

**RESEARCH**

Biomedical innovation and ethics: alternatives to animal testing

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Abstract

The use of non-human animals has been incorporated into scientific practices as an essential biomedical research tool and in industry tests for human consumption. The systematic review of protocol results of preclinical phases is not a common practice, but recent meta-analyses question the projection accuracy of these data for humans. Currently, along with scientific questioning, there is a comprehensive ethical discussion about the conflicts in the instrumentalization of non-human life, which reached its peak with the creation of transgenic animals. This article discusses the application of the concept of vulnerability to non-human animals in experiments and reflects on the implicit power relations of these practices. We propose to implement and develop alternative techniques to the animal model, combining ethics and innovation.

Keywords: Models, animal. Animal experimentation. Ethics, research. Vulnerability study.

Resumo**Inovação biomédica e ética: técnicas substitutivas na experimentação animal**

A utilização de animais não humanos como ferramenta de pesquisa biomédica e em testes da indústria para consumo humano foi incorporada às práticas científicas e assimilada como fundamental. A revisão sistemática dos resultados de protocolos de fases pré-clínicas não é prática corrente, mas metanálises recentes questionam a capacidade de projeção desses dados para a espécie humana. Atualmente, junto com o questionamento científico há abrangente discussão ética sobre os conflitos inerentes à instrumentalização da vida do animal não humano, cujo ápice é alcançado na criação de animais transgênicos. O objetivo deste artigo é discutir a aplicação do conceito de vulnerabilidade ao animal não humano no contexto da experimentação e pensar as relações de poder implícitas nessas práticas. Como aplicação prática da teoria exposta, propõe-se implantar e desenvolver técnicas substitutivas ao modelo animal, que conjuguem ética e inovação.

Palavras-chave: Modelos animais. Experimentação animal. Ética em pesquisa. Estudo sobre vulnerabilidade.

Resumen**Innovación biomédica y ética: técnicas alternativas a la experimentación animal**

El uso de animales no humanos como herramienta para la investigación biomédica y en pruebas de la industria para el consumo humano se ha incorporado a las prácticas científicas y se ha asimilado como fundamental. La revisión sistemática de los resultados de protocolos de fases preclínicas no es una práctica corriente, pero metaanálisis recientes cuestionan la capacidad proyección de estos datos a la especie humana. Actualmente, junto con el cuestionamiento científico, hay una discusión ética sobre los conflictos inherentes a la instrumentalización de la vida del animal no humano, que alcanza su ápice en la creación de animales transgénicos. Este artículo tiene como objetivo discutir la aplicación del concepto de vulnerabilidad al animal no humano en el contexto de la experimentación y proponer una reflexión sobre las relaciones de poder implícitas en estas prácticas. Como una aplicación práctica de la teoría expuesta, se propone implantar y desarrollar técnicas alternativas al modelo animal, que conjuguen ética e innovación.

Palabras clave: Modelos animales. Experimentación animal. Ética en investigación. Estudio de vulnerabilidad.

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Alternative techniques to the animal model in biomedical and industrial research are the most reliable expression of ethics applied to defend, protect, and recognize the moral status of non-human animals in contexts of vulnerability and oppression. When comparing the ethical conduct with humans to animal experimentation, we find a great gap between the ethical care adopted in the first and the procedures described in preclinical phases. While with humans one should avoid or minimize any harm to the participants, in preclinical phases the outcome is death or irreparable harms^{1,2}. The same applies to product testing for human consumption – especially in the chemical industry – that causes suffering to animals.

In developing countries, such as Brazil, despite the evidence of suffering and harm inflicted on non-human life, they are still used in industry tests. However, in countries that traditionally discuss this matter and where social movements of animal protection are more consolidated (as in the European Union), such practices are no longer accepted¹.

The application of the vulnerability concept of non-human animals in experimentation is the basis of this study. By recognizing their vulnerable status in this context, this article presents a theoretical approach committed to changing how contemporary science treats non-human animals. The goal is to promote the consolidation of public policies that aim at implementing alternative techniques in research, education, and industry – especially in developing countries that do not yet treat this issue as a necessity.

Method

This study undertook a non-systematic and extensive literature review on the scientific use of the animal model, also analyzing official documents from regulatory agencies of the European Union, Great Britain, Brazil, the United States and Canada. We also collected data from the National Council for Animal Experimentation Control (Concea) – an organ of the Brazilian Ministry of Science, Technology and Innovations (MCTI) – regarding registrations of research centers that had approved protocols for animal testing. The ethical analysis focused on the vulnerability state of non-human animals in the experimentation context, whose participation is established from a utilitarian perspective.

Animal model in oncotoxicity tests

The non-human animal is considered a basic tool for biomedical research – an idea perpetuated by science that is still used today^{1,2}. But current public health issues, such as studies on the effects the Zika virus has on the fetal brain, have helped questioning this concept. The lack of scientific knowledge on what would be the ideal animal model to understand the action of Zika on human brain cells led researchers to create alternative techniques, developing brain organoids from human stem cells or neuronal cells, since the use of mice failed to provide the necessary answers³.

It is common to question which animal would be suitable for a study at the beginning of the investigation. However, no definitive answers to this question can be found, and in previous research, such as polio, the inappropriate use of animals and misinterpretation of data have jeopardized the development of a human vaccine⁴. Although this model is part of the scientific culture and practice, historically it has not always been well accepted by the scientific community. It only became the gold standard in the 1950s. Until then, small animals – guinea pigs, rabbits, and mice – were bought in markets or directly from breeders, and the scientific environment would question the results due to the non-standardization of animals⁵.

Science is affected by the market policies that drive the world, and the use of animals in studies has also been motivated by industrial interests. The technical-scientific evolution of the twentieth century was strongly associated with the post-Industrial Revolution and led to major changes in scientific and drug production (from artisanal to industrial, on a large scale). Mass production of medications intensified this model in preclinical and chemical tests of products for human consumption⁶.

Since the first reported bioassay, in 1915, when Yamagiwa and Ichikawa showed that coal tar caused skin cancer on the ear of rabbits^{6,7}, toxicity tests have been routinely carried out, and not just for medicinal purposes, killing millions of sentient animals, mostly mammals⁸. Besides requiring an exorbitant number of animals, bioassays for carcinogenic potential are characterized by a high degree of suffering, pain and stress^{2,9,10}. Long-term toxicity tests for pesticides, for example, are conducted with dogs (beagles), always resulting in long suffering followed by death. These tests use two different species (rodents and non-rodents) in subchronic (90-day long) and

chronic (12-month long) studies of repeated dose intake – that is, long-duration^{11,12}.

An important factor in biomedical research is the need to replicate results, which makes a non-human animal a standard in a study or test. The repeated use of a given species to compare data perpetuates the cycle. Depending on the methods used and how invasive they are, a huge number of animals are submitted to suffering¹.

Difficulty in projecting interspecies data

Despite the increasing and excessive use of non-human creatures in toxicity tests, the results are insufficient to ensure safety, efficiency, and real projection of data for the human species. Basically, traditional toxicity tests are impractical, because they require an absurdly high number of animals to meet the requirements of regulatory agencies, which leads to sampling tests, making the safety assessment for human use of the substance quite questionable². Such requirement goes against the reduction of animal use, advocated by the principles of the 3Rs (replacement, reduction, refinement) proposed by Russel and Burch¹³ in 1959.

The difficulty of assessing liver toxicity is the biggest problem of the pharmaceutical industry and the major reason for withdrawing drugs from the market. This is due to the difference in the histo- and biochemical metabolizing properties of the liver cells of other species in comparison with humans^{14,15}. The interspecies difference in hepatic and renal metabolism is the main cause of the high failure rates of preclinical studies with non-human animals^{7,16}, and may explain why millions of dollars spent on basic research lead to few clinical advances.

Regarding carcinogenesis, the physiological variables and their expressions are quite different even between species with similar DNA (large primates and humans), affecting test results of medications and products¹⁷. Other factors that increase the disparity of results are the large methodological variation of the protocols, type of research, species, and interspecies and intersex variations, which influence the analysis of toxicokinetic and pharmacokinetic parameters, although scientists try to control the variables of preclinical research protocols.

Conducting meta-analysis studies in basic research is a complex task because standardizing protocols in the preclinical phase is difficult compared with the clinical phase protocols with

humans. The feeding route itself, whether *ad libitum* or oral gavage (force-feeding to control intake), leads to divergent results, as well as altered physiological factors and differences in the speed of cellular metabolism of animals (rodents and humans, for example). Even so, meta-analysis studies showed frequent methodological errors: use of only one animal strain (rodents) or one sex; use of young animals, without age variation; inadequate group size; physical and psychological stress; inadequate exposure to drugs (related to time and amount), among others^{2,17,18}.

Vulnerability of animals in testing

Animals are not only oppressed by a cage, but by the powerful structure of a dogmatic science that strongly influences society, producing and reproducing itself as an opinion-maker. The industry also controls them, holding exorbitant profits, and the political structure determines laws that allow questionable practices^{1,2}. Thus, a complex structure naturalizes these processes and denies the suffering and vulnerability of sentient beings.

In experimentation, they are stripped from their identity as animals and treated as objects to satisfy scientific curiosity. It is in this context that the most critical situations are found, with several ethical issues, since they include keeping animals restricted and in physical and psychological suffering.

The maximum instrumentalization is reached with transgenic animals, whose life is limited to biosafety laboratories. Their process of life and death is determined by professionals, and the only purpose of their existence is to participate in an uncertain study^{1,2,9} that, if successful, would not benefit them. The physiology of these animals is not well known, and there are indications that their sensitivity to pain is greater than the expected by scientists¹⁹.

Adopting only two of the 3Rs principles, reduction and refinement, is not a definitive solution to the ethical issues involved in this case. Substitution is the only way to achieve ethical scientific development, and the two principles mentioned are only the minimum when dealing with animals¹³. Improving their well-being is not enough to end the suffering caused by the current practices; it is necessary to develop alternative methods. How to quantify suffering? Not even individuals of the same species show the same responses to physical pain, or to fear in situations of imminent

danger or intense discomfort, confinement, cold and impersonal contact of those who manipulate them².

The instrumentalization of life reached its peak when the technological advances of the twenty-first century allowed the creation of genetically modified animals for various purposes, inserting human genes or blocking native genes. And why has the development of alternative techniques not evolved at the same speed? Why is reflecting on ethical issues of animal use and rapidly changing current practices still not a priority?

In this process, everyone involved is responsible: the researcher, who conceives the project and defines methods, may decide to use or not alternative methods; the assistants, who directly participate in the protocol; and all those who handle the animals. Publishers should analyze whether the studies they are disseminating were conducted in an ethical manner by establishing publication policies that stimulate good experimentation practices. This is an effort that should also be undertaken by the industry, which could invest in the research of alternative techniques, instead of maintaining traditional testing methods to ensure profit.

Moreover, we must mention scientific research funds that favor traditional techniques and do not stimulate other research models; regulatory agencies that do not punish institutions that use animals inappropriately; and ethics committees that do not determine alternative methods. Finally, we call attention to universities, responsible for future generations of researchers and professors, who do not approach the topic and maintain what has been done for centuries: a strict form of teaching based on tradition, without reflection or innovation, naturalizing knowledge production when it comes to non-human animals, in a different posture than with humans.

A utilitarian perspective guides decisions concerning animal experimentation, addressing only human interests. Animals are not at the heart of decisions regarding the various phases of the process – they are only submissive objects within a power and property sphere, from the drafting of the protocol, through the analysis of ethics committees, to the regulations that guide the procedures and destination of the animals involved.

To date scientific production has been ruled by classical ethical concepts, according to which only human beings are worthy of moral consideration². Verdú Delgado and García García²⁰ highlights the need to strengthen critical perspectives in the social sciences regarding the treatment of non-human

animals, and to develop a reflexive attitude on the dysfunctional exercise of power. Thus, the authors suggest introducing the interests of non-human animals in bioethical and socio-ethical debates by three methodological perspectives: distributive research, structural and dialectical (or critical). With them, we can observe objective (absolute qualities), interpretable (relative qualities) and transforming (reflective qualities) data.

Anthropocentrism is the absolute quality, as the power imbalance between different biological beings legitimizes the human superiority discourse and the control of the planet's resources by humankind. The relative quality points out the existence of other points of view and that animal exploitation should be rethought. Finally, the reflexive analysis proposes that the needs of non-human beings should be considered.

The legitimization of the exercise of power depends on the culture of each society. If an act is deemed legitimate and even beneficial in a social environment, it will not be characterized as bad or unethical; on the contrary, it will be legal. In short, the analysis shows to what extent truth and justice are built by cultural systems that reaffirm the power imposed by the strongest. Sometimes this results in making animals invisible in processes in which they are victims – experimentation or slaughter, for instance –, as if everything had been obtained without them. The exploitation is dissociated from the idea of a living being, to maintain it as an object, and to reduce the impact of the act, minimizing or erasing the aggression²⁰.

Since the 19th century, violence against animals has become increasingly organized and structured, a trend that has been intensified by the development of markets that mobilize the economy in the 20th century. Economic interest is one of the factors that lead to the exclusion of these beings from our moral system. In this context of exploitation and ownership, abuse is explained by animal objectification and the limitless human conduct in relation to other species.

Although continental moral philosophy, also called “modern European philosophy,” maintains an anthropocentric view, the animal issue has become more widely discussed and organized from the 20th century onwards, influenced by social movements and liberal and humanistic perspectives²¹. The preference utilitarianism proposed by Singer²² argues for the inclusion of non-human animals in our moral sphere and the valorization of their life. But some obstacles still make this perspective impractical.

There is a limit from which the barrier between human and animal interests becomes insuperable. This is well exemplified when analyzing data from official agencies of the European Union, Great Britain and Canada, which still reveal significant numbers of animals exposed to intense degrees of pain and suffering, in addition to using less anesthetic than what should be admitted. It is even acceptable to perform painful procedures without anesthesia. Where are the concepts of maximization of pleasure and the non-infringement of pain and suffering to others in exchange for dubious results? If the interest of animals was really within our moral sphere, such acts would not be allowed.

Even if the animal model served perfectly to project scientific results, such suffering and aggression are not ethically justified. The non-human animal, completely vulnerable in this structure, should be protected^{23,24}. The utilitarian argument commonly used to justify experimentation – the suffering of some animals for the benefit of millions of humans – is weak, because in reality the dilemma is the suffering of millions of sentient beings for hypothetical – and impossible to quantify – benefit of people¹.

Moreover, drugs or technologies produced by the pharmaceutical or medical equipment industry are inaccessible to most people because of their high cost. Therefore, the discourse that the use of animals benefits humans hides its real goal: profit.

In the classical utilitarian analysis – which considers the maximization of pleasure and the minimization of pain compared with the future benefit generated for others – the non-human animal, submitted to pain and suffering, should be protected, and so the current practices would not be justified. In preference utilitarianism, the maximization of pleasure or the minimization of pain are not in question, but the interests of those affected by the act^{22,25}. And it is clear that no being, including animals, wants to suffer.

When one speaks of “pain,” it is not only a matter of momentary physical pain, which can be suppressed with anesthetics, but the suffering imposed at all stages: fear, pain after the procedure and the perception of what is done with other animals, including puppies¹⁹. The old idea that animals can be used in experiments because they do not realize what happens to them or what could happen to them (therefore suffering less than humans) has been losing its scientific and ethical support^{2,24} (neurocognitive capabilities have already been detected in sentient animals).

However, the discourse that maintains current practices is disseminated in the media, classrooms, congresses and scientific publications of specialized journals or addressed to the general public. Animal experimentation and its results are always presented as great advances, even if they are only indications that will most likely have no application. The procedure is described, but it is not highlighted what was done with the non-human animal, that is, the adopted methodology. It is not disclosed that the animals used in the testing were healthy and intentionally injured for research purposes¹, rendering both the aggression and victims invisible²⁰.

Applying the 3R principles from the well-being perspective and advocating the reduction of suffering without focusing on alternative techniques serve as moral protection for the researcher. It allows procedures to be carried out within the current morality, without establishing new moral and scientific norms – as would be ethically desirable and expected – and without practical results to improve the welfare of animals¹⁹. From a perspective that associates well-being with abolitionism, the initial and immediate purpose is restriction: implementing actions to extinguish the use of animals in the near future^{26,27}. While this does not occur, millions of beings need measures to reduce and refine their use, as to minimize their suffering.

Laboratory animals are not chosen by chance, nor because they are the best model for studying a particular human disease (especially since this information is not previously known). Based on published studies, a model is exhaustively repeated to compare results. The selection considers certain characteristics, such as size (preferably small) and how easy they are to handle, contain and keep in captivity, also permitting the use of puppies. Animals that fit this “scientifically” oriented selection are the most vulnerable. The most fragile are deliberately chosen¹.

The concept of vulnerability is commonly addressed in bioethics and research ethics when applied to human groups, but its extension to animals is still little discussed. All living things are vulnerable^{28,29}, susceptible to assault or aggressions. But this vulnerability can shift from a latent state to a real state, without the possibility of defense^{23,29}. The fact that animals do not morally (or rationally) understand what happens to them, as well as the real magnitude of the aggression they are experiencing, makes them even more vulnerable.

Vulnerability can be passive or active, and the definition will have moral implications, especially

in an anthropocentric society, where humans are traditionally considered as active and animals as passive³⁰. If their vulnerability is considered passive, one can corroborate the idea of supposed disability, which would decrease its value in relation to humans. The non-human animal would be a moral patient, subjected to the wills of the moral agent (humans) capable of judging one's own actions. But animals have capabilities intrinsic to themselves and their species, so sentience and vulnerability can be considered active characteristics.

Contributing to animal ethics, Derrida³¹ highlights one interpretation of Bentham's writing about animals, capacity to suffer: Bentham used the verb "can," which in English emphasizes this capacity to suffer as an active capacity, as actually *being able to suffer*³⁰. For the English philosopher³² neither rationality nor speech were important, but rather the active capacity to suffer.

According to Calarco²¹, Derrida also associates this ability with the inability to avoid pain, highlighting and exposing the vulnerability, so as to call for moral response^{30,31}. According to Derrida³¹, we become moral subjects when we recognize the vulnerability of others. It is passive vulnerability that makes ethics necessary. Thus, just as Levinas³³ mentioned the "face of the other," Derrida³¹ addressed "the gaze of the other," also considering the gaze of non-human animals (which did not occur in Levinas). This encounter between man and animal, by merely looking to each other, would lead humans to rethink and change their egoistic existence^{21,30-32}.

Those who maintain an anthropocentric mentality do not become aware of the suffering of non-human animals, and do not realize the need for a moral response. Seeing the impossibility of fighting against aggression as a weakness, the anthropocentric man fails to recognize the vulnerability of animals, considering them inferior³⁰. However, humans are also passive in their vulnerability. In this perspective, the rupture caused by animals in humans is not due to the differences between them, but to the similarities, such as finitude and suffering.

Momentarily leaving anthropocentrism out, one realizes that non-human animals and humans share vulnerability, sustained not in passivity, but in blocked activity – the impossibility to manifest. Both are active, but unable to defend themselves while restrained and hurt. Suffering therefore is not passivity, but a frustrated action. In this context, sentience is between activity and passivity: it

empowers the animal to conduct its actions, but it also means that the animal is vulnerable to the action of others³⁰.

For Acampora^{34,35}, the vulnerability of the body, common to humans and animals, is the basis for extending moral compassion to other animals. Thus, the author opens the possibility of a moral consideration that does not appeal to similarities to describe feelings based on shared vulnerability. According to Thierman²⁴, the author seems to suggest that one can act without a moral definition of obligations and responsibilities regarding other animals. It would be enough to put the body at the forefront of ethical thinking to recognize our vulnerability, as animals that we are.

The association between the bioethical framework of vulnerability and the laws that protect humans in biomedical research is clear. Even though the term "vulnerability" does not appear explicitly in regulatory documents, it is assumed that some groups are more susceptible to harm¹. This recognition must be extended to non-human animals.

What to do? An ethical proposal

With more than 30,000 substances waiting to be tested in the European market (which would require millions of vertebrates), the European Consensus Platform on 3R Alternatives estimated the possibility of using alternative methods³⁶. Responding to the same concern, the CarcinoGenomics project was developed to optimize *in vitro* methods to detect carcinogenic potential of substances, replacing bioassays with rats and mice³⁷.

Some measures taken by the European Union – such as the abolition of animal testing throughout its territory in the cosmetic industry, in 2009; the import and use prohibition of raw materials tested in countries that allow animal experimentation, in 2013 – helped to reduce the use of animals in the industry and promote research and development of alternative techniques³⁸. In Brazil, initial steps were taken with Ordinance 491/2012 of the MCTI³⁹, which created the National Network on Alternative Methods (Renama), and the Conceia Normative Resolution 18/2014⁴⁰ that recognized 17 alternative techniques and established a five-year period for them to be put into practice. It is also worth mentioning the Brazilian Center for Validation of Alternative Methods (Bracvam) created by the Oswaldo Cruz Foundation in 2013⁴¹.

Recently a positive movement in Latin America has emerged with the creation of the Regional Platform for Alternative Methods to Animal Experimentation (Premasul), a training program in the area of alternative techniques that promotes the exchange of technologies between members of the Southern Common Market (Mercosur) and the European Union, which has more experience in this area. This movement was encouraged by market needs to maintain commercial relations with European countries, as described on the MCTI web page:

In view of the European Union's initiative to ban cosmetic products tested on animals, in order to be competitive in an increasingly globalized market, it is necessary to adapt production in the light of technological innovations that provide new toxicological tests capable of generating results as or more reliable than those generated through animal experimentation. (...) Brazil wishes to exchange its experience in the area of alternative methods to the use of animals with the other Mercosur countries and with European partners. This is because in the very near future there is likely to be a scenario in which there will be a drastic decrease in the use of experimental animals for testing various products. This scenario will contribute greatly to the knowledge-based and biotechnology-based economy⁴².

To this end, it is necessary to adopt measures such as monitoring research protocols registrations in the Concea system, and building consistent databases on existing alternative methods to assist researchers and students, since a transparent data system on the use of animals in research and testing is not yet available in Brazil.

Ethics committees are also essential to demand the use of current alternative techniques and those already validated in other countries, as to avoid repeating the whole process, which would lead to the use of more animals without justification. Research promotion foundations and universities are also fundamental and should encourage young researchers to think of projects that validate these alternative methods. Similarly, it is up to publishers to take responsibility for their submission policies, detecting unethical works and creating mechanisms to ensure the publication of negative data that resulted from animal experimentation.

Final considerations

The vulnerability of the non-human animal, so explicit in the context of experimentation, demands a moral response. Public policies are essential to stimulate the development and adoption of techniques that replace the use of animals in industrial testing, teaching and research, and to promote the exchange of innovation. The level of biotechnological development achieved in the 21st century reveals the ability to create morally adequate technologies, benefiting both humans and animals.

There is a moral need to remove the non-human animal from the cycle of suffering and death, which benefits exclusively humans. The arguments in favor of maintaining the current model – the supposed gold standard, as well as the utilitarian arguments about the benefits and safety they offer to humans – are debatable. Thus, if a morally preferable alternative exists, it must be prioritized.

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Tatiana Tavares da Silva conceived the article and, with Marilena Cordeiro Dias Villela Corrêa, wrote the text and worked on the final revision.

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