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The animal experimentation quandary: stuck between legislation and scientific freedom

More research and engagement by scientists is needed to help to improve animal welfare without hampering biomedical research

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Many European citizens see animal welfare a matter of great importance [1]. Initiatives such as *Stop Vivisection*, which petitions politicians to abandon all support for animal experimentation in biomedical and toxicological research (http://ec.europa.eu/citizens-initiative/public/initiatives/successful/details/2012/000007/en?lg=en), might suggest that a majority of Europeans want to see the use of all animals in testing and research banned. However, a recent Eurobarometer survey on Science and Technology implies a different attitude: Although public opinion is divided when it comes to the use of dogs and monkeys in animal testing, a vast majority accept the use of mice in research if it produces new information on human health problems [2].

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These different perspectives on animal experimentation are reflected in the European Directive 2010/63/EU on the protection of animals used for scientific purposes [3]. On the one hand, the Directive clearly spells out a final goal of fully replacing all procedures that use live animals. On the other hand, it also recognizes that animal testing is still necessary for basic research and to protect human and animal health and the environment (Recital 10). Another key element of the Directive is the 3R principle—replace, reduce, refine—which seeks not only to ultimately replace all animal testing, but in the meantime to reduce the number of animals being used and to refine their use in experiments.

> *"Together, all parties have to find a solution that assures a high level of legal security, which can be implemented easily by both scientists and competent authorities"*

It was a well-considered decision by the European Commission to enact a directive rather than a regulation because doing so provides enough flexibility for member states to implement the Directive's objectives into national legislation, considering the specific characteristics of the respective country. This approach ensures that all EU member states with their different cultural backgrounds can work under the same provisions and achieve harmonization and high standards of animal welfare. However, there is also a downside to this flexibility: Many parts of the Directive remain vague, which makes it more difficult for states to put its requirements into practice. Ultimate responsibility for adopting the new regulations falls into two groups: competent authorities, who are responsible for the implementation of the law, especially of the provisions on project evaluation, and scientists, who face ambiguous legal provisions that seem to restrict their day-to-day work. The indeterminacy of the Directive leads to a situation where the competent authorities are pretty much left alone with the "hows" of the regulation's transposition on a practical basis and where scientists feel overregulated and limited in their scientific freedom and the generation of medical progress.

By implementing the Directive, it has become evident that there is a large gap between the legal obligation to ensure animal welfare and the lack of objective biomedical indicators for measuring animal well-being to do so. A recent example of this discrepancy is the generation of genetically altered animals. The Directive now requires the authorization of breeding of genetically altered animals if the progeny is expected to experience pain, suffering, distress, or lasting harm as a result of their genetic modification. This implies that European researchers now have to keep a record on the degree of impairment their genetically altered animals might exhibit.

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However, neither European nor national legislations determine how such documentation is to be conducted and, more importantly, how to objectively measure alterations in the animal's physiological state and to correlate these changes with the degree of pain, distress, suffering, or lasting harm.

Annex VIII of the Directive, which tackles the classification of the severity of procedures, only mentions the breeding of genetically altered animals but does not provide any details for the assessment of severity. The working document on genetically altered animals by an expert working group of the European Commission [4] describes some key elements for assessing the welfare of genetically altered rodents, but leaves enough room for different interpretations and ways of documenting it. As a result, there is a widespread uncertainty not only among scientists, but also among the competent authorities, which in the end have to approve whether a genetically altered animal line is determined to exhibit an adverse phenotype or not. Considering that genetically altered animals are exchanged between laboratories worldwide, uniform severity assessment rules will become essential. Moreover, further scientific knowledge is needed to reliably and efficiently evaluate phenotypes and to sufficiently apply refinement, which will guarantee a high standard of animal welfare.

What can be done to solve this quandary—balancing animal welfare legislation and scientific freedom—which exists since at least the late 1950s and was picked up by William Russel and Rex Burch in *The Principles of Humane Experimental Technique* [5]? First, scientists should take animal welfare and its legislation into their own hands by developing innovative solutions to improve animal welfare standards. This would require additional funding to promote progress in 3R research. This was also the argument made by the Chief Executive of the Society of Biology, Mark Downs, in reaction to the response of the EU Commission to the *Stop Vivisection* initiative. He stated that, "[w]e would welcome stronger signals from the Commission that a well-funded Horizon 2020 will include resource to advance the important challenge of developing and validating refinements and alternatives" (http://www.rsb.org.uk/component/content/article?id=1284:society-of-biology-welcomes-eu-commission-s-decision-to-keep-directive-on-protection-of-research-animals).

Second, biomedical research for animal welfare should foster global interdisciplinary collaboration and communication between medical and biological scientists and colleagues from veterinary research. Such collaboration can expeditiously help to determine endpoints that objectively describe any deviations from an animal's "normal" state.

> *"Scientists are now in charge of the generation of valid data on how to measure welfare in all laboratory animal species"*

Third, a close cooperation between scientists, veterinarians, lawyers, and competent authorities is needed to put the current legislation and the culture of care into practice. Lawyers have to provide definitions of the relevant terms to set up a legal framework and to determine the margin of appreciation for those who apply the law. Scientists and veterinarians have to contribute their expertise to objectively measure welfare in animals, and regulatory authorities have to confirm that a recommendation is of practical use. Together, all parties have to find a solution that assures a high level of legal security, which can be implemented easily by both scientists and competent authorities.

Recital 48 and Article 49 of the Directive already foresee an instrument to promote an appropriate level of coherence and consistency on matters relating to the care and use of animals and especially to provide consistency of project evaluations. Each EU member state now has to establish an independent and impartial National Committee to advice animal welfare bodies and competent authorities, and to provide information on best practices at the national and European level [6]. In Germany, the National Committee is located at the Federal Institute for Risk Assessment (BfR) as part of the German Centre for the Protection of Laboratory Animals [7], which is characterized by a scientific, research-driven approach. To ensure that it can carry out its work without influence from political, economic, or social interests, the institute is scientifically independent under the law that established the BfR [8].

The BfR has already initiated two workshops to bring together the expertise of scientists, veterinarians, and regulatory authorities to define criteria for the severity assessment of genetically altered rodents. The recommendation of the workshops [9] was met with high acceptance within the scientific community, as well as among the competent authorities, and has led to a harmonized evaluation process of research projects on genetically altered rodents in Germany. However, such recommendations can only be a compromise based on the present scientific evidence and therefore need to be regularly adapted to include current knowledge. Scientists are now in charge of the generation of valid data on how to measure welfare in all laboratory animal species. More initiatives like the consensus document for the care and welfare of cephalopods published by scientists from different institutions in several countries, together with members of competent authorities [10], are necessary to fill this gap. Only in this way can scientists maintain their option to participate in the practical application of a law that fundamentally affects their work.

Conflict of interest

The authors declare that they have no conflict of interest.

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