



## Literature Review

### International Research Collaborations: The Perspective of Modern Experimental Research

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#### Abstract

**Study background:** The contribution of animal studies in biomedical research and science evolution worldwide is invaluable. Each country has developed a national regulatory framework to oversight the conduct of animal research, based on its social structures, culture and ethical values.

**Aim:** The primary objective of this article is to detect the most important similarities and differences in laws, regulations and guidelines among Europe, United States, Canada, China, Korea and Japan.

**Method:** Literature search (MEDLINE, PubMed, Embase and Google) has been conducted to identify published studies and the current legislation related to the protection of laboratory animals used for scientific purposes worldwide.

**Results:** Our findings documented that the various laboratory animal welfare regulations amongst different countries correspond to various interpretation and adjustments. Although this is acceptable for some parameters such as 3Rs (Replacement, Reduction and Refinement) profound variances in the definition of animal, role of attending veterinarian and inspection have been detected.

**Conclusion:** The aforementioned appraisal could guide the development and adoption of a universally lawgiving that meets international standards. This approach will ensure standardized animal care and ethical use in animal experimentation.

**Keywords:** Animal welfare; Experimental research; International collaborations; 3Rs (Reduction, Replacement and Refinement); Regulatory framework

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#### Introduction

Animal research is one of the key areas in the development of science, facilitates the improvement in the quality of life of humans and animals, and ensures the protection of the environment. The medical breakthroughs and achievements are undeniable benefits which prove the necessity of the use of live animals in procedures. For this reason, in order to maintain balance and protect animals' rights, each country has developed regulatory frameworks and guidelines to ensure the proper care and use of live animals for scientific purposes [1-4]. The foundation stones of most regulations are the internationally established principles of replacement (avoid or replace the use of animals), reduction (minimize the number of animals used per experiment by resorting to other methods or strategy) and refinement (implementation of methods which ensure that animal suffering is minimized and improve welfare). These three principles are very important and are considered to be the common basis for scientists worldwide [3-6]. The purpose of our study is to compare the laws and regulations related to the protection of laboratory animals used for scientific purposes, among various countries and regions. We attempt to record similarities and identify differences in the current legislation, aiming at the elimination of variations and the construction of a universal law-giving.

#### Literature Review

We conducted a literature search (MEDLINE, PubMed, Embase and Google) to identify published studies and the current legislation related to the protection of laboratory animals used for scientific purposes worldwide.

#### Results

Through the comparison of laws and guidelines of European Union, United States, Canada, China, Japan and Korea, we managed to identify the most significant differences that are summarized in table 1.

#### Discussion

During the past decades, there has been arise in international collaborations in animal research. As a result new perspectives in science and education have been established. Nevertheless, this effort is experiencing difficulties due to the lack of a unified, globally applicable legislation. This could be due to different social structures, culture, economy potential or even religious beliefs that characterize each country. So, despite the existence of common core principles, there are some differences that need to be overcome in order to accomplish the harmonization of legislation and better science in general. Another factor that should be taken into account is that evolution and progress may vary among countries. Thus, there are countries that have not come forward with proposals for a revision of former laws, in order to improve their system and ensure a higher level of protection of animals. Fortunately, the scientific community of these countries has developed strong ethical awareness and they usually choose to follow international standards or adopt guidelines from other countries even if it is not required by national laws [2-4].

	European Union	United States	Canada	Asia		
				China	Korea	Japan
Animals used (covered by law)	a) Live non-human vertebrate animals, including independently feeding larval forms and foetal forms of mammals as from the last third of their normal development b) Live cephalopods [5]	Any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm-blooded animal. This term excludes birds, rats of the genus <i>Rattus</i> , and mice of the genus <i>Mus</i> [6]. However for the above mentioned species an IACUC approval is an essential [7,8]	A vertebrate or a cephalopod [9]	Artificially raised and bred animals with controlled microbes and parasites and definite genetic background and clear sources [10]	Cattle, horse, swine, dog, cat, rabbit, chicken, duck, goat, sheep, deer, fox, mink and others species [11]	Animal of mammalian, avian or reptilian species used in animal experiments. This term excludes fish and amphibians [12]
Provision on the use of certain animals in procedures: -Endangered species -non-human primates -animals taken from the wild	Shall not be used in procedures only after ethical and scientific justification of the use of these laboratory animals [5,13]	There are not specific reports in the legislation but detailed guidelines for the use of these animals are reported in a special published issue [6,14,15]	No reference	No reference	No reference	No reference
3Rs (Replacement, Reduction and Refinement)	Required by law [5]	Required by guideline [1,16]	Proposed by guidelines [17,18]	Required by guidelines [19]	Required by law [20,21]	Required by law [12]
Attending Veterinarian	Required [5,22,23]	Required [6]	Required by CCAC [24-26]	Required [27]	Required [11,27]	Recommended by guidelines [12,27]
IACUC or other scientific bodies	Protocol evaluation committee [5]	Required [1,3,6,28]	Animal Care Committee established by Canadian Council on Animal Care (CCAC) [26,29]	Required [19,23]	Required [20,21]	Recommended but not required [27,30]
Members of IACUC or other scientific bodies	a) Scientist of biomedical research, as chairman, with his deputy. If required, his vote counts twice b) Attending veterinarian with his deputy c) Biostatist with his deputy d) Suitably qualified experts	AWA: At least 3 members a) A chairman b) A doctor of veterinary medicine c) An individual who is not affiliated in any way with the institution [6]  PHS policy: At least five members a) A doctor of veterinary medicine with program responsibility b) A scientist c) An individual whose expertise is a nonbiological science d) An individual who is not affiliated with the institution [7]	a) Scientists and/or teachers experienced in animal care and use b) A veterinarian c) An institutional member whose normal activities, past or present, do not depend on or involve animal use for research, teaching or testing; d) At least one person (s) representing community interests and concerns, who has (have) had no affiliation with the institution, and who has (have) not been involved in animal use for research, teaching or testing; community representation must be ensured for all ACC activities throughout the year; e) Technical staff representation (a) technical staff member(s) f) Student representation in the case of institutions that have programs where students use animals; and g) The ACC coordinator	a) A doctor of veterinary medicine. b) A person representing an animal protection organization [27]	3-15 members including: a) A specialized veterinarian b) An external animal welfare specialist [31]	Researchers conducting animal experiments, laboratory animal specialists, and other persons of knowledge and experience there is no request for the attending veterinarian to be a member [30]
Animal Welfare Bodies for the monitoring and implementation of protocols	Animal welfare body which includes: a) The person or persons responsible for the welfare and care of the animals b) A scientific member [5]	Office of Laboratory Animal Welfare - Public health service policy on humane care and use of laboratory animals [1,3]	Animal Care Committee [26,29]	Chinese Association of Laboratory Animal Science Animal Welfare Committee [19]	Animal Experimentation Ethics Committee [11,21]	Institutional Animal Experiment Committee [32]
Licensing/ registration for animal facility	Required [5]	Required [6,33]	Not required [34]	Required [19,27,35]	Required [27,21]	Not required [27,30]
Inspections	a) One third of the users each year (risk-based inspection system). b) Breeders, suppliers and users of non-human primates at least once a year [5]	Every year by USDA/APHIS (risk-based inspection system) [6]	Self-regulation [26]	Every year [19]	Supervision by MFDS [27]	Self-regulation [30]

**Table 1:** Comparison of laws and regulations relevant to laboratory animals between different countries.

Another significant reason that necessitates the urge for the establishment of a common legislation is the public awareness. The use of animals in scientific and medical research has become a debated issue as far as the ethical and legal aspects are concerned. Public wants to be reassured that the procedures are likely to cause the minimum pain, suffering or distress while at the same time it requires transparency and publication of scientific reports in order to supervise and ensure the animal welfare globally. In the United States, the American Association for Laboratory Animal Science (AALAS) is a non-profit organization which brings awareness to the general public about animal experimentation. AALAS offers free resource materials to anyone who wants to be informed and organizes training and education programs for professionals working in the field of laboratory animal science. Furthermore it enables lay observers to express their opinion and exchange information. Consequently, AALAS is promoting an open dialogue between scientists and public and the importance of public participation is emphasized [36,37]. In Europe, an example to be followed is the ethical framework of UK which has some of the strictest animal research regulations. The implementation of amended animals (scientific procedures) Act 1986 and the UK Freedom of Information Act promote transparency and accountability [38]. Public interest in animal welfare is taken into account and anyone is permitted free access to information about the design and conduct of all procedures involving laboratory animals (non-technical abstract). For this reason there is a tendency for continuous improvement on behalf of the authorities and as a result existing laws and guidelines are constantly evolving. In order to achieve this goal, collaboration of regional organizations with international is essential. Also, the recent European legislation (Directive 63/2010) adopted this procedure and the publication of non-technical abstract [4-7,39-41]. We consider that the definition of animal for experimental use, globally accepted, is of fundamental importance. The term animal should include all species which are being used or intended for use for research purposes worldwide. However, the collaboration among research facilities of different countries is not facilitated due to the exclusion of certain species in certain countries. Thus, authorization, import and breeding of laboratory animals are variable [5,6,9-12].

Moreover, it is necessary to ensure that the use of animals in procedures does not pose a threat to biodiversity. Given that the use of Non-Human Primates (NHP) and endangered species is of the greatest concern to the public, their use should be strictly limited and permitted only when there are no suitable alternative methods or species, as Directive 2010/63/EU mentions. Instead, USA's Animal Welfare Act does not include restrictions and provisions on the use of non-human primates. It specifies handling, care, transportation, treatment and housing facilities and includes provisions regarding environmental enhancement to promote psychological well-being. These requirements are also included at USA's Institute of Laboratory Animal Resources guide for the care and use of laboratory animals with many details and specific guidelines for these animals. On the contrary, in several other countries especially in Asia, an oversight framework for the protection of NHP is absent. As a result of the heterogeneity of the legal framework non-human primate research is forced outside European and United States in countries with less strict regulation. This leads to an increase of international collaborations but has a negative impact on animal welfare. Therefore the implementation of a harmonized international legislation for non-human primates is of vital importance and any type of tolerance should not be accepted [5,6,13-15,38,42-44].

Another significant factor is the role of Attending Veterinarian (AV). Regulations should prerequisite the active role of an expertise veterinarian in every research facility. His/Her role should be distinct to ensure valid experimental conditions and processes. He/she must be in charge with advisory duties in relation to the well-being and treatment of the animals. In the legislation of European Union and United States, the role of the attending veterinarian is clearly defined. Moreover, the latest version of the Guide incorporated significantly expanded responsibilities while AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care) International highlights the leading role of veterinarians in its assessments and programs [45,46]. In Canada, the Canadian Association for Laboratory Animal emphasizes the importance of adequate veterinary care and requires each institution participating in the CCAC (Canadian Council on Animal Care) Program to employ at least one veterinarian. Although it has become clear that AV role is fundamental, many countries as China and Japan do not designate or even mention the accountabilities and responsibilities in their legislation. It is also worth mentioning that in Japan, a veterinarian is not required by law in laboratory animal research institution. Consequently, the quality of animal research is probably downgraded. However the public opinion due to religious beliefs is very sensitive in the use of laboratory animals and the respect for their use in research and education is very high. According to article 49 of Directive 2010/63/EU (an obligation for every member state) most European countries recently published extra legislation concerning the training of researchers and staff for the use of laboratory animals for scientific purposes. In this regard, continuous training, revalidation and even relicensing are measures in the direction of good animal practice [5,6,22,23,26,27,47-49].

Regarding the principles of replacement, reduction and refinement, although they are internationally accepted and established, diverse interpretation and adjustment are documented [50-53]. In the European Union, Directive 2010/63/EU states that 3Rs should be strictly implemented in animal research. Worth mentioning is the UK-based National Centre for Replacement, Refinement and Reduction (NC3Rs) which has re-defined the 3Rs definitions. This independent scientific organization has an impact on international level. It has also develop ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines which intend to improve the reporting of research using animals [38,39,41,54-56]. In the US, the 3Rs are implicit in the Animal Welfare Act and are also required in public health service policy on humane care and use of laboratory animals (PHS policy) and in the guide for care and use of laboratory animals. IACUC (Institutional Animal Care and Use Committee) is responsible to ensure institutions' compliance. Therefore in the US regulatory system the ethical principles of 3Rs have been implemented explicitly [57,58]. In Canada, the Canadian Council on Animal Care (CCAC) follows the principles of NC3Rs but because of the lack of an integrated framework the whole approach is different [46,59-61]. China has incorporated adherence to the Three Rs through the implementation of the guideline on humane treatment of laboratory animals. Although most regions have successfully integrated these principles, more effort needs to be done. It seems that all the new Chinese research centers are working hard to align their national framework with the European and American legislation as well as to adopt guidelines from the western world. For this reason the Chinese Association of Laboratory Animal Science (CALAS) recently established an animal welfare committee to guide the ethical implementation of 3Rs.

In Japan, the law for the humane treatment and management of animals was amended in order to add these fundamental principles but with a differentiation of 3R conception. However, the proper implementation of the principles cannot be ensured due to the self-regulation system. This results in the need for external inspection, following the example of other countries [62,63]. In Korea, there are two laws for the protection of laboratory animals, the Animal Protection Act (APA) and the Laboratory Animals Act (LAA). Both laws include the 3Rs and require for the establishment of Institutional Animal Care and Use Committees. Nonetheless, there is a significant problem with the correct application of legislation and its control by international bodies due to the language problem. It is therefore understandable that although the basic principles are common, their application varies from country to country, but also among national research facilities due to different capabilities and ethical responsibilities [64-66].

The Institutional Animal Care and Use Committee has a fundamental role and an established role in the United States, and an emerging role in Canada and Asia. Every institution that uses animals for federally funded laboratory research must have an IACUC. Each local IACUC reviews research protocols and conducts evaluations on the institution's animal care and use, which includes the results of inspections of facilities that are required by law. Consequently, it would be advisable for Europe and other countries to adjust an equivalent committee with an analogous structure and responsibilities. Currently in Europe inspections are performed by the authorities and not from an established committee. This could be a way to correct problems in animal care, as well as, in research [3,6,7,25-28,49]. Although the license is a basic requirement for animal facilities in almost every country and region (Table 1) inspection are more variable. In the US and Europe, there is a risk-based inspection system [5,6], whilst in other countries there is a self-regulation system [26,27]. The latter doesn't ensure transparency and strict law implementation. Therefore, inspections on a regular basis by an independent body would be beneficial for animal care and research quality. If a project is not carried out in accordance with the regulations or in case of failure of compliance, fines, suspension or revocation of the license should be imposed [5,6,11,19,21,26,27,30,67].

## Conclusion

Our literature and bibliographical research documented the differences in the current legislation worldwide regarding laboratory animal research. According to our research, legal provisions seem to be acceptable for some parameters such as the 3Rs, however, profound variances are noted in other parameters such as the definition of animal, the role of attending veterinarian and the inspections performed. Such variations should be eliminated in order to reach the desirable unified approach in the legislation worldwide that can be applied globally. This approach will ensure standardized animal care and finally better science.

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