Use of animals in research

New Rules for Europe

A European Union directive on animal experiments is currently being revised. Scientists, pharmaceutical industry and animal welfare groups lobby fiercely for their point of view.

The European Union (EU) is currently revising a directive, which regulates the protection of animals used for experimental and other scientific purposes. EU directive 86/609/EEC, which dates back to 1986, is aimed at standardising animal welfare in research labs across Europe. In March, the Committee on Agriculture and Rural Development of the European Parliament voted on 524 amendments to the directive; 161 amendments were adopted. With its decisions, the Agriculture Committee intended to limit animal testing without hampering scientific progress. Members of the European Parliament (MEPs) voted for regulations that would ensure planned tests were subjected to compulsory ethical assessment, to take account of the public's concerns. The use of animals in scientific procedures should only be considered where a non-animal alternative is not available, the final report of the Agriculture Committee suggests.

Testing on great apes banned

Around twelve million animals are used for scientific research in the EU every year. Approximately ten thousand of these are non-human primates (NHPs). Two-thirds of NHPs are used to test the safety and efficacy of pharmaceutical products and devices. The remaining third is used for fundamental biological studies and for research and development in dentistry, human and veterinary medicine.

With their recent decisions, MEPs endorsed a ban on the use of great apes (chimpanzees, bonobos, gorillas and orang-utans), except for experiments intended to conserve these species. In the EU, testing on great apes is already banned in Austria, Great Britain, The Netherlands and Sweden. Additionally, such testing has not been carried out in the EU since 2002. Therefore, the ban does not greatly affect current research.

Tests on other species of non-human primates allowed

The European Commission and the Council of the Union initially intended "to reduce the use of non-human primates to an absolute minimum" by introducing very restrictive measures. However, MEPs decided that tests using other species of NHPs, other than great apes, should not be restricted to "life-threatening or debilitating" conditions. This would seriously hinder research into some forms of cancer, multiple sclerosis and Alzheimer's disease. Moreover, European and international guidelines require that some drugs be tested on primates before they are approved. Therefore, tests using these animals should be allowed in medical research as a whole. In this respect, MEPs followed the opinions of scientists, the pharmaceutical industry and medical research charities.

Total replacement of non-human primates unlikely in the near future

The Scientific Committee on Health and Environmental Risks (SCHER), an advisory Committee of the European Commission, published a detailed report this year on "The need for non-human primates in biomedical research, production and testing of products and devices". The SCHER points out in its analysis that animal safety testing of pharmaceuticals is intended to safeguard patients through risk assessment. The report says that NHPs are currently only used in circumstances where no alternative methods are available and no other species may suffice for the purposes of the research.

In some cases, NHPs are the best available model for humans due to close similarities in physiology and anatomy, the SCHER explains. The full embryopathic potential of lenalidomide, for example, became evident in monkeys but not in rodents or rabbits. Lenalidomide is a derivative of thalidomide (trade name Contergan) and was recently approved for the treatment of multiple myeloma. As a result of these tests, specific measures need to be taken if lenalidomide is to be given to women of child-bearing potential. NHPs have also been used for safety assessment during the development of Xolair, a humanised recombinant antibody to treat severe asthma and during the development of Lucentis, an antibody injected into the eye to prevent neovascular age-related macula degeneration.

In the fields of HIV/AIDS, malaria and Hepatitis C research, NHPs are the only susceptible animals. They are, therefore, used to study these diseases and to develop safe and effective vaccines and therapies. Before starting clinical trials in humans, studies on

the efficacy and safety of such vaccines in a relevant surrogate species, such as NHPs, will remain necessary, the SCHER states.

In the neurosciences, NHPs currently provide the only model besides humans to systematically study the relationships between the activity of a single nerve cell and higher cognitive functions. Due to the large evolutionary distance between humans and rodents, the study of neurotransmitters and related molecules at the level of the entire brain requires research on NHPs. A model of Parkinson's disease in NHPs has been highly valuable in studying its pathophysiology and led to the therapy of deep-brain stimulation. Stem cell technologies to repair brain tissue of patients with Parkinson's or Huntington's Disease, after stroke, spinal cord or brain injuries, are currently being developed but will likely require safety and efficacy testing in NHPs, the report remarks.

The SCHER recognises that there are promising developments that have replaced NHP use including genetically altered animals. However, replacing animals in medical research is a long and difficult process. "Application of *in vitro* or *in silico* methods is often not yet feasible due to highly complex systems and limited knowledge of basic biology and pathophysiology," the report says. The SCHER concludes that the total replacement of NHPs in many areas of use, either by other animal species or by non-animal methods, is unlikely to be achieved in the foreseeable future.

The SCHER recommends applying the "Three R concept" of replacement, reduction and refinement. Research into areas that advance replacement, reduction and refinement in the use of NHPs in scientific procedures should be promoted, the SCHER suggests.

Efforts to develop non-animal methods

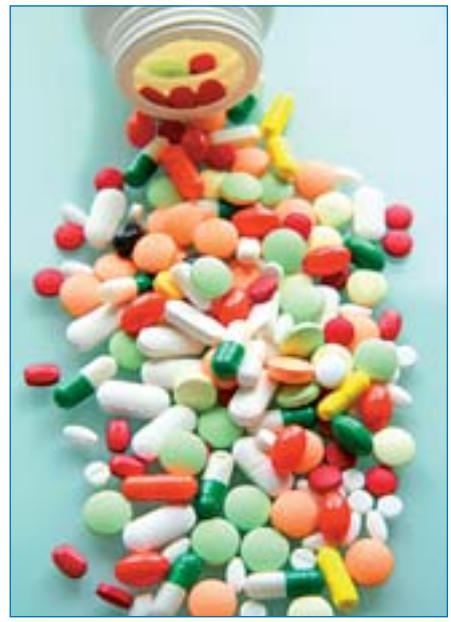
Accordingly, MEPs suggested that the "European Centre for the Validation of Alternative Methods (ECVAM)" should co-ordinate and promote the development and use of methods that can replace animal testing. The Commission and the Member States should provide material support. In 2005, the European Commission and industry already set up the "European Partnership for Alternative Approaches to Animal Testing" to promote the development of the new "Three R" methods as alternative approaches to the use of animals in safety assessment.

Re-use of animals and authorisations required

The Agriculture Committee also adopted amendments to clarify the text for the legislation, giving definitions for the three categories of pain inflicted during a test ("up to mild", "moderate" or "severe"). MEPs suggested the re-use of animals, if the pain inflicted during a test is not only "up to mild" but "moderate". The latter category of tests includes blood tests and implants under anaesthetic. With their proposal, MEPs intend to reduce the number of animals used for research purposes. They also want the prior authorisations required for animal tests to be limited to projects where the pain would be "severe" or to those carried out on primates.

Feasibility studies before animal captures are halted

MEPs supported the goal to end the capturing of wild animals for research purposes. However, so far it is unclear, whether there can be a sufficient supply of second-generation specimens born in laboratories. Therefore, they recommended feasibility studies and a transition period of ten years.



European guidelines require that some drugs be tested on primates.

Fish and amphibian eggs not to be covered by the directive

Lastly, they do not want the directive to cover larval forms and embryonic or foetal forms other than mammals. The final report by the Agriculture Committee gives the following explanation: "Some fish and amphibian species produce vast numbers (more than ten thousand per female) of larval or embryonic forms. To record such numbers would entail a vast amount of work and make the statistics on the numbers of animals used meaningless for these species."

Complacency, cowardice and a setback for animal protection

The revision of EU directive 86/609/EEC is accompanied by intense lobbying from the bioscience sector and animal welfare groups. The Dr Hawden Trust, a UK-based charity which funds non-animal techniques to replace animal experiments, said it was shocked at the complacency and cowardice of MEPs who have so easily allowed dishonest industry tactics to ambush what should have been Europe's chance to make its animal research laws respectable and progressive. The only saving grace of the vote was support for the creation of new EU and member state facilities to develop more alternatives to animal experiments, as the Dr Hawden Trust remarked on the website *www.politics.co.uk*.

Animal Defenders International claims that the amendments accepted by the Agriculture Committee would end authorisation and licensing of the majority of animal research and would allow animals to suffer severe and prolonged pain. Additionally, the Agriculture Committee's vote would allow the almost unlimited re-use of animals in all but a handful of experiments. The aim to stop the trapping of wild monkeys would be delayed indefinitely and the scientific justification needed to experiment on monkeys would be reduced. "Some measures could set animal protection back decades," Animal Defenders International judged.

An acceptable compromise?

Brian Ager, Director General of the European Federation of Pharmaceutical Industries and Associations commented on the Agriculture Committee's vote, "We consider this as a step towards striking the balance between the protection of laboratory animals, biomedical research reality and patients' needs."

Understanding Animal Research, a London-based advocacy group, acknowledges on its website that many of the amendments proposed by the Agriculture Committee address the concerns of the UK bioscience sector "...at this stage, the consensus from the scientific community is that the report is balanced and an acceptable compromise. If adopted, it will significantly improve the Directive originally proposed by the Commission." The group calls on scientists to contact their MEPs to ask them to support the Agriculture Committee's report in the forthcoming vote of the European Parliament on the revised directive in May.

However, some points of controversy remain. The Agriculture Committee's report emphasises that the issue of data sharing and duplication of animal tests must be addressed. Data from animal tests should be shared, wherever possible. "This is a contentious area, however, the industry cannot hide behind their intellectual property, whilst animals needlessly face experiments," the report says. Representatives of the UK bioscience sector argued that mandatory data-sharing proposals failed to recognise the technical and legal difficulties involved, the existing initiatives to avoid unnecessary duplication of animal research and the degree of success already achieved.

Nation implementation of final rules might take years

Following the votes of the Agriculture Committee, the European Parliament and the EU Council have to find an agreement so that the new directive can be formally adopted. Several rounds of debate and negotiations might be necessary. Matters are further complicated by the forthcoming election of a new European Parliament in June, which also means formation of a new Agriculture Committee. An agreement on amendments to EU directive 86/609/EEC is not expected before 2010, according to Hélène Cuisinier from the European Parliament Press Service.

After the adoption of the directive, Member States have 18 months to transpose it into national law.

Some transitional arrangements are possible but it might take several years before the whole set of new rules can be implemented.

BETTINA DUPONT