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3R principle as minimum ethics in animal experimentation

Renata Batista da Silva [1], *Tatiana Tavares da Silva* [1]

1. Universidade do Estado do Rio de Janeiro, Rio de Janeiro/RJ, Brasil.

Abstract

Non-human animals are routinely used in research, although studies refute the premise that results generated in this way benefit society. Law 11,794/2008 established ethics committees on the use of animals, with the authority to normatively and ethically evaluate teaching and research protocols. However, gaps in the bioethics training of committee representatives and a lack of incentive to implement substitute techniques, in addition to the more significant concern with compliance with the standard than with animal ethics, end up disregarding non-human animals morally. Despite the advancement of animal welfare practices, the commitment of institutions to support the work of ethics committees on the use of animals is low, as is the commitment of the National Council for the Control of Animal Experimentation in the formation and guidance of these committees so that they can exercise their powers and raise awareness among researchers regarding the ethical principles of animal experimentation.

Keywords: Animal care committees. Animal experimentation. Animal models. Animal use alternatives.

Resumo

Princípio dos 3R como ética mínima na experimentação animal

Animais não humanos são utilizados rotineiramente em pesquisas, ainda que estudos refutem a premissa de que resultados gerados dessa forma tragam benefícios à sociedade. A Lei 11.794/2008 instituiu as comissões de ética no uso de animais, com competência para avaliar normativa e eticamente protocolos de ensino e pesquisa. Entretanto, lacunas na formação em bioética de representantes das comissões e falta de incentivo à implementação de técnicas substitutivas, além da maior preocupação com o atendimento da norma que com a ética animal, acabam por desconsiderar moralmente animais não humanos. Apesar do avanço de práticas de bem-estar animal, é baixo o comprometimento das instituições no apoio à atuação das comissões de ética no uso de animais, bem como o empenho do Conselho Nacional de Controle de Experimentação Animal na formação e orientação dessas comissões para que elas possam exercer suas competências e sensibilizar pesquisadores quanto aos princípios éticos em experimentação animal.

Palavras-chave: Comitês de cuidado animal. Experimentação animal. Modelos animais. Alternativas ao uso de animais.

Resumen

Principio de las 3R como ética mínima en la experimentación animal

Los animales no humanos se utilizan rutinariamente en la investigación, aunque los estudios refutan la premisa de que los resultados generados de esta manera aportan beneficios a la sociedad. La Ley 11.794/2008 creó comités de ética en el uso de animales, con competencia para evaluar normativa y éticamente los protocolos de enseñanza e investigación. Sin embargo, las brechas en la formación bioética de los representantes de los comités y la falta de incentivos para implementar técnicas sustitutivas, además de la mayor preocupación por el cumplimiento de las normas que por la ética animal, terminan por despreciar moralmente a los animales no humanos. A pesar del avance de las prácticas de bienestar animal, aún es escaso el compromiso de las instituciones para apoyar la actuación de los comités de ética en el uso de animales, así como el compromiso del Consejo Nacional para el Control de Experimentación Animal en la formación y orientación de estos comités para que puedan ejercer sus competencias y sensibilizar a los investigadores sobre los principios éticos en la experimentación animal.

Palabras clave: Comités de atención animal. Experimentación animal. Modelos animales. Alternativas al uso de animales.

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Update

In Brazil, the Ethics Committees on the Use of Animals (CEUA) were established by Law 11,794/2008 [1], also known as the Arouca Law, which regulates the scientific use of non-human animals in teaching and research. CEUAs must be linked to a teaching/research institution of origin. Their primary competence is the assessment and analysis of projects involving non-human animals. This analysis requires an interdisciplinary effort from different groups and professional careers to make the debate about the ethical use of non-human animals equitable.

These groups include veterinarians, biologists, professors, researchers, and members of animal protection organizations and societies, as guided by Normative Resolution (RN) 51/2021 [2] of the National Council for the Control of Animal Experimentation (CONCEA). This body is part of the Ministry of Science, Technology, and Innovation (MCTI) and regulates the installation of CEUAs and vivariums or animal facilities in Brazil.

While interdisciplinarity allows for broad debate, it is questionable to what extent the individuals involved in this process are qualified to discuss ethically the use of non-human animals in experiments and the implementation of alternative methods without prior knowledge of animal ethics. Given this lack of conformity, the assessment may become merely technical, focused on meeting legal requirements in a kind of checklist, keeping the human animal—represented by the researcher—but not the non-human animal, as the central figure in the decision-making process.

This article discusses the challenges of applying the 3R principle in scientific research to ensure the well-being and ethical treatment of non-human animals. These are the minimum precepts for developing experiments that comply with the law and fully protect the non-human animal.

Method

An extensive non-systematic bibliographic review was conducted to prepare the article using documentary research of scientific articles and books in official databases, such as SciELO and Google Scholar. The research was conducted using the descriptors "comitês de cuidado animal," "experimentação animal," "alternativas ao uso de animais," and "modelos animais." The exploratory method was used to select relevant articles and have their full text available.

The search resulted in many articles not being analyzed because they did not discuss the proposed topic or were already obsolete due to legislation changes. National and international government websites containing regulatory standards that addressed the proposed topic were also researched and analyzed.

Results and discussion

Animal vulnerability and the moral status of non-human animals

It is well known that non-human animals feel hunger, thirst, pain, and suffering, contrary to René Descartes and other scientists' arguments in the 16th and 17th centuries. In his mechanistic theory, Descartes argued that organic functions in non-human animals were directly linked to the basic need for the body to function [3].

Silva [3] points out that, for Descartes, non-human animals are devoid of sentience and soul due to their inability to use verbal language and, therefore, do not participate in the sphere of the morality of the human animal, so the latter becomes the holder of the power to enjoy the "body" of the former. This thought permeated the imagination of different scientists from Antiquity until the mid-18th century, demonstrating the relationship of ownership between human-non-human animals and the total absence of any moral obligation on the part of the human animal.

In the 18th century, Immanuel Kant, unlike Descartes, recognized that non-human animals were sentient beings and, therefore, capable of feeling pain. However, they would not be holders of moral obligations on the part of the human animal, reaffirming Descartes' theory of animal instrumentalization.

For Kant, as Silva [3] states, any harm caused to an animal directly and solely harmed the interests of its owner, but not the non-human animal itself, since it would be mere property. Kant argued that only those who possess reason, capable of legislating and making choices autonomously, should be considered morally.

This idea reinforces the anthropocentric thesis that the human animal has rights over non-human animals, considered things:

Beings whose existence does not depend on our will but on nature, however, if they are beings devoid of reason, have only relative value as means, and for this reason are called things, while rational beings are called persons because their nature already distinguishes them as ends in themselves, that is, as something that cannot be used only as a means (...) [4].

At the same time, Kant argued that if it were possible to treat non-human animals without suffering, this should be appropriate since violence inflicted on a non-human animal could later be applied to a human animal. Camenzind [5] states that, according to the philosopher, the duties of human animals toward non-human animals would be considered duties of the former toward themselves, in respect of the feelings shared between the species, interpreted as being of moral value.

The utilitarian Jeremy Bentham, in the 18th century, emphasized the need for rapprochement between human and non-human animals by arguing that pain and pleasure were presented in a connected way between the two forms of being, i.e., all sentient beings should be respected and worthy of rights. The capacity to suffer, and not the capacity to think, would be decisive for including non-human animals in the sphere of the morality of the human animal, according to Dardenne [6].

Furthermore, Dardenne [6] recalls that already in the 20th century, Peter Singer, also a utilitarian, stated that there was no moral argument capable of defending that any type of suffering should be inflicted on a sentient being since the principle of equal consideration of interests interprets all sentient beings as equivalent. For Singer [7], the satisfaction of the individual preferences of all subjects involved and affected by an action, in an impartial manner, makes a conduct morally correct. Therefore, the principle of equal consideration of interests could not be speciesist and applicable only to human animals due to their capacity to think. Thus, since they can suffer, non-human animals should be compared, by approximation, to species that also suffer and, therefore, deserve equal consideration.

In animal experimentation, the argument that research with non-human animals can bring more benefits to human animals than the suffering imposed on non-human animals cannot be defended based solely on the hypothesis that such experiments can save lives. Pain and suffering are similar among non-human vertebrate animals, especially birds and mammals, and their inability to communicate or argue does not diminish their intrinsic value [7].

Consciousness in non-human animals was recognized in July 2012 after a conference at the University of Cambridge. At the time, professionals from different areas related to neuroscience re-evaluated the neurobiological substrate of conscious experience and behaviors related to it in human and non-human animals:

At the end of the event, the *Cambridge Declaration* was drawn up, which concludes as follows:

(...) *Convergent evidence indicates that non-human animals have the neuroanatomical, neurochemical, and neurophysiological substrates of conscious states along with the capacity to exhibit intentional behaviors* (...) *indicates that humans are not unique in possessing the neurological substrates that generate consciousness. Non-human animals, including all mammals and birds, and many other creatures, including octopuses, also possess these neurological substrates* [8].

The observations contained in the *Cambridge Declaration* [8] are not merely informative in nature but seek to demonstrate the need for ongoing evaluations in research involving studies on the consciousness of non-human animals. Given the evidence, they also aim to broaden the debate on how these beings should be treated, given a moral obligation established with such confirmations.

If non-human animals are sentient beings, potential holders of rights, and are within the sphere of human morality—at least in common sense—why does the discussion about their use in research or how they should be treated when it is not possible to use substitute methods still generate so much controversy and debate? Non-human animals are trapped in historical,

cultural, and political constructs that place them as mere objects for the benefit of science and the market, even if they are inflicted with suffering and pain, among other harms [9].

The inability to freely consent to their use in experiments and the discourse defended by the academic community that this use is essential for scientific advancement in the cure of human diseases is the foundation for non-human animals to continue being oppressed and mistreated.

Ethical principles for animal experimentation

The publication of the Arouca Law standardized the application of the ethical principles internationally known as 3R, which must be considered in animal experimentation. These principles were described in the 1950s by Russel and Burch, as mentioned by Jankoski and Fischer [10]. These are replacement, when there is a validated replacement method, making the use of non-human animals unjustifiable; reduction to the smallest number of non-human animals necessary to obtain reliable results; and refinement in the application of procedures that minimize animal suffering, pain, or stress when their use is essential.

In India, since 2004, the concept of a fourth R, rehabilitation, has been officially recognized as a continuation of the 3R principle. According to it, non-human animals receive care aimed at alleviating pain and physical and psychological trauma suffered during experiments in reference sites financially supported by the government. Expenses for research development should include the costs for the rehabilitation of non-human animals based on the species' life expectancy, and the higher the level of sentience of the species, the greater the expense corresponding to rehabilitation [11].

Although the term "bioethics," a neologism constructed from the Greek words *bios* (life) + *ethos* (ethics), was used by some authors before the 20th century, its current definition was established in 1971 by oncology researcher Van Rensselaer Potter, who was concerned with technological advances related to human health and their consequences for the human animal, non-human animal and the environment, as highlighted by Garutti and Palma [12]. Potter sought to build a dialogue between scientists and humanists that would trigger ethical reflections and a sense of moral responsibility in the search for the survival of the human animal and improvement of the quality of life based on ethical values.

The dialogue proposed by Potter between ethics and science would be capable of giving rise to actions to generate individual and collective behavioral changes, on which the survival of human animals and the protection and survival of other species and ecosystems, including future generations, would depend [13]. Zanella understands Potter's bioethics as *a new ethic that combines humility, responsibility, and interdisciplinary and intercultural competence, enhancing the sense of humanity* [14].

In Brazil, discussions on animal ethics began after the 1970s, with the movements for the rights of non-human animals [15]. It was only in the 1990s that the first specialization course in bioethics was created, subsequently triggering an increase in the offer of postgraduate courses but restricting the debate to the academic environment. Since bioethics has a solid social character, it can establish bridges between scientific and humanistic knowledge and society [16].

Until that time, only the common sense of the researcher was responsible for outlining their moral conduct in experiments with non-human animals, as well as in teaching practices in institutions. In 1991, the Brazilian College of Animal Experimentation (COBEA) published 12 articles entitled "Princípios Éticos na Experimentação Animal," which aimed to regulate the use of non-human animals in experiments, in addition to filling a legal gap that would be capable of protecting professionals involved in animal experimentation [17].

With the implementation of institutional CEUA after the publication of the Arouca Law, any research project evaluated by these committees was inferred as necessarily including practices aimed at animal welfare, especially those aimed at reducing suffering during experiments, such as analgesia, anesthesia and early euthanasia in the event of signs of pain, techniques considered to be experimental refinement. However, since the committees were established, it has been clear that the accredited institution has been more concerned with complying with legal requirements

than with the actual application of bioethics and the principle of equal consideration of interests in protecting non-human animals in experiments.

Animal experimentation and use of substitute methods

Non-human animals are routinely used for experimental purposes in basic research, under the claim that they form the basis for subsequent experimental design with human animals and in applied research aimed at curing diseases of human interest. They are also used in safety tests to market products of human interest, study the mechanisms and cures of various diseases, and search for new drugs to treat and prevent diseases.

In tests for the approval of medicines, foods, cosmetics, and cleaning products, many countries have already approved alternative methods and prohibited using non-human animals for some products. Despite this, in other countries, applying these methods is still uncommon and, at times, only recommended.

Replacement allows for a reduction in the number of non-human animals used in research. It characterizes a form of refinement of the technique, thus consolidating the three principles systematized by Russel and Burch. Alternative methods for using non-human animals are validated procedures, strategies, or resources that guarantee safety in the testing process of medicines, cosmetics, and cleaning products, among other products. Many methods also enable cost reduction in testing, faster approval process, and the availability of new products to the population [18].

Replacement methods may include *in vitro* techniques, such as the identification of eye irritants and substances that cause contact allergies; computer programs containing extensive databases capable of predicting the chemical toxicity of a substance; or even microphysiological systems that use structured human cells in an environment capable of mimicking the function of an organ, as is the case of a study underway in the United States for the SARS-CoV-2 virus, which causes COVID-19.

The limitation on the use of non-human animals of different species, which may not develop or only show mild symptoms of COVID-19, led a group of researchers to strive to create organs-on-a-chip lungs, enabling both the study of the disease and testing the efficacy of drugs to treat it [19].

In 1991, in response to European Directive 1983/609/EEC protecting the use of non-human animals for scientific purposes, the European Centre for the Validation of Alternative Methods (ECVAM) was created. The agency finances and manages studies to validate methods that replace non-human animals in research for regulatory purposes, such as safety testing of chemical, cosmetic, pharmaceutical, and biological products, among others [20].

With the initial purpose of validating alternative methods, ECVAM expanded its role in 2010, seeking to replace the use of non-human animals in studies completely. Since 2013, the center has prohibited marketing any cosmetic product containing ingredients or raw materials tested on non-human animals. In addition, it has published 49 alternative methods internationally recognized by the Organization for Economic Cooperation and Development (OECD), which cover skin corrosion and irritation, eye injuries, and endocrine disruptors [21].

Research published in 2020 points to promising alternative methods for studying respiratory diseases using three-dimensional (3D) cultures, spheroids, organoids, and microfluidic systems (organ-on-a-chip). The same occurs in surrogate techniques in breast cancer studies, using two-dimensional (2D) and 3D cultures, mammospheres, and microfluidic systems, especially in studies of the molecular basis of the early development of the disease [22].

A report by the European Commission [23] published in May 2020, containing data on the use of non-human animals in testing, research, teaching, and product safety trials from 2015 to 2017, indicates that mice were the most used species, followed by rats and rabbits. Germany, the United Kingdom, and France were the countries that used these species the most.

Data from Animal Use Reporting (ALURES) [24], a database that includes 28 European Union countries plus Norway and presents data since 2015, revealed that in 2019, more than 10 million non-human animals were used in research and testing. Of these, 52.5% were mice, followed by 19.3% of

"other fish" and 9.4% of rats, demonstrating a tendency in the scientific community to change the selection of animal models.

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was created in the United States in 2000. This permanent National Institutes of Health committee comprises 17 regulatory and research agencies that generate and disseminate information about product safety testing so that alternative methods to using non-human animals can be developed, promoted, and recommended. Currently, the committee recognizes 128 methods for chemical and biological substances, among others, although the documents are considered recommendatory and do not give rise to legal liability [25].

Data published in a study using inventories from research laboratories in the United States indicate that mice and rats represent approximately 99% of all mammals used in experiments. The number of animals of these species, vastly underreported, may have reached 111 million per year between 2017 and 2018, with many of these experiments funded by government agencies. Of the estimated total, almost 45 million were included in "pain category" experiments, i.e., when non-human animals are subjected to procedures that generate pain and/or suffering, with or without the use of drugs that take into account their well-being [26].

Within the countries that make up the Southern Common Market (MERCOSUR), the MERCOSUR Regional Platform for Alternative Methods to Animal Experimentation (PReMASUL), created in 2015, aims to adapt the production of food, pharmaceuticals, and cosmetics, among others, to technological innovations that provide toxicological tests capable of generating results that are as reliable (or more so) than those generated through animal experimentation. Except for Brazil, the countries of the economic bloc do not have policies aimed at reducing the use of non-human animals in testing, experiments, and teaching [27].

The platform seeks to enable knowledge exchange between MERCOSUR countries and European partners. It also provides laboratory infrastructure and human resources training for implementing alternative methods to use non-human animals so that member countries can become a reference in Latin America in replacing non-human animals in pre-clinical or non-clinical trials [27].

The National Health Surveillance Agency (ANVISA) approved the Collegiate Board Resolution (RDC) 35/2015 [28], which provides for alternative methods to animal experimentation approved and recognized by CONCEA in its RN 18/2014 [29], RN 31/2016 [30], RN 45/2019 [31], and RN 56/2022 [32]. CONCEA defines in its RN 54/2022 [33] five years from publishing the recognized alternative method for the adequacy of institutions [34]. However, no content is mentioned about the inspection of institutions to confirm whether the method has been implemented and is in use.

Only in February 2023, CONCEA published RN 58/2023 [35], effective March of the same year, prohibiting the use of non-human vertebrate animals in development and quality control tests for personal hygiene products, cosmetics, and perfumes for ingredients and components that already have scientifically proven safety and efficacy. The regulation states that validated alternative methods must be mandatory for those whose safety and efficacy have not been scientifically proven.

It is essential to mention that CONCEA does not publish data on its website regarding the number of non-human animals used in experimental research, only disclosing which institutions are accredited by the council. In a direct consultation with the organization in January 2023, it did not comment on data publication or any type of information processing.

The Brazilian Center for Validation of Alternative Methods (BraCVAM), created in 2012 and located at the Oswaldo Cruz Foundation, has the mission of promoting the development and dissemination of alternative methods for using non-human animals in the areas of experimentation and teaching, supported by the 3R principle. Together with the National Network on Alternative Methods (RENAMA), it comprises central and associated laboratories, providing the physical structure and human resources capable of implementing alternative methods supported by internationally adopted methodologies. In addition to reducing the use of non-human animals in research and testing, it ensures reliability and increases Brazil's competitiveness in the global production market [36].

Bioethics training for representatives of ethics committees

Upon receiving a research project submitted for analysis, the CEUA must verify the requirements to ensure that ethical principles were considered in the preparation of the project, such as the suitability of the species to be worked with and its biological relevance for the study in question experimental design and use of a minimum number of non-human animals capable of producing statistically satisfactory and reproducible results; analgesia and anesthesia techniques applied to minimize the suffering of the non-human animals used; and demonstration that the study is not duplicated and that the benefits obtained from the expected results outweigh the harm caused by their use. It must also be assessed whether the team responsible for the experiments and care of non-human animals has proven experience, in addition to justifying the lack of alternative methods that prevent the project's approval.

RN 49/2021, from CONCEA, determines that any user—understood as *all individuals involved in handling animals in production, maintenance, or use in scientific research or teaching activities* [37]—must have practical and ethical training and specific training applicable to animal experimentation. This training must be proven through a course, specific training, experience, or academic discipline in Laboratory Animal Science (CAL). With this determination, the offer of courses in the area of CAL increased, with the institutional CEUA being responsible for validating the certification of the training according to the profile of the activities developed by the requesting user at the institution.

Only in September 2022, almost a year and a half after the publication of RN 49/2021 [37], did CONCEA publish on its website a text with guidelines regarding the resolution of a merely accessory and non-normative nature to present the minimum requirements for the committees to be able to validate the proof of the qualification presented [38].

RN 51/2021 [2] of CONCEA does not expressly guide in Art. 10 the need for CEUA members to present knowledge in bioethics. This requirement is restricted to the training area, including recognized technical competence and notorious knowledge. Despite this, its Art. 3, IV, c states that it is the duty of the institution to which the CEUA is linked to provide *material and financial support for the training and technical updating of CEUA members in ethics and in the care and use of animals in experimentation*, ensuring the support needed to fulfill their obligations before the CONCEA and the provisions of the Arouca Law [2].

Application of animal ethics by the ethics committee

CEUA members responsible for evaluating the training of non-human animal users are expected to have extensive knowledge in the technical area and matters related to animal welfare, ethics, and legislation aimed at animal protection. Likewise, they can count on legal and institutional support to constantly implement updates and training. Only in this way can it be possible to judge whether project applicants are qualified to handle non-human animals and ethically monitor associated practices.

While this prerogative is evident, it is not considered in RN 51/2021 [2] of CONCEA, which only determines that CEUA members have training in specific areas and have technical and renowned knowledge in their areas of activity, without mentioning anything about bioethics or animal ethics. The same legal provision also recognizes, in § 3 of Art. 10, that the committee may be made up of members from other professional categories as long as this is determined in its internal regulations, which makes the task of judging the training of users even riskier and not in line with animal vulnerability and the principles governing ethics and animal welfare in scientific research.

It is worth noting that bioethics and animal ethics are not part of the mandatory curriculum of most undergraduate and/or graduate courses in the areas of training listed in RN 51/2021 [2]. It is, therefore, clear that an inadequately trained – or even untrained – member of the CEUA will not be able to consistently assess the training of the user involved in a research project with non-human animals, as well as the project as a whole in terms of ethical requirements, which is a significant challenge for members of these Committees.

CONCEA, as a regulatory and guidance body, should provide means to standardize and even offer a training model for CEUA members. This model would, by extension, serve as a basis for evaluating the training of users involved in research with non-human animals. We currently see groups of CEUA representatives meeting on social media, discussing questions and ideas about the Committee's work to fill a gap overlooked by the regulatory body or even associations promoting courses on the subject.

CONCEA should consider communication and technical guidance with training for CEUA work as highly urgent. Only in 2022, ten years after the mandatory implementation of ethics committees in educational and research institutions in Brazil, did CONCEA begin its calendar of technical visits to learn about the CEUA's work routine, verify the applicability of the relevant legislation, and assist in enriching the work developed [39].

When discussing a research protocol submitted to a CEUA, a series of questions are evaluated, such as:

1. Was the study previously tested *in vitro*, and do the results reinforce the need to continue the research on non-human animals?
2. Was a pilot study aimed at reducing the number of non-human animals used and adequate planning for subsequent tests planned?
3. Is the study not duplicated or already widely repeated?
4. Are refinement practices foreseen, in addition to permanent care and animal monitoring?

Despite being considered critical points for research ethical approval, most of these questions are not even considered in the experimental design. Projects are frequently and repeatedly returned to applicants because they do not contain basic information such as that set out above. They do not present the scientific basis required to endorse the need to apply specific techniques, many of which are considered unethical.

CEUA assists researchers by providing information and guidance on alternatives or methodologies for the proposed study, which can reduce animal suffering without invalidating results. In these cases, without any justification, the researcher responds that the alternatives presented may "negatively influence" the expected results, which denotes ethical distance and lack of knowledge on the part of those who should know their study objects and the characteristics of the chosen animal model. Currently, the idea that non-human animals were created to serve the human animal and that favoring the moral agent—with results that benefit their fellow animals—to the detriment of the moral patient should prevail is still observed [40].

It is imperative to consider that the suffering caused to a being that has consciousness and sensitivity and is the holder of intrinsic value has the same weight as similar suffering inflicted on a human animal. Non-human animals have the perception of lived memories, accumulation of learning, continuity of life, and future time and, therefore, belong to a moral community that should not treat them as instruments sentenced to meet human needs and satisfy human desires.

On the other hand, the CEUAs must move away from the purely utilitarian argument used by researchers that the benefits obtained from research are more significant than the harm caused to non-human animals. This is a kind of overvaluation of human interests, especially concerning experiments aimed at basic research, which will not necessarily present relevant discoveries for the health or improvement of the quality of life of the human animal. In addition, and no less critical, the reproducibility and repeatability of experiments must be evaluated so that the lives of non-human animals are not used in vain without an adequate experimental design.

Regarding the ability of institutions to apply alternative methods (which allow for reduced use of non-human animals or refinement of the technique) or substitute methods (which completely replace the use of non-human animals), the following stand out: the complexity of the steps involved in the process of approving alternative/substitute methodology, which depend on financial and/or government support; the necessary change of paradigms; and partnerships between industries and academia, among many others that end up making the process slow and bureaucratic.

No less important, the resistance of large industries to changing traditional and less expensive techniques, the research support funds that do not encourage experiments that

use alternative methodology to the use of non-human animals, and the lack of technical and guidance incentives from the CEUA to recommend the use of the methods are also evident. All of these obstacles prevent the implementation of substitute techniques from becoming an active reality. Alternative/substitute methodologies must be widely publicized and duly demanded from those involved in the experiments, with frequent monitoring by the CEUA and the transfer of information to higher bodies.

It is also necessary to develop public policies to raise awareness among the academic population so that researchers, technical staff, and undergraduate and graduate students are aware and humane regarding the vulnerability and sentience of animals in scientific research and so that the old maxim, "We have always done it this way and there has never been a problem" does not continue to be institutionalized.

In the United States and countries of the European Union, researchers are charged a fee for each animal and day of accommodation required to keep them in animal facilities. Implementing this practice in Brazil could not only cover the costs of maintaining non-human animals but also instill a sense of responsibility since the financial aspect, in many cases, seems more relevant than ethical concerns and animal welfare.

Frequent and proven training, guidance, and monitoring of projects approved by the CEUA must be supported by law and the management of the institution to which the committee is linked. This seeks to ensure the complete protection of its members and their respective judgments, often considered mere obstacles to the approval of research projects.

Final considerations

Establishing the ethical review system for animal use protocols in Brazil, with its central body at CONCEA and the various CEUAs, expresses the philosophical perspectives that address ethics in the relations with non-human animals [41]. The contribution of the animal ethics movement in this context should be central, as it postulates that the circle of moral consideration for other animal species and humans should be expanded [42].

The use of non-human animals in experimental research aimed at reproducing diseases in humans and developing new drugs is the subject of frequent discussions about its efficacy. This is because most studies fail to mimic diseases, and only 9.6% of tests for new drugs are approved in phase I of clinical trials. Therefore, using non-human animals in research cannot ensure the discovery of new therapies for critical diseases, such as Alzheimer's disease and cancer [22].

The lack of efficient awareness programs among the academic population and research on the rational use of non-human animals and the absence of routine inspection procedures for institutions accredited by CONCEA and institutional CEUA may lead to ineffective application of the Arouca Law. Furthermore, it may compromise the joint involvement of legal representatives of institutions certified by CONCEA—or even of those that use non-human animals for scientific and teaching purposes and are not yet accredited, as well as researchers, professors, members of CEUA and the entire chain of professionals involved and working in the institutions.

Furthermore, *in loco* guidance and inspections by CONCEA were only initiated in accredited institutions, albeit tentatively, in 2021, reinforcing the need for closer monitoring by the regulatory body, which can generate knowledge and improve the work carried out by ethics committees.

In this sense, producing knowledge about the functioning and performance of these bodies is required to educate the scientific community about the ethics of animal protection and the concrete consequences of the ethical review of protocols to reduce the suffering and death of non-human animals [41].

In addition, the scientific community must be informed about the morality of their actions, warning them that research sites will no longer accept the issue of ignorance and/or lack of ethics being ignored in trials with non-human animals [17]. Ethics can support scientific research based on critically investigating the fundamental principles and concepts included in the moral debate.

References

1. Brasil. Lei nº 11.794, de 8 de outubro de 2008. Regulamenta o inciso VII do § 1o do art. 225 da Constituição Federal, estabelecendo procedimentos para o uso científico de animais; revoga a Lei nº 6.638, de 8 de maio de 1979; e dá outras providências. Diário Oficial da União [Internet]. Brasília, 8 out 2088 [acesso 21 fev 2023]. Disponível: https://tny.im/MomEc
2. Brasil. Ministério da Ciência, Tecnologia e Inovações. Conselho Nacional de Controle de Experimentação Animal. Resolução Normativa Concea nº 51, de 19 de maio de 2021. Dispõe sobre a instalação e o funcionamento das Comissões de Ética no Uso de Animais – CEUAs e dos biotérios ou instalações animais. Diário Oficial da União [Internet]. Brasília, 24 maio 2021 [acesso 21 jan 2023]. Capítulos II e IV. Disponível: https://tny.im/Xh2za
3. Silva A. O status moral dos animais segundo o ordenamento jurídico brasileiro. Jusbrasil [Internet]. 2019 [acesso 20 jan 2023]. Disponível: https://tny.im/gOs81
4. Mañalich Raffo JP. Animalidad y subjetividad: los animales (no humanos) como sujetos-de-derecho. Revista de Derecho (Valdivia) [Internet]. 2018 [acesso 28 fev 2023];31(2):321-37. p. 331. Tradução livre. DOI: 10.4067/S0718-09502018000200321
5. Camenzind S. Kantian ethics and the animal turn: on the contemporary defence of Kant's indirect duty view. Animals (Basel) [Internet]. 2021 [acesso 17 fev 2023];11(2):512. DOI: 10.3390/ani11020512
6. Dardenne E. From Jeremy Bentham to Peter Singer. Revue d'*Études* Benthamiennes [Internet]. 2010 [acesso 25 jan 2023];7. DOI: 10.4000/etudes-benthamiennes.204
7. Singer P. *Ética* prática. 2ª ed. Lisboa: Gradiva, 2002.
8. Low P. The Cambridge declaration on consciousness [Internet]. In: Proceedings of the Francis Crick Memorial Conference; 7 jul 2012; Cambridge. Cambridge: Francis Crick Memorial Conference; 2012 [acesso 17 fev 2023]. Tradução nossa. Disponível: https://tny.im/weCSv
9. Silva TT, Corrêa MCDV. Ética na Experimentação animal: limites e controvérsias de uma prática. Saarbrücken: Novas Edições Acadêmicas; 2016.
10. Jankoski LGQ, Fischer ML. O papel da bioética nas comissões de ética animal. Rev. bioét. (Impr.) [Internet]. 2019 [acesso 21 jan 2023];27(3):549-65. DOI: 10.1590/1983-80422019273340
11. Pereira S, Tettamanti M. Ahimsa and alternatives: the Concept of the 4th R: the CPCSEA in India. Altex [Internet]. 2005 [acesso 4 fev 2023];22(1):3-6. Disponível: https://tny.im/dfVH5
12. Garutti S, Palma B. Experimentação científica com animais: considerações sobre os comitês de ética. Revista de História Comparada [Internet]. 2010 [acesso 4 fev 2023];4-2:107-24. Disponível: https://tny.im/GS2Ea
13. Schramm FR. Uma breve genealogia da bioética em companhia de Van Rensselaer Potter. Revista Bioɛthikos [Internet]. 2011 [acesso 17 fev 2023];5(3):302-8. Disponível: https://tny.im/XvlbS
14. Zanella DC. Humanidades e ciência: uma leitura a partir da Bioética de Van Rensselaer (V. R.) Potter. Interface Comun Saúde Educ [Internet]. 2018 [acesso 7 fev 2023];22(65):473-80. p. 474. DOI: 10.1590/1807-57622016.0914
15. Lacerda BA. Pessoa, dignidade de justiça: a questão dos direitos dos animais. Revista Ética e Filosofia [Internet]. 2012 [acesso 6 fev 2023];2(15):38-55. DOI: 10.34019/2448-2137.2012.17725
16. Ramos FRS, Brehmer LCF, Canever BP, Padilha MI, Silveira LR. Desafios atuais da bioética brasileira. Rev. bioét (Impr.) [Internet]. 2019 [acesso 4 fev 2023];27(3):446-54. DOI: 10.1590/1983-80422019273328
17. Rezende AH, Peluzio MCG, Sabarense CM. Experimentação animal: ética e legislação brasileira. Rev Nutr [Internet]. 2008 [acesso 16 fev 2023];21(2):237-42. DOI: 10.1590/S1415-52732008000200010
18. Moretto LD. Métodos alternativos ao uso de animais em pesquisa reconhecidos no Brasil [Internet]. São Paulo: Limay; 2019 [acesso 10 jan 2023]. p. 15. Disponível: https://tny.im/CmVyF
19. Sprankle C. Organs-on-a-chip for COVID-19 research group led by NTP center. Environmental Factor [Internet]. 2021 [acesso 20 fev 2023]. Disponível: https://tny.im/rwoWL

20. Halder M, Hartung T. European Centre for the Validation of Alternative Methods (ECVAM): its role and contribution [Internet]. In Proceedings of the International Symposium Alternatives to Animal Testing: New Approaches in the Development and Control of Biologicals; 2008; Strasbourg. Strasbourg: Council of Europe; 2008 [acesso 5 jan 2023]. p. 23-32. Disponível: https://tny.im/CjEsj

21. EURL Ecvam Activities. Alternatives to Laboratory Animals [Internet]. 2021 [acesso 3 jan 2023];49(6):229-34. DOI: 10.1177/02611929211063560

22. Gribaldo L, Dura A. EURL ECVAM Literature review series on advanced non-animal models for respiratory diseases, breast cancer and neurodegenerative disorders. Animals (Basel.) [Internet]. 2022 [acesso 7 jan 2023];25;12(17):2180. DOI: 10.3390/ani12172180

23. European Commission. 2019 report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017. EUR-Lex [Internet]. 2019 [acesso 11 jan 2023]. Disponível: https://tny.im/D20iQ

24. European commission. Alures: animal using reporting: EU system [Internet]. 2020 [acesso 25 jan 2023]. Section 1, Numbers of animals used for research, testing, routine production and education and training purposes in the EU. Disponível: https://tny.im/rZCAg

25. U.S. Department of Health and Human Services. Alternative methods accepted by US agencies [Internet]. 2023 [acesso 30 jan 2023]. Disponível: https://tny.im/sGtX0

26. Carbone L. Estimating mouse and rat use in American laboratories by extrapolation from Animal Welfare Act-regulated species. Sci Rep [Internet]. 2021 [acesso 1 fev 2023];11:493. DOI: 10.1038/s41598-020-79961-0

27. Plataforma Regional de Métodos Alternativos à Experimentação Animal do MERCOSUL (PReMASUL). Informe [Internet]. 2018 [acesso 3 jan 2023];1. Disponível: https://tny.im/gl6f4

28. Agência Nacional de Vigilância Sanitária. Resolução da Diretoria Colegiada – RDC nº 35, de 7 de agosto de 2015. Dispõe sobre a aceitação dos métodos alternativos de experimentação animal reconhecidos pelo Conselho Nacional de Controle de Experimentação Animal – Concea. Diário Oficial da União [Internet]. Brasília, 10 ago 2015. [acesso 22 set 2023]. Disponível: https://tny.im/5HrrF

29. Brasil. Ministério da Ciência, Tecnologia e Inovações. Resolução Normativa Concea nº 18, de 24 de setembro de 2014. Reconhece métodos alternativos ao uso de animais em atividades de pesquisa no Brasil, nos termos da Resolução Normativa nº 17, de 03.07.2014, e dá outras providências. Diário Oficial da União [Internet]. Brasília, 25 set 2014 [acesso 21 set 2024]. Disponível: https://tny.im/qIFjG

30. Brasil. Ministério da Ciência, Tecnologia e Inovações e Comunicações. Resolução Normativa Concea nº 31, de 18 de agosto de 2016. Reconhece métodos alternativos ao uso de animais em atividades de pesquisa no Brasil. Diário Oficial da União [Internet]. Brasília, 19 ago 2016 [acesso 21 set 2024]. Disponível: https://tny.im/IdHxg

31. Brasil. Ministério da Ciência, Tecnologia e Inovações. Resolução Normativa Concea nº 45, de 22 de outubro de 2019. Reconhece método alternativo ao uso de animais em atividades de pesquisa no Brasil. Diário Oficial da União [Internet]. Brasília, 25 out 2019 [acesso 21 set 2024]. Disponível: https://tny.im/9wK3

32. Brasil. Ministério da Ciência, Tecnologia e Inovações. Resolução Normativa Concea nº 56, de 5 de outubro de 2022. Reconhece métodos alternativos ao uso de animais em atividades de pesquisa no Brasil. Diário Oficial da União [Internet]. Brasília, 7 out 2022 [acesso 21 set 2024]. Disponível: https://tny.im/aig1d

33. Brasil. Ministério da Ciência, Tecnologia e Inovações. Resolução Normativa Concea nº 54, de 10 de janeiro de 2022. Dispõe sobre o reconhecimento de métodos alternativos ao uso de animais em atividades de ensino e pesquisa científica e dá outras providências. Diário Oficial da União [Internet]. Brasília, 17 jan 2022 [acesso 21 set 2024]. Disponível: https://tny.im/40gTB

34. Brasil. Ministério da Ciência, Tecnologia e Inovação. Métodos alternativos reconhecidos pelo Concea. Gov.br [Internet]. 2022 [acesso 26 set 2023]. Disponível: https://tny.im/TBsOW

35. Brasil. Ministério da Ciência, Tecnologia e Inovação. Resolução Normativa Concea nº 58, de 24 de fevereiro de 2023. Dispõe sobre a proibição do uso de animais vertebrados, exceto seres humanos, em pesquisa científica, desenvolvimento e controle de produtos de higiene pessoal, cosméticos e perfumes que utilizem

em suas formulações ingredientes ou compostos com segurança e eficácia já comprovadas cientificamente e dá outras providências. Diário Oficial da União [Internet]. Brasília, 1 fev 2022 [acesso 2 mar 2023]. Disponível: https://tny.im/JhFXo

36. BraCVAM: Centro Brasileiro para Validação de Métodos Alternativos [Internet]. 2023 [acesso 5 jan 2023]. Disponível: http://www.bracvam.fiocruz.br/

37. Brasil. Ministério da Ciência, Tecnologia e Inovações. Resolução Normativa Concea nº 49, de 7 de maio de 2021. Dispõe sobre a obrigatoriedade de capacitação do pessoal envolvido em atividades de ensino e pesquisa científica que utilizam animais. Diário Oficial da União [Internet]. Brasília, 10 maio 2021 [acesso 21 jan 2023]. Disponível: https://tny.im/MjF4n

38. Brasil. Ministério da Ciência, Tecnologia e Inovação. Orientações acerca da RN Concea/MCTI nº 49/2021 (Capacitação). Gov.br [Internet]. 23 set 2022 [18 out 2024]. Disponível: https://tny.im/W1zkS

39. Brasil. Ministério da Ciência, Tecnologia e Inovação. Concea inicia visitas técnicas. Gov.br [Internet]. 1º set 2022 [acesso 20 jan 2023]. Disponível: https://tny.im/RamAD

40. Felipe ST. Valor inerente e vulnerabilidade: critérios éticos não-especistas na perspectiva de Tom Regan. Ethic@ [Internet]. 2006 [acesso 25 fev 2023];5(3):125-46. Disponível: https://tny.im/OjrbO

41. Corrêa Neto JLC, Lorenzo C, Sanchez MN. Influência de uma comissão de ética na proteção de animais. Rev. bioét. (Impr.) [Internet]. 2017 [acesso 28 dez 2023];25(3):630-5. DOI: 10.1590/1983-80422017253220

42. Tréz TA. A caracterização do uso de animais no ensino a partir da percepção de estudantes de ciências biológicas e da saúde. Hist Ciênc Saúde Manguinhos [Internet]. 2015 [acesso 4 fev 2023];22(3):863-880. DOI: 10.1590/S0104-59702015000300012

Update

Renata Batista da Silva – PhD – renatabatsil@gmail.com
0009-0002-9915-5733

Tatiana Tavares da Silva – PhD – tavares_tatiana@yahoo.com.br
0000-0001-5738-0321

Correspondence
Renata Batista da Silva – Rua Garibaldi, 193, bloco 2, ap. 1104, Tijuca CEP 20511-330.
Rio de Janeiro/RJ, Brasil.

Participation of the authors
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