Progress in science and medicine has and will continue to require the use of animal experimentation. However, the acceptability of animal testing has been justly questioned in view of the fact that animals, because they are sensitive beings, are worthy of respect, a major ethical issue. There have been calls to question the whole or parts of animal experimentation in Europe. A petition to this end was addressed to the European Union, whose Directive 2010/63/EU on the protection of animals used for scientific purposes stipulates in Article 58 that it should be reviewed at the latest by 10 November 2017. It is against this background that four French academies have drafted and signed, after joint reflection on this issue, the following analysis and recommendations.

1- Importance of scientific and medical progress

1-1- Scientific, fundamental and applied research is of major importance for our societies. Many human and animal diseases are still poorly understood and remain even today major public health challenges. Research on new diagnostic tests is necessary and for many diseases it is essential to find new drugs and in some cases new treatment strategies. This is the case for emerging infectious and genetic diseases, neurodegenerative diseases such as Alzheimer, cancer, some chronic diseases such as metabolic disorders (obesity, diabetes) and inflammatory diseases the frequencies of which are increasing worldwide. Protection of the environment is another major challenge facing our societies. In order to be well prepared to face issues such as these, it is necessary to maintain a high level of fundamental research. This is essential to advance knowledge and to make progress in the development of original applied research programmes with far-reaching scopes. The answer to these challenges requires the use of various experimental approaches. Among these is animal experimentation. Its contribution is still irreplaceable.

1-2- The marketing of new drugs is based on controlled therapeutic trials on human subjects. These trials cannot be carried out without prior studies on the mechanism of action, efficacy and eventual secondary effects. In the absence of other approaches, all of these can only be done on animals. It would be ethically inconceivable and contrary to all international treatises to replace animal experimentation with human experimentation, even on volunteers. Phase I studies on human subjects are still necessary but expose the subjects to less risk if they are preceded by studies carried out on animals. The latter do not allow us to completely exclude the occurrence of adverse events in human subjects but they do reduce the risk significantly. Likewise, the identification of toxic effects of some molecules on foetal development, which has recently been at the forefront of the news, must initially rely on animal

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1 The European Citizens' Initiative (ECI) “Stop vivisection”.

experimentation since it is inconceivable that the evaluation of such effects be carried out on pregnant women. These comments apply also to biotechnology products, gene and cellular therapies and some medical devices such as heart valves and pacemakers. Finally, without animals it will not be possible to establish rigorous experimental methods to identify the environmental factors that might have adverse effects on human health. Although epidemiological studies are rightly favoured, they are not sufficient in and of themselves. They must be supplemented with animal studies to confirm causes and explore the underlying mechanisms and their eventual impact on the progeny.

1-3- The independence of Europe in matters of research remains a strategic issue. This prevents dependence on third countries regarding our health and the health of future generations, and insures that our researchers are not compelled to relocate to countries where the protection of animals used for scientific purposes is not subject to rules of good technical, scientific and ethical practice as strict as those in Europe. This risk is already an unfortunate reality as is evidenced by the numerous relocations and out-sourcing. It is therefore important to ensure that European research does not weaken in an already increasingly competitive international environment.

2- Transposition to humans of results from animal studies

It would be incorrect to assert that animal experimentation is useless under the pretext that humans and animals differ from a physiological point of view. Whilst there are no animal species identical to humans, it should be remembered for instance that there is a high degree of similarity between the genetic maps and organic functions that are common to all mammals, including the human species. There are as well numerous examples of experimental research on animals that have led to essential applications for humans (vaccines, organ transplant, metabolic diseases among others). Similarly the transgenerational transmission of certain characteristics and diseases of recognized importance can only be studied in animals with a short reproductive cycle such as mice (5 to 6 generations per year).

It should finally be recalled that animal experimentation is carried out on a great number of species, mostly rodents, but also invertebrates. The use of animals closer to humans such as domestic mammals and certain primates bred for this purpose remains the exception but cannot be avoided in certain cases. Such experimentation is vital for progress in zootechnics and veterinary care.

3- Alternative methods

In vitro or in silico alternatives to animal experimentation are already widely used in all cases where it is scientifically possible to do so. The best-informed about these methods are the researchers, most of whom develop these themselves and readily promote their use for scientific, ethical and economic reasons. For example, organoids (three-dimensional cell cultures) developed from stem cells make it possible to study the fundamental biological processes of an organ as well as simulate a diseased organ using genetic modification techniques. Another example is the use of microfluidic chips (Organ-on-a-Chip) that simulate the biological activity of an organ as well as the mechanical constraints it is submitted to (blood pressure in blood flows, the interface between capillaries and alveoli in the lung, among others).

Alternative methods have made it possible to lower the number of animals used for scientific purposes, as evidenced by the European Union statistics\(^\text{\textsuperscript{3}}\). Contrary to some claims, today, these methods cannot on their own bring pertinent answers to many of the questions still outstanding in matters of

\(^{3}\) European Union reports on the use of animals for scientific purposes [http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm].
understanding the pathological and physiological mechanisms of diseases and the identification and evaluation of the efficiency and safety of new treatments. Today, there is no known alternative that allows us to understand all the interactions that exist between the organs of an individual and to reproduce the different functions of a single organ. This is why it is essential to rely on whole animals in their full complexity. Many examples can be mentioned to illustrate this necessity: research in neurobiology, for example on sleep and stress; in cancer immunotherapy which is about to transform prognosis for many cancers in particular lung cancer; in establishing causal relationships between the gut microbiota and certain diseases; in the prenatal programming of phenotypes and its underlying epigenetic mechanisms; in the development of tissue and cell transplantation programmes; in research in gene replacement and gene editing therapies which could lead ultimately to a cure for some genetic diseases, and many more.

4- Respecting ethical rules

The principle of the “Three Rs” – Replacement, Reduction and Refinement (to “improve”) – according to the terms used by W.M.S. Russell and R.L. Burch in 1959, is embedded in Directive 2010/63/EU. It is one of the ethical principles at the basis of this regulation and it is the regulatory transposition of the good practices already commonly applied by scientists when using animals for research, as is illustrated by this quote from Jean Bernard: “What is not scientific is not ethical”. According to the terms of the Directive this principle should be understood as an optimizing principle aimed at limiting to the strict minimum both the number of animals used and the burdens applied to them (Art. 4 [...] The Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.). Against this background, researchers have tried to expand on this rule by improving the reproducibility of the experiments they carry out and organizing the reuse of the data from animals by using proteomics, bio-banking and meta-analyses. New infrastructures for coordination and pooling of technical means can produce models that can be used by all of the scientific community, thus avoiding redundant experiments. Furthermore, good animal welfare ensures the physiological pertinence and reliability of scientific observations.

Conclusion

The use of animals for scientific purposes remains at present essential both for fundamental research and medical research in order to:

- improve fundamental knowledge – which has an intrinsic value as an element of culture and progress – and understanding of the complexity of pathophysiological mechanisms and the interactions that control the various levels of complexity in living organisms – molecule, cell, organ, organism and the relations between organisms;
- reach the progress expected by society regarding human medicine and veterinary medicine (pets, farm animals and protected and unprotected wild animals;
- ensure the quality and safety of animal productions;
- acquire the data indispensable for the implementation of future work methods that bring together in vivo, in vitro and in silico approaches within the framework of combinatorial strategies based on bioinformatics.

The use of animals is acceptable today only to the extent that ethical rules concerning the use of animals, as they have been set out in various charters concerning the obligations of investigators, are scrupulously respected. Directive 2010/63/EU, which requires that researchers comply with strict rules in matters of animal protection and welfare, places the European Union at the highest level worldwide in terms of regulations regarding the protection of and respect for animals.
Recommendations

Recognizing that it is impossible at present to abolish the use of animals for scientific purposes, our four signatory academies recommend that:

- vigilance should be strengthened with regard to the application of regulation requiring that animals are used for scientific purposes in strict accordance with the regulatory and ethical framework formally stated in Directive 2010/63/EU relative to the protection of animals used for scientific purposes, in particular the principle of the “Three Rs” (Replacement - Reduction - Refinement) which is one of its cornerstones. Likewise, the use of animals for scientific or educational purposes can only be undertaken in the absence of an appropriate alternative method and after consultation with an ethics committee;

- the objectives of continuous improvement in the welfare of animals used in scientific protocols should be fully supported, integrating the most recent advances in matters of validated alternative methods;

- care should be taken to avoid increasing the burden of constraints, mainly administrative, imposed on European research while at the same time rigorously applying Directive 2010/63/EU, to be enforced unanimously in all European research laboratories;

- regulatory procedures should be reviewed in order to simplify, whenever possible, the procedures for drug marketing authorization in the light of recent scientific progress, with the aim of limiting the use of animal experimentation and firmly promoting the emergence of active research in regulatory science in France, as other drug agencies already do (Canada, United States, Japan), an action that the European drug agency is trying to promote.

- preparation should be made to address in an explicit and educational way those persons or legal entities that expressed concerns about the use of animal experimentation.