



ANIMAL RESEARCH ETHICS: AN OVERVIEW

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ABSTRACT

The use of laboratory animals in biomedical research is a topic of debate. Animals are utilized in study and research for centuries. We give an integrative approach explaining why biomedical research cannot neglect laboratory animal testing by outlining scientific, historical, ethical, and philosophical factors. Irrespective of the ethical attitude one takes, there is widespread agreement that animals have moral value and that their welfare must be regarded at the very least. It is not possible to replace in vivo animal experimentation because animal physiology and pathology are the same as humans, and this environment is not possible in vitro labs. National/international regulatory authorities have implemented a policy over 3 Rs (replacement, reduction, and refining) so that cruelty to animals could be prevented and animals should be used if and only if there are no alternatives available.

KEYWORDS: Animals ethics, 3Rs, Ethical issues, Biomedical Research.

INTRODUCTION

The word ethics is derived from the Ancient Greek word ethikos that's meaning "relating to one's character", which itself comes from the root word ethos meaning "character, moral nature".^[1] Rushworth Kidder states that "standard definitions of ethics have typically included such phrases as 'the science of the ideal human character' or 'the science of moral duty'".^[2] Richard William Paul and Linda Elder define ethics as "a set of concepts and principles that guide us in determining what behavior helps or harms sentient creatures".^[3] Animal research ethics is referred to as "a freshly coined word" by Tom L. Beauchamp in his contribution to *The Routledge Companion to Bioethics*.^[4] The term "animal research ethics" has been around since at least the 1980s. Jerrold Tannenbaum and Andrew N. Rowan concluded that "animal research ethics is still at a rudimentary state of development".^[5] They contrast this situation with the state of human research ethics today.

In human history, animals have been utilized in study and research for centuries. Research suggests that Aristotle used animals in his research even in ancient Greece, mostly to deepen our comprehension of living things. However, the use of animal models did not become widespread until the 18th and 19th centuries. J B Van Helmont, Francesco Redi, and Pasteur used animals in their research on the beginning of life. Animals were employed to better understand human and animal

anatomy, physiology, pathology, and pharmacology in addition to investigating the fundamentals of life. The most significant discoveries in biological understanding have been made using animal models.^[6] Animals have aided in the creation of novel medications, vaccines, surgical procedures, and anesthetic regimes. Although there is some concern about extrapolating clinical relevance from animal data,^[7] there is no denying the advancements made through the use of animal models. Nearly 90% of the discoveries made by Nobel Prize winners in Physiology and Medicine were made using animal experiments. Animal species must satisfy particular requirements in line with the ultimate objective of the research to be used as a model. Many species, including insects (*Drosophila*), nematodes (*Caenorhabditis elegans*), zebrafish, and frogs (*Xenopus*), are utilized in biomedical research and several mammals due to their close evolutionary relationship to humans, including mice, rats, dogs, cats, pigs, and monkeys.

Genetic engineering techniques can now be utilized to create knockout or transgenic animals that are employed in research with the advancement of genetic and genomic technologies. The health of the model animal plays an important role in obtaining correct results. For a correct outcome, healthy and humanely raised animals must be used. Research ethics refers to the set of rules, principles, and norms that guide responsible, morally acceptable scientific research in biomaterials and other fields of

study. Biomaterials research, like almost every other field, has been tainted by research misconduct from time to time.^[8,9] The Animal Welfare Act passed in the United States in 1970, stipulates that all experiments using animals provide adequate veterinary care, including the appropriate use of anesthetic, analgesic or tranquilizing drugs.^[10] Current work discusses historical, ethical, and philosophical issues that arise from the understanding that using animals in biomedical research is necessary to advance that field of study and is necessary for the creation of medications and vaccines.

A historical perspective on animal research: The first animal that was domesticated was the dog, which was “the culmination of a process that initiated with European hunter-gatherers and the canids with whom they interacted”.^[11] An interesting example is the creation of a model by Vivien Thomas and Alfred Blalock that simulated the congenital heart defect tetralogy of Fallot (commonly referred to as the blue baby syndrome) in a dog. This concept permitted the creation of the surgical procedure that presently saves more than half a million children per year.^[12] The parallels between human and animal physiology and pathology were noted long ago, and the practice that we today call ‘animal research’ is rooted back to the period of ancient Egypt and Greece.^[13] On the Origin of Species Utilizing Natural Selection or the Preservation of Favored Races in the Struggle for Life Charles Darwin's classic work, was published in the 19th century,^[14] where he demonstrated the remarkable parallels between nonhuman species and humans. New scientific fields, including pharmacology and immunology, were created in the 20th century as a result of the indispensable contribution made by laboratory animal research.

The emergence of animal research ethics: The history of the regulation of animal research was a fundamental step toward the emergence of animal ethics. In the Helsinki Declaration, the welfare, rights, and interests of the study subject take preference above scientific or social goals.^[15] Research that is likely to cause harm, impairment, or death to research subjects is explicitly prohibited by the Nuremberg Code.^[16]

First of all, we discuss whether the animal has moral concerns or not if the animal has then ethics is needed for protection from cruelty to animals.

Do animals have moral legitimacy? What characteristics an entity must possess to achieve the status necessary to access the protections provided by the moral and ethical standards of society? As Rosoff and colleagues point out, the moral and legal status of animals is a matter of significant debate, and the arguments are unresolved.^[17]

If an animal has the following features then we said that animal has moral legitimacy there are five features, at least one or all of which may apply to specific animals.

■ **Sentience:** Sentience, for Bentham, was usually understood as the capacity to feel pleasure and pain. It is now uncontested that many animals are capable of feeling pain. Equally, it is uncontested that causing pain is morally problematic and so needs to be taken into account in moral reasoning.

■ **Higher cognitive capacities:** such as the use of language or the ability to act according to plans, can be understood as signs of intelligence. Some would say that these attributes are exclusive to humans. For example, Chimpanzees communicate through vocal sounds, facial expressions, postures, and touch they alert other chimpanzees to the whereabouts of food sources with grunts and barks.^[18] Tool use Tufted capuchin monkeys have been observed in the wild using stones to dig in the ground to forage for food and to crack seeds.^[19] In captivity they have been observed carrying probing tools to a fixed apparatus baited with syrup in order to obtain the syrup.^[20] There are also examples of situations when animal behavior has been interpreted as altruistic toward humans. For example, in 2004 a group of swimmers reported that a pod of dolphins protected them from a great white shark off the coast of New Zealand.^[21]

■ **The capacity to flourish:** to consider what environmental enrichments can be provided to attend to the species-specific needs. Animals may fail to flourish in laboratory conditions.

■ **Sociability:** Reciprocity is commonly seen within groups of capuchin monkeys and chimpanzees, involving behaviors such as food sharing, grooming, and cooperation.^[22] These activities are not always restricted to family members but also extend to unrelated animals i.e. non-kin reciprocity.

■ **The possession of life:** How far human research ethics applies to animals depends quite strongly on the moral status we accord to animals. The fundamental guideline of morality is to live virtuously, by treating animals with kindness and justice. Currently, the welfare, rights, and interests of the animals utilized for research are subordinate to our scientific and social interests. This distinction between human and animal research ethics can only be justified if animals are morally inferior to humans. The moral status of nonhuman animals is a hotly debated topic, and no one can agree on what exactly constitutes it or even if the concept has any real application.

Some important ethical theories that can explain how ethics in animal research is necessary: In what ways animal clinical ethics can be applied, and what are those characteristics that provide this access? It is here where ethical theorists have a variety of perspectives.

Utilitarianism: An ethical theory founded by the philosophers Jeremy Bentham and John Stewart Mill between the 18th and 19th centuries. According to

utilitarianism, the right action is the one that promotes happiness or prevents pain for every affected subject. “If a being is not capable of suffering, or enjoyment, there is nothing to take into account” morally.^[23] A related approach by Raymond Frey, a strong promoter of the use of animals in research, agrees that if the value of life equals as abilities like intelligence, consciousness, and self-direction develop, the value of that life rises as well, deserving higher ethical standards.^[24] Frey wants us to understand that some humans have a lower quality of life than some animals for instance, compare a person in a persistent vegetative state (PVS) who has no living family or friends to a healthy chimpanzee who lives in a social group in West Africa. In this unique case, according to Frey, the greater level of protection should go to the chimpanzee because its life is of a higher quality.

Speciesism: The practice of considering and treating members of a species as morally superior to members of the other species. Establishing access to species membership alone has been referred to as speciesism by Peter Singer and is understood by him to be a negative characterization analogous to sexism or racism.^[25]

Awareness: The capacity to be aware of what is seen, felt, heard, thought, and so on.

Responsibility: The capacity to anticipate the effects of one's behavior and change it as a result.

The use of animals in laboratory testing increased significantly in the 20th century as a result of the growth in the biomedical sciences, paving the way for the development of a brand-new field of research and laboratory animal science. This is a multidisciplinary area of science that aims to enhance the welfare of animals used in experiments and contribute to their quality. It covers the biology of laboratory animals, their environmental needs, genetic standardization, microbiological control, as well as illness prevention and treatment, experimental methods, anesthesia, analgesia, and euthanasia, as well as alternatives to their use and ethics.^[26]

Advance research raised questions on the claim that the current state of animal research is equal to that of human research. The release of a special animal research issue “Theoretical Medicine and Bioethics” in 2006 is one potential catalyst for the development of animal research ethics.^[27] In 2006 Walker and Pulhar, this special issue includes two articles that draw a comparison between the use of humans and the use of animals in biomedical research.^[28,29] “Animal Research Ethics: Changing Perspectives and Practices” was a Special Report written by the Hastings Center and released in 2012^[30] here questions about autonomy, consent, vulnerability, and harm are directly addressed. In 2014 Cambridge Quarterly of Healthcare Ethics published a special section entitled “Neuroethics and Animals”^[31] and a year

later the same journal published a special section on “Moving Forward in Animal Research Ethics”.^[32] Both special sections contain articles that discuss the question of the autonomy of research animals in terms of the possibility to assent or dissent.^[33,34] In Europe, the use of laboratory animals for research was first regulated by EU Directive 86/609EEC and more recently by Directive 2010/63/EU^[35] that applies to all live nonhuman vertebrate animals, including independently feeding larval forms, fetal forms of mammals from the last third of gestation during normal development, and live cephalopods. 2010/63/EU is a well-balanced directive that was passed after years of discussion between various stakeholders, including researchers, patient associations, and animal protection associations. The US Institute of Medicine report on the use of chimpanzees for biomedical and behavioral research, which was published in 2011, served as the trigger for this debate about animal autonomy.^[36] Despite the recognition that the scope of discussion on animal research in the context of research ethics has been expanding quickly, this does not mean that animal ethics are no longer a topic of discussion.

Issue of Validity and Ethical justification: To more fascinating questions of autonomy, harms and benefits, justice, and vulnerability, which have definite analogies in human research ethics, from the general question of whether animal research is at all justified. There are obvious differences, such as animals’ lack of autonomy and personhood. The issue of informed consent, so central to human research ethics, does not come up in animal research ethics for obvious reasons. The critics have asked why lack of autonomy or personhood leads to stronger protections in the human case but weaker protections in the animal case.^[29] Others have drawn parallels comparison between autonomy concerns in pediatric research and animal research, in particular regarding nonhuman primates but possibly other higher mammals as well.^[33,34]

The majority of us that torturing animals is unethical, yet we can utilize animals and take their lives to further our own goals if doing so has justifiable benefits. Nonhuman primates are an especially significant case because animals with better cognitive capacities may have larger welfare concerns since they have a stronger sense of self. This evaluation of hazards and benefits raises at least two significant issues. **One cause for concern** is the assertion that many suggestions for animal research hold that the suffering of the animals can only be justified if their interests are given a significant discount.^{[37],[38]} **The second issue is that we are unable to evaluate benefits or harms** in a way that would allow us to properly compare one against the other, whether it be in a study with nonhuman primates or more generally in animal research. However, we can assess the anticipated benefits and the potential drawbacks to determine whether the trade-off is morally right. This method accepts the impossibility of precise, objective, quantifiable

measurements as well as the incommensurability of benefits and damages without minimizing moral judgment. Although a more thorough defense of this strategy is outside the purview of this study, this argument has been presented in great depth elsewhere with nonhuman monkey research.^[39] If we want to draw on human research ethics in our discussion of animal research ethics, this is the sort of issue that may be seen to apply directly to animals, since they cannot give informed consent either.^[40] In the case of nonhuman primates and great apes, some animal advocates argue that animal research, like nontherapeutic pediatric research, is only justifiable if it poses no more than minimal risk and burden to the research subjects.^{[41][42]} Beauchamp and Morton, have argued for upper severity limits for animal research in general, excluding all research that causes significant suffering.^[43]

In whatsoever scenario, drawing comparisons between the ethical requirements for research involving incompetent humans and research involving animals in terms of upper limits of risk and harm is intellectually stimulating and useful. It is also worth noting that the justification for having different limits for humans and animals, and, more broadly, treating human and animal interests differently, is based on an argument about the moral status of both humans and animals.^[44] As equal moral standing with humans would suggest, setting the upper limit of risk and harm in animal research at "minimal risk and minimal harm" would undoubtedly result in the elimination of the majority of animal research; however, a higher limit of severe pain or distress over an extended period, as is the case in EU law, would have a significantly smaller impact on biomedical research.^[45]

Ethical concern for using animals in biomedical research: It is significant to mention that, in addition to having the necessary technical skills, animal experimentation needs ethical considerations to take priority over scientific ones. Each researcher must have a complete understanding of the biology and behavior of the species animal model being used. Additionally, researchers must understand the significance of the work being performed and take into account all the justifications for each unique project depending on a strong scientific foundation. Animal ethics share a defining quality with medical ethics: the limited direct benefit of the "classical" moral theories. No overarching theoretical framework in ethics can be used to determine something with any degree of certainty. The right kind of animal research ethics, the moral standing of animals, or whether or not animal research is ethical. In addition to viewpoints in favor of animal research.^[46,47] A position in favor of nonhuman primates research specifically, utilitarian arguments has also been used to support positions that are close to being nonhuman primates research.^[48] Peter Singer's preference for utilitarianism, which he established in his works *Animal Liberation*^[25] and *Practical Ethics*, is the most well-

known utilitarian viewpoint in animal ethics.^[49] The view holds that we should act in a way that best serves our carefully studied preferences or objective interests, which in the case of animals equates to issues with pleasure and suffering.

The majority of the current regulatory frameworks for animal research are utilitarian. They strive to minimize animal suffering, which must be justified by the research's prospective scientific or medicinal benefits. In stark contrast, deontological issues predominate in the ethics of human research. We have, to use a phrase from Robert Nozick, "utilitarianism for animals Kantianism for people".^[50] The animal rights approach has produced some of the strongest positions against the use of animals in research. Rather than focusing on rights and duties, some deontological theories are based on the concepts of dignity and justice, such as Nussbaum's capabilities approach to animal ethics.^[51] Nussbaum's theory would vastly limit human uses of animals but with the notable exception of allowing the use of animals for biomedical research. Ethical theory by itself offers little direction, much as arguments may be made for a variety of viewpoints on the use of animals in biomedical research from both utilitarian and deontological moral perspectives. Rosalind Hursthouse, argues that what we can and cannot do with nonhuman animals depends on the circumstances and our relationship with the animals.^[52] The fundamental guideline of morality is to live virtuously, in this case by treating animals with kindness and justice. Garret Merriam similarly argues that from the standpoint of virtue ethics, much of animal research is unjustified, very little of it is justified, and the rest is in between, requiring careful moral judgment.^[53] Walker has specifically applied virtue ethics to nonhuman primate research, focusing on the moral character development of primate researchers as well as the social and institutional frameworks that play a role in that process.^[54] Several approaches to virtue ethics promote moral reflection, moral character development in people who undertake animal research, and the formation of caring relationships between researchers and their animal subjects, but none of them promote an absolutist position on the conduct of animal research.

The "Replace, Reduce, Refine" (3R) principle, proposed by English researchers William Russell and Rex Burch in 1959,^[55,56,57] is a general principle that underpins these laws and is also validated by the internationally recognized and accepted guidelines of the Guide for the Care and Use of Laboratory Animals.^[58] According to the 3Rs, experimental procedures must always adhere to the three basic principles listed below.

To replace animals with alternative methods (or lower species) if possible. Replacement is the major goal for the use of animals in science. Animals should be replaced with *in vitro* or *silico* tests^[59,60] or with invertebrates,^[61-63] microorganisms, cell cultures, organs, or even cellular fractions. The ideal replacement would

be a protocol conducted with no use of animals. For example, the regulation prohibited the use of great apes for study unless there are extremely specific circumstances, although this has not been the case in Europe since 1999.^[64] The National Institutes of Health are gradually ceasing to use chimpanzees in research. In the United States, effectively terminating the usage of great apes.^[65,66]

To reduce the number of animals to the minimum required for statistically valid results. Reduction is the application of methods that allow a reduced number of animals to be used in a protocol. This can be achieved by detailed planning of the experiments, guaranteeing that results will have statistical significance. The use of animals presenting the same or a similar genetic background also ensures a low fluctuation of the data, thereby reducing the number of animals that need to be used in a study. Many websites are available to access statistical methods that allow an accurate calculation of the number of animals to be used in an experiment. Nowadays, access to several available databases sometimes allows the number of animals used to be reduced or in some cases allows their use to be avoided completely.

To refine the use of animals by minimizing their pain and suffering as well as improving husbandry, housing, and welfare. Refinement consists of the application of methods that avoid animal suffering, such as the use of anesthesia during a procedure and analgesic regimens for pain relief during recovery; the use of non-invasive techniques; housing conditions that provide a comfortable and safe environment and training the animal to cooperate with procedures

The most adamant opposition to using animals in research is cautious of or openly antagonistic to any theoretical base of its beliefs. This opposition uses an "exposure and persuasion" technique and appeals to people's concern for animals. The premise is that animals are cruelly abused and exploited and that the most effective way to get people to oppose using animals for research or other purposes is to bring their suffering and injustice to public attention.^[67] Every theoretical approach, according to this perspective, just obstructs or detracts from the goals of political activists. Instead of engaging in philosophical discussions, organizations that support the use of animals in research frequently highlight the benefits of animal research for children and pets but are not aware of any academic discussions by animal research advocates about the value of a comparable anti-theoretical position in favor of animal research. The objective of the guidelines is to promote the humane care of animals used in biomedical research and provide the legal aspect for the experimentation on the animals.

Today's application of laboratory animals: Experiments on laboratory animals are now carried out

on a global scale for a variety of purposes and fields of study. Laboratory animals are used to model the pathologies of humans and other animals, develop new pharmaceutical products, manufacture vaccines, and conduct toxicological studies. According to a recent report, in 2015, 37 countries with available statistics reported the use of the most common use of experimental animals, with an estimated number of 20,496,670 procedures, followed by Japan and the United States, each with an adjusted number of approximately 15,000,000 procedures. Mice and rats are by far the most commonly used animals, followed by birds, fish, reptiles, amphibians, and cephalopods. Dogs and monkeys are used far less frequently, primarily in China and the United States. The total number of dogs and monkeys used in the 36 countries that shared data was 112,265 and 92,431, respectively. Another statistical report found that between 2014 and 2016, the total number of procedures performed on laboratory animals in Europe remained relatively stable, ranging from 10,356,578 to 10,853,401.^[68] Animal experimentation is strictly regulated in all countries and can only be carried out by the 3Rs laws.

Can biomedical research avoid using laboratory animals? Consistent with the 3Rs is a commitment to engage in animal testing only when valid alternatives are unavailable. The main possible alternatives to *in vivo* tests are *in vitro* cell and tissue cultures or *in silico* computer-assisted experiments.^[69] These alternative methods are indeed largely practiced in biomedical research, and their use has greatly contributed to the reduction of laboratory animals. While the complexity of various organs such as the brain and difficulty mimicking the function of a human organism *in vitro* or *in silico* make it impossible to fully replace *in vivo* laboratory animal testing. In fact, in most cases, the only way to study pathologies that afflict both humans and other species is by replicating them in animal models. The efficacy and toxicity of new drugs and vaccines, at some point in their development, can only be studied in living animals.^[70] Testing a drug on a single cell or using an *in silico* approach or both would undoubtedly aid in identifying important properties of molecules that determine whether they are viable for further development. However, only animal testing allows for verification of their efficacy and safety profile. The alternative is an unsustainable and thus unethical risk of developing treatments with unknown safety and efficacy. To mitigate these risks, drug regulatory agencies require that any new medication, vaccine, or cure, in general, be tested in laboratory animals before being approved for clinical use.

Thalidomide tragedy history of thalidomide is the most well-known example of what can happen when drugs are developed without adequate preclinical testing. After only being tested in rodents and never during pregnancy, this drug was commercialized in 1957 to treat insomnia, headaches, and nausea. Unfortunately, it was widely

used by pregnant women to treat nausea and vomiting.^[71] During that time, there were an unprecedented number of cases of phocomelia and other birth defects in all 46 countries where the drug was sold. Many Years later, thalidomide was identified as the cause of this disaster and was removed from the market. This sparked some debate about the predictive power of animal experimentation.^[72] This dramatic experience led to the establishment of new guidelines and laws to regulate the preclinical testing of drugs. For example, these new guidelines stipulated that any new molecule or vaccine must be tested on at least two different animal species before moving to the clinical stage. Thanks to advances in the optimal use of laboratory animals, the risks for humans can be minimized by detecting the toxicity of new drugs very early during development. Recent data indicate that approximately 80% of compounds that are under development fail to enter the clinical stage, and approximately 40% of them are stopped after a lack of tolerability or signs of toxicity is found in laboratory animals.^[73]

How ethical issues can be resolved: Animals are essential in the development of biomaterials, particularly in clinical translation.^[74] but their use raises ethical concerns for many stakeholders. Biomaterials scientists should incorporate these principles, known as the 3Rs, into their experimental designs, use strategies to comply with them when possible, and be aware of biomaterials' important role in developing additional strategies that can help reduce or replace animal use in research in the long run.^[75] The ethical issues may be resolved by.

In Vitro Animal Replacement: When assessing host-material interactions, in vitro assays cannot replicate the complex immune, mechanical, and cellular factors provided by animal models. Recent advancements in tissue-/Microfluidics, organ-on-a-chip technology, and bioprinting are being used to investigate isolated physiological systems by simulating highly complex microenvironments.^[76] Many of these biomaterial-based platform technologies offer greater spatial and temporal control than in vivo animal models, positioning them as potential alternatives to animal models, future cost-cutters in preclinical development, and valuable time-saving preclinical models.^[77] While cell monolayers have long been used for drug screening or toxicology,^[78] biomaterials now allow for multi-dimensional, physiologically relevant studies. Tissues with similar constructions are better able to predict in vivo tissue functions and drug activities.^[79,80] The combination of biomaterials and microfluidics has been crucial in allowing precise manipulation of chemical gradients, fluid dynamics, three-dimensional tissue architecture, and cell behavior in vitro models.^{[81][82]} Microfluidics is also being used for elevated nanoparticle screening, which is speeding up clinical translation and replacing animal models with arguably more effective and time-efficient models.^[83] Advanced biofabrication and bioprinting techniques are also being used to create

complex in vitro models of biomaterial-cell interactions.^{[84][85]}

Consolidation of preclinical animal testing: While in vitro tests should not be used in place of animal testing in many cases, well-designed large animal studies can effectively consolidate in vivo testing requirements to reduce the number of animals used.^[86] The Food and Drug Administration (FDA) and the Center for Devices and Radiological Health (CDRH) of the United States have recently issued guidance that encourages the replacement, reduction, and refinement of in vivo biocompatibility testing with International Standard ISO 10993-1 (Biological evaluation of medical devices). As stated by Hampshire and Gilbert, Large animal model studies, according to this guidance, can provide robust biological data that can be used to replace small animal models, particularly in tests for systemic toxicity, chronic implantation, and in vivo thrombogenicity. By recognizing potential improvements in medical device testing efficiency, the FDA and CDRH have helped to reduce the animal burden and economic resources for biocompatibility testing of biomaterials. When conducting in vivo biomaterial testing, biomaterial researchers should continue to collaborate across academic, industry, and regulatory bodies to address the 3Rs.

Ethical principles in the indian scenario: In the Indian Scenario Animal use in the institutions are supervised by the Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA) now called CCSEA (Committee for Control and Supervision of Experiments on Animals) guidelines which are controlled by Ministry of Environment and Forests (Animal Welfare Division), Government of India. CCSEA mainly controls the Institutional Animal Ethics Committee (IAEC) and Institute Biosafety Committee (IBSC/IBC).

The objective of guidelines is to promote the humane care of animals used in biomedical research and provide the legal aspect for the experimentation in the animals

Principle 1 "Experiments on animals" including experiments involving operations on animals may be carried out for the purposes of advancement by new discovery of physiological knowledge; or of knowledge which is expected to be useful for saving or prolonging human life or alleviating suffering; or for significant gains in the wellbeing for the people of the country; or for combating any disease, whether of human being, animals or plants.

Principle 2 Animals lowest on the phylogenetic scale i.e., with the least degree of sentience, which may give scientifically valid results, should be used for any Experimental procedure. Experiments should be designed with the minimum number of animals to give statistically valid results at 95% level of confidence. Alternatives not involving animal testing should be given

due and full consideration and sound justification provided, if alternative, when available, are not used.

Principle 3 Proper use of animals in experiments and avoidance or minimization (when avoidance is not possible) of pain and suffering inflicted on experimental animals should be an issue of priority for research personnel, and unless the contrary is scientifically established, investigators should proceed on the basis that procedures that cause pain or suffering in human beings will also cause similar pain or suffering in animals. All scientific procedures adopted with animals that may cause more than momentary or slight pain and/or suffering should be performed with appropriate sedation, analgesia, or anesthesia.

Principle 4 Persons engaged in animal experimentation have a moral responsibility for the welfare of the animals after their use in experiments. Investigators are responsible for the aftercare and/or rehabilitation of animals after experimentation and may be permitted to euthanize them. Animals only in the following situations are euthanizing (a) When the animal is paralyzed and is not able to perform its natural functions; it becomes incapable of independent locomotion; and/or can no longer perceive the environment in an intelligible manner. (b) During the course of the experimental procedure, the animal has been left with severe recurring pain and the animal exhibits obvious signs of long-term extreme pain and suffering. (c) In situations where non-termination of the animal experimented upon would be life-threatening to human beings or other animals. Costs of aftercare and/or rehabilitation of animals post-experimentation are to be part of research costs and should be scaled per animal in positive correlation with the level of the sentence of the animals.

Principle 5 The living conditions of animals should be appropriate for their species and contribute to their health and comfort. The housing, feeding, and care of all. Animals used for biomedical purposes must be directed by a veterinarian or other scientist in a relevant discipline who is trained and experienced in the proper care, handling, and use of the species being maintained or studied. In all circumstances, veterinary care shall be provided as necessary.

DISCUSSION

In current practice, animals are thought to have a moral status that is lower than humans; that is, they matter morally but less than humans. How much they matter depends not only on the species but also on our relation to them. As a result, companion animals are frequently thought to be more important than animals raised for food. In animal research ethics, some animal advocates argue for an equal moral status of sentient animals to humans. This would make human research ethics fully applicable to animals as vulnerable subjects that are not competent to give consent but would not necessarily lead to the complete abolition of animal research.^[87] The use

of laboratory animals in biomedical research is a matter of intense public debate. Indication of Recent statistics that about half of the western population, sensitive to this discussion, would be in favor of animal testing while the other half would oppose it. Outlining the scientific, historical, ethical, and philosophical aspects, we provide an integrated view explaining the reasons why biomedical research can hardly abandon laboratory animal testing. Here we retrace the historical moments that mark the relationship between humans and other animal species. Then starting from Darwin's position on animal experimentation, we outline the steps that over time allowed the introduction of laws and rules that regulate animal use in biomedical research. In our analysis, we present the perspectives of various authors, intending to delineate a theoretical framework within which to insert the ethical debate on laboratory animal research. Through the analysis of fundamental philosophical concepts and some practical examples, we propose a view according to which laboratory animal experimentation becomes ethically acceptable as far as it is guided by the goal of improving humans and other animal species i.e., pet's life. Among the elements analyzed, there is the concept of responsibility that only active moral subjects have towards themselves and passive moral subjects. We delineate the principle of cruelty that is useful to understand why research in laboratory animals should not be assimilated into a cruel act. Moreover, we touch upon the concepts of necessity and "good cause" to underline that, if biomedical research would have the possibility to avoid using animals, it would surely do that. To provide an example of the negative consequences occurring from not allowing laboratory animal research, we analyze the recent experience of the Covid-19 epidemic. Finally, recalling the principle of "heuristics and biases" by Kahneman, scientists should reconsider the way they are conveying information about their research to the general public. Most animal research is harsh and pointless and the morally upright and courageous person should support initiatives and groups that seek to end cruel and pointless animal research.

CONCLUSION

Animals, or some higher mammals such as nonhuman primates, are accorded the same moral status as humans, it will be difficult to avoid human research ethics will apply to them, giving them the same protections as human research subjects who are not competent to give informed consent. Current situation state of knowledge and technology, it is not possible to replace in vivo animal experimentation because animal physiology and pathology are the same as humans no such environment is provided by in vivo background in several scientific disciplines with alternative methodologies.

REFERENCES

1. Linddell and Scott's. An intermediate Greek-English lexicon. New York: Harper & Brothers, 1889; 7: 349.

2. Kidder R. How good people make tough choices: resolving the dilemmas of ethical living. New York: HarperCollins, 2003; 63.
3. Richard P, Elder L. The miniature guide to understanding the foundation of ethical reasoning. United State: Foundation for Critical Thinking Free Press, 2006; 1.
4. Beauchamp TL. The ethics of biomedical research involving animals. In: Arras JD, Fenton E, Kukla R, editors. The Routledge companion to bioethics. New York: Routledge, 2014; 1: 261-73.
5. Tannenbaum J, Rowan AN. Rethinking the morality of animal research. *Hastings Cent Rep*, 1985; 15(5): 32-43.
6. LIESCHKE GJ, CURRIE PD. Animal models of human disease: zebrafish swim into view. *Nat Rev Genet*, 2007; 8(5): 353-67.
7. GREEK R, MENACHE A. Systematic reviews of animal models: methodology versus epistemology. *Int J Med Sci*, 2013; 10(3): 206-21.
8. Fanelli D. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLOS ONE*, 2009; 4(5): e5738.
9. Cyranoski D. Artificial-windpipe surgeon committed misconduct. *Nature*, 2015; 521(7553): 406-7.
10. Public Law. 91-579 animal welfare Act amendments of 1970. Animal Welfare Information Center| NAL | USDA [internet] [cited may 23 2023]. Available from: <https://www.nal.usda.gov/awic/public-law-91-579-animal-welfare-actamendments-1970>.
11. Thalmann O, Shapiro B, Cui P, Schuenemann VJ, Sawyer SK, Greenfield DL, et al. Complete mitochondrial genomes of ancient canids suggest a European origin of domestic dogs. *Science*, 2013; 342(6160): 871-4.
12. TIMMERMANS S. A black technician and blue babies. *Soc Stud Sci*, 2003; 33(2): 197-229.
13. National Research Council (US) Committee to Update Science M, and Animals. *Science, medicine, and animals*. Washington, (DC): National Academies Press. US, 2004.
14. Darwin C. *On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life*. London: John Murray, 1859.
15. WMA, World Medical Association, 2013. Declaration of Helsinki. Ethical principles for medical research involving human subjects [cited may 23 2023]. Available from: <https://www.wma.net/policiespost/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.
16. Shuster E. Fifty years later: the significance of the Nuremberg Code. *N Engl J Med*, 1997; 337(20): 1436-40.
17. Rosoff PM, Moga J, Keene B, Adin C, Fogle C, Ruderman R, et al. Resolving ethical dilemmas in a tertiary care veterinary specialty hospital: adaptation of the human clinical consultation committee model. *Am J Bioeth*, 2018; 18(2): 41-53.
18. The Jane Goodall Institute chimp calls [cited may 25 2023]. Available from: <http://www.janegoodall.org/jane/studycorner/chimpanzees/chimp-calls.asp>.
19. Moura ACdeA, Lee PC. Capuchin stone tool use in Caatinga Dry forest. *Science*, 2004; 306(5703): 1909.
20. Cleveland A, Rocca AM, Wendt EL, Westergaard GC. Transport of tools to food sites in tufted capuchin monkeys (*Cebus apella*). *Anim Cogn*, 2004; 7(3): 193-8.
21. BBC NEWS. Dolphins prevent NZ shark attack, 2004 [cited may 25 2023]. Available from: <http://news.bbc.co.uk/1/hi/world/asia-pacific/4034383.stm>.
22. See Brosnan SF, de Waal FBM. A proximate perspective on reciprocal altruism. *Hum Nat*, 2002; 13(1): 129-52.
23. Singer P. *Animal liberation: a new ethics for the treatment of animals*. 2nd ed New York Review. New York, 1990.
24. Frey R. Ethics, animals, and scientific inquiry. In: Gluck JP, Di Pasquale T, Orlans FB, editors. *Applied ethics in animal research: philosophy, regulation, and laboratory applications*. West Lafayette: Purdue, 2002; 13-24.
25. Singer P. *Animal liberation: a new ethics for the treatment of animals*. New York review, New York, 1975.
26. Baumans V. Science-based assessment of animal welfare: laboratory animals. *Rev Sci Tech*, 2005; 24(2): 503-13.
27. DeGrazia D. Regarding animals: mental life, moral status, and use in biomedical research: an introduction to the special issue. *Theor Med Bioeth*, 2006; 27(4): 277-84.
28. Walker RL. Human and animal subjects of research: the moral significance of respect versus welfare. *Theor Med Bioeth*, 2006; 27(4): 305-31.
29. Pluhar EB. Experimentation on humans and nonhumans. *Theor Med Bioeth*, 2006; 27(4): 333-55.
30. Gilbert S. Progress in the animal research war. *Animal research ethics: evolving views and practices*, Hastings Center report special report, 2012; 42(6): S2-3.
31. Buller T, Shriver A, Farah M. Broadening the focus. *Camb Q Healthc Ethics*, 2014; 23(2): 124-8.
32. DeGrazia D, Beauchamp TL. Guest editorial: reassessing animal research ethics. Cambridge, 2015.
33. Fenton A. Can a chimp say "no"? *Camb Q Healthc Ethics*, 2014; 23(2): 130-39.
34. Kantin H, Wendler D. Is there a role for assent or dissent in animal research? *Camb Q Healthc Ethics*, 2015; 24(4): 459-72.
35. Directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 on the

- protection of animals used for scientific purposes. *Off J Eur Union*, 2010; 276: 33-79.
36. IOM, Institute of Medicine. *Chimpanzees in biomedical and behavioral research: assessing the necessity*. Washington, DC: The National Academies Press, 2011.
 37. Arnason G. The ethical justification for the use of nonhuman primates in research: the weather all report revisited. *J Med Ethics*, 2018b; 44(5): 328-31.
 38. Faria C. A fimsy case for the use of nonhuman primates in research: A reply to Arnason. *J Med Ethics*, 2018; 44(5): 332-33.
 39. Arnason G, Clausen J. On balance: weighing harms and benefits in fundamental neurological research using nonhuman primates. *Med Health Care Philos*, 2016; 19(2): 229-37.
 40. Wendler D. Should protections for research with humans who cannot consent apply to research with nonhuman primates? *Theor Med Bioeth*, 2014; 35(2): 157-73.
 41. Ferdowsian H, Fuentes A. Harms and deprivation of benefits for nonhuman primates in research. *Theor Med Bioeth*, 2014; 35(2): 143-56.
 42. Gagneux P, Moore JJ, Varki A. The ethics of research on great apes. *Nature*, 2005; 437(7055): 27-9.
 43. Beauchamp TL, Morton DB. The upper limits of pain and suffering in animal research: A moral assessment of the European Union's legislative framework. *Camb Q Healthc Ethics*, 2015; 24(4): 431-47.
 44. Walker RL. Beyond primates: research protections and animal moral value. *Hastings Cent Rep*, 2016; 46(4): 28-30.
 45. European Parliament, the Council of the European Union. Directive 2010/63/EU on the protection of animals used for scientific purposes. *Ofcial J Eur Union L*, 2010; 276: 33. adopted.
 46. Brody B. Defending animal research: an international perspective. In: Garrett JR, editor. *The ethics of animal research: exploring the controversy*. Cambridge, MA: The MIT Press, 2012; 53-66.
 47. Cohen C. Animal experimentation defended. In: Garattini S, van Bekkum DW, editors. *The importance of animal experimentation for safety and biomedical research*. Dordrecht: Kluwer Academic Publishers, 1990; 7-16.
 48. Weatherall D. *The use of nonhuman primates in research*. London: Academy of Medical Sciences, 2006.
 49. Singer P. *Practical ethics*. Cambridge: Cambridge University Press, 1979.
 50. Nozick R. *Anarchy, state, and utopia*. New York: Basic Books, 1974.
 51. Nussbaum MC. Beyond "compassion and humanity": justice for nonhuman animals. In: Sunstein CR, Nussbaum MC, editors. *Animal rights: Current debates and new directions*. Oxford: Oxford University Press, 2004; 299-320.
 52. Hursthouse R. Applying virtue ethics to our treatment of the other animals. In: Welchman J, editor. *The practice of virtue: Classic and contemporary readings in virtue ethics*. Indianapolis: Hackett Publishing Company, 2006; 136-55.
 53. Merriam G. Virtue, vice, and vivisection. In: Garrett JR, editor. *The ethics of animal research: exploring the controversy*. Cambridge, MA: The MIT Press, 2012; 125-46.
 54. Walker RL. Virtue, vice, and "voracious" science: how should we approach the ethics of primate research? *Perspect Biol Med*, 2018; 61(1): 130-46.
 55. Rusche B. The 3Rs and animal welfare—conflict or the way forward? *ALTEX.*, 2003; 20, 1: 63-76.
 56. Hendriksen CF. Replacement, reduction and refinement alternatives to animal use in vaccine potency measurement. *Expert Rev Vaccines*, 2009; 8(3): 313-22.
 57. Russell WMS, Burch RL, Hume CW. *The principles of humane experimental technique*. London: Methuen, 1959.
 58. Council CftUotGftCaUoLANR. *Guide for the care and use of laboratory animals*. Washington, DC: National Academies Press, 2010; 8.
 59. Doke SK, Dhawale SC. Alternatives to animal testing: a review. *Saudi Pharm J*, 2015; 23(3): 223-9.
 60. Balls M. Future improvements: replacement in vitro methods. *ILAR J*, 2002; 43: S69-73.
 61. Giacomotto J, Ségalat L. High-throughput screening and small animal models, where are we? *Br J Pharmacol*, 2010; 160(2): 204-16.
 62. Wolf MJ, Rockman HA. *Drosophila melanogaster as a model system for genetics of postnatal cardiac function*. *Drug Discov Today Dis Models*, 2008; 5(3): 117-23.
 63. Nass R, Merchant KM, Ryan T. *Caenorhabditis elegans in Parkinson's disease drug discovery: addressing an unmet medical need*. *Mol Interv*, 2008; 8(6): 284-93.
 64. Home Ofce UK. *Annual statistics of scientific procedures on living animals; Great Britain 2013*. House of Commons, London, 2014.
 65. Beauchamp TL, Wobber V. Autonomy in chimpanzees. *Theor Med Bioeth*, 2014; 35(2): 117-32.
 66. Reardon S. NIH to retire all research chimpanzees. *Nature news*, 2015. [cited may 27 2023]. retrieved Aug 29, 2019 from <https://www.nature.com/news/nih-to-retire-all-research-chimpanzees-1.18817>.
 67. Aaltola E. The philosophy behind the movement: animal studies versus animal rights. *Soc Animals*, 2011; 19(4): 393-406.
 68. Taylor K, Rego Alvarez L. A summary of EU national statistical reports of animal experiments in 2014-2016. *ALTEX.*, 2019; 36(2): 314-9.
 69. Ranganatha N, Kuppast I. A review on alternatives to animal testing methods in drug development. *Int J Pharm Pharm Sci*, 2012; 4, 5: 28-32.

70. Lipinski C, Hopkins A. Navigating chemical space for biology and medicine. *Nature*, 2004; 432(7019): 855-61.
71. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res C Embryo Today*, 2015; 105(2): 140-56.
72. Shanks N, Greek R, Greek J. Are animal models predictive for humans? *Philos Ethics Humanit Med*, 2009; 4(2): 2.
73. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov*, 2015; 14(7): 475-86.
74. Liguori GR, Jeronimus BF, de Aquinas Liguori TT, Moreira LFP, Harmsen MC. * Ethical issues in the use of animal models for tissue engineering: reflections on legal aspects, moral theory, three rs strategies, and harm-benefit analysis. *Tissue Eng Part C Methods*, 2017; 23(12): 850-62.
75. Tannenbaum J, Bennett, BT. Russell and burch's 3 Rs then and now: the need for clarity in definition and purpose. *J Am Assoc Lab Anim Sci*, 2015; 54(2): 120-32.
76. Gibbons MC, Foley MA, Cardinal KO. Thinking inside the box: keeping tissue-engineered constructs in vitro for use as preclinical models. *Tissue Eng B*, 2012; 19: 14-30.
77. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. *Science*, 2010; 328: 1662-8.
78. Davila JC, Rodriguez RJ, Melchert RB, Acosta D. Predictive value of in vitro model systems in toxicology. *Annu Rev Pharmacol Toxicol*, 1998; 38: 63-96.
79. Bhatia SN, Ingber DE. Microfluidic organs-on-chips. *Nat Biotechnol*, 2014; 32(8): 760-72.
80. Shuler ML. Organ-body- and disease-on-a-chip systems. *Lab Chip*, 2017; 17(14): 2345-6.
81. Kobel S, Lutolf MP. Biomaterials meet microfluidics: building the next generation of artificial niches. *Curr Opin Biotechnol*, 2011; 22(5): 690-7.
82. Oliveira MB, Mano JF. High-throughput screening for integrative biomaterials design: exploring advances and new trends. *Trends Biotechnol*, 2014; 32(12): 627-36.
83. Valencia PM, Farokhzad OC, Karnik R, Langer R. Microfluidic technologies for accelerating the clinical translation of nanoparticles. *Nat Nanotechnol*, 2012; 7(10): 623-9.
84. Bajaj P, Schweller RM, Khademhosseini A, West JL, Bashir R. 3D biofabrication strategies for tissue engineering and regenerative medicine. *Annu Rev Biomed Eng*, 2014; 16: 247-76.
85. Seol YJ, Kang HW, Lee SJ, Atala A, Yoo JJ. Bioprinting technology and its applications. *Eur J Cardiothorac Surg*, 2014; 46(3): 342-8.
86. Hampshire VA, Gilbert SH. Refinement, reduction, and replacement (3R) strategies in preclinical testing of medical devices. *Toxicol Pathol*, 2019; 47(3): 329-38.
87. Arnason G. Animal research and the political theory of animal rights. In: Garmendia da Trindade G, Woodhall A, editors. *Ethical and political approaches to nonhuman animal issues*. Cham, Switzerland: Palgrave Macmillan, 2017; 327-45.