental and scientific awareness for a better acceptance of alternative methods.

ECOPA is based on national consensus platforms that consist of the representatives of the four major stakeholders — academia, animal welfare, industry and government — and is therefore well-positioned to give well-founded statements on alternatives. This certainly will facilitate the acceptance of validated animal alternatives.

Another important step forward is that the European Science Foundation (ESF) strongly endorses the principles of the Three Rs. The ESF is a non-governmental association of 67 leading science-funding agencies from 23 European countries. Its role is advancing cooperation in research in Europe and providing advice on science policy matters.

In a position paper published in September 2000 (7), the ESF sets out its view and argues that it is essential that ESF Member Organisations adopt guidelines for the ethical use of animals in research. This ESF publication contains a few epoch-making statements:

- *The ESF recognises that laboratory animals not only have instrumental value but also an intrinsic value in themselves, which must be respected. Animals should always be treated as sentient creatures.*
- *Prior to the performance of a programme of research, animal use should be subjected to independent expert review for both scientific and welfare considerations.*
- *Investigators and other personnel involved in the design and performance of animal-based research should be adequately educated and trained. Member organisations are urged to organise courses on laboratory animal science. These courses should provide information on animal alternatives, welfare and ethics.*

Not only in Europe, but also in Canada and the USA, support for the Three Rs as guiding principles for animal-based research is growing. In Canada, some institutions, such as Health Canada, have begun to make substantial investments in this field. An example is the work on developing humane endpoints for animals used in potency testing. In Canada, there is no ban on the use of animals for the production of monoclonal antibodies. However, any proposed production of monoclonal antibodies by using the ascites method requires justification of an Animal Care Committee.

In the USA, progress has been made in the acceptance of the Three Rs. Most scientists no longer scoff at the words refinement, reduction and replacement. Due to the efforts of organisations like the Humane Society of the United States, the ARDF and the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), the Three Rs are increasingly being accepted by the biomedical science community. CAAT was founded in 1981, “to be a leading force in the development and use of reduction, refinement and replacement alternatives in research, testing and education to protect and to enhance the health of the public”. CAAT serves as a forum among diverse groups, leading to creative approaches to

facilitate acceptance and implementation of alternatives, and it provides reliable information on the science philosophy and public policy of alternatives to academia, government, industry and the general public.

In contrast to the situation in Europe, US law only requires the *consideration* of alternatives — not the use of these methods. The US government has founded the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The main task of ICCVAM is to validate alternative methods rather than developing alternatives to animal use. Milestones, as mentioned in the interview, are that the NIH is urging institutions to use *in vitro* methods for monoclonal antibodies, and that the National Toxicology Program has announced that three federal agencies have accepted an *in vitro* test (CORROSITEX®) as a replacement for the use of animals in skin corrosivity and dermal irritation testing.

## Conclusions

- Legislative regulations as to the protection of animals used in research are widely implemented and have become stricter during recent decades.
- During recent decades, the number of animals used has decreased considerably, while formalisation of the (ethical) review process has become a significant trend.
- Worldwide, there is growing support for the Three Rs concept; whether or not it is more than just verbal support remains to be answered in the years to come.

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