





## The dark side of the animal experiments

Elif Akkaya, Stu<sup>1</sup>, Harun Reşit Güngör, MD<sup>2</sup>

<sup>1</sup>Uskudar American Academy, High School, Istanbul, Türkiye

<sup>2</sup>Department of Orthopedics and Traumatology, Pamukkale University Faculty of Medicine, Denizli, Türkiye

Many animals have similar body compartments and physiology as humans; therefore, they are used in scientific research and studies. The use of animals in medical research has a long history dating to the anatomical studies of Aristotle on various animals. Although there are serious concerns about the appropriate methodology and moral issues in animal studies and the transfer of data to humans, the use of animals in experiments has increasingly continued to the present day.<sup>[1]</sup> Currently, millions of animals are sacrificed worldwide annually, and many are suffering in harmful conditions for medical research involving the development of several medicines, vaccines, or surgical techniques.<sup>[2-4]</sup>

The 3Rs (Replace, Reduce, Refine) are recommended as fundamental principles for the use of animal model.<sup>[5]</sup> Replacement involves the alternative models to animal experiments such as *in vitro* methods or computer modelling. Reduction means to propose the minimum number of animals required to achieve the purpose of the research. Refinement consists of many

### ABSTRACT

The use of animals in research has increasingly continued, although there are serious concerns about appropriate methodology, moral issues and translation to clinical practice. The aim of the present article is to review the insufficiency of statements in ethical approvals to obtain animal welfare in real life practices and to draw attention to the need for an additional evidence-based audit system. In many countries, local Animal Ethics Committees are established to ensure that animals are treated in accordance with 3Rs (Replace, Reduce, Refine) principles. Although the ethical approval certificate which is taken before the start of research is considered as the proof of animal welfare, footages released from all over the world reveal the maltreatment. However, due to the scientific resource provided by animal models, it does not seem possible to expect animal experiments to be terminated in the near future. Addition of previously suggested welfare section to methods of study or including the ethical approval certificate does not seem to be sufficient practices to guarantee the animal welfare, since they are not based on audited evidence. The welfare certificate, in which the welfare is supervised by independent auditors, would serve as a proof of both the well-being of subjects and consequently the scientific reliability of data. Application of review and publication priority for the animal researches which have the welfare certificate in addition to the ethical approval would encourage the researchers to obtain this certificate. The achievement of worldwide consensus about content, requirements, and application methods of the welfare certificate should be in the scope of scientists in the near future to reach the more humane and more qualified animal experiments.

**Keywords:** Animal ethics committee, animal research, animal welfare, welfare certificate, 3Rs.

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**Correspondence:** Harun Reşit Güngör, MD, Pamukkale Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Anabilim Dalı, 20160 Kınıklı, Denizli, Türkiye.

E-mail: hrgungor@gmail.com

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different applications to minimize the suffering, distress, and the potential pain exposure throughout the research.<sup>[5,6]</sup> Guidelines for research ethics stipulate the principles to be applied throughout the scientific study from planning to publication and recommend a set of ethical standards including the welfare of animal subjects. Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes

designated that the measures should be taken for animal welfare and that animal testing is replaced, when there are possible alternative methods.<sup>[7]</sup>

All over the world in many countries, local Animal Ethics Committees are established to ensure that animals are treated in accordance with 3Rs principles.<sup>[5]</sup> In Türkiye, institutional local Animal Ethical Committees approve, revise or reject each application, whereas ethical committees in some countries have only consultant role.<sup>[5,8]</sup> Researchers are expected to perform all experimental applications in accordance with 3Rs principles and to take necessary measures for animals to prevent suffering, distress, and pain.<sup>[3,9]</sup> Whereas replacement and reduction principles can be controlled and modified by the supervision of ethical committee before the approval of the experimental study, among the 3Rs principles, refinement is the most ambiguous one and the least monitored rule.<sup>[5]</sup> Several authors have suggested adding an animal welfare section to the methods part of publications to ensure that the refinement rule of 3Rs principles has been properly applied.<sup>[10,11]</sup> Although the certificate of ethical committee approval which is taken before the start of research is considered as the proof of animal subjects' welfare based on ethical and scientific standards, many footages released from many experienced animal research centers all over the world reveal the maltreatment and abuse of animals.<sup>[12-15]</sup> Addition of previously suggested welfare section to the methods part of the study or claiming that the refinement principle of the 3Rs is complied with in the ethics committee document does not seem to be sufficient practices to guarantee the welfare of animals, since they are not based on audited evidence. Therefore, although ethical guidelines and approvals are useful and required tools to establish the ethical limits of experiments on animals, there is a clear need for a new measure to achieve the welfare of animal subjects.

Examples of animal cruelty in the international media reveal the insufficient application of 3Rs in real life for a variety of reasons and the urge need for an evidence-based audit system throughout the research in addition to the ethical approval. First, some laboratories continue to neglect their animals or ignore the negative effects of certain practices on animals unrelated to the scientific purpose of the experiment as long as they achieve their goals. One of the largest primate research centers in the United States (US) - University of California, Davis (UC Davis) has also been the target of animal rights activists over several mistreatments of primates.<sup>[13]</sup> In 2005, the facility was fined, when seven monkeys

died from exposure to extreme heat. Additionally in 2016, UC Davis was investigated about a primate which broke its legs, while escaping through an unsafe door and another primate which was injured in a similar incident. UC Davis has typically used dyes to identify individual primates; however, in 2018, a few weeks old seven baby monkeys died due to the toxic allergic reaction caused by the dye accidentally transferred from their mothers, although the baby monkeys were not the subjects of that experiment.<sup>[13]</sup> Both repeated similar incidences and addition of new different maltreatments by years from the same research center, even if it is a specialized center for these researches, suggest that ethical approval could not be the guarantee of animal subjects' welfare.

Another reason why additional measure besides ethical approval is needed to ensure the well-being of animal subjects is that some staff abuses or makes fun of animals in the laboratory. To illustrate, in a footage published by Cruelty Free International from an animal experimentation laboratory in Spain, Vivotecnia, a male monkey was seen as pinned down on the table by a staff member who was collecting blood from its leg, while a senior staff member was seen as drawing a face on the monkey's genitals. Vivotecnia is a Madrid-based research center conducting animal experiments for the biopharmaceutical, cosmetic, chemical, tobacco, and food industries from all over the world.<sup>[14]</sup> In such experienced experimental centers, laboratory workers after a while may begin to ignore that experimental animals are actually living beings and begin to think of them as tools that lead to a goal.

Finally, most of the animals in experiments may suffer from unnecessary pain and stress beyond the aim of experiment. Exposure of animals to this unnecessary stress affects not only the welfare of the animals, but also the scientific reliability of collected data. However, laboratory staff do not care that animals are exposed to this unnecessary stress as long as they can collect the data. A footage published by Cruelty Free International and Soko Tierschutz from a toxicology laboratory in Germany revealed the maltreatments of animal subjects for toxicology and dose ranging experiments. The Laboratory of Pharmacology and Toxicology carries out toxicity tests for agrochemical, pharmaceutical, and industrial companies worldwide. As evident in the footage from toxicology tests, although it did not serve for the purpose of the trial, it was ignored that the monkeys - fixed by their necks while waiting their turn - were exposed to watching the applications of experiment

on other monkeys and experienced intense stress.<sup>[15]</sup> Although animal toxicity tests include the application of the dose causing serious harm to animal subjects, in an attempt to predict what a safe dose for humans may be, the results are not actual predictors of safety and effectivity in humans. Yet, the reactions to a particular substance for all species and humans might be quite different.<sup>[16,17]</sup> Moreover, collected data becomes unreliable due to the physiological changes in animal subjects caused by the severe stress exposure beyond the purpose of experiment.<sup>[18]</sup> Consequently, obtaining unreliable data due to unnecessary stress exposure of animals in addition to the scientific limitations of toxicology testing methods for predicting the safety of human use actually refers that many animals are wasted for nothing. However, if toxicology experiments are required, the endpoint should be clearly defined according to the purpose of the experiment and necessary measures should be taken to ensure both animal welfare and data reliability by preventing animal subjects from suffering pain, distress and abuse beyond the purpose of research.

In addition to these examples of abuse in animal experiments, a topic that has been discussed recently is that although thousands of animals are spent on scientific experiments, the majority of these studies are not published<sup>[3,19-23]</sup> or the impact of the published ones on scientific progress is controversial due to the limited transfer of animal experimental data to humans.<sup>[3,17,19,20]</sup> Öztürk and Ersan<sup>[3]</sup> reported that more than 40% of animal experiments that were represented at national orthopedic congress in Türkiye over a nine-year period were never published, and 38% of those that were published never cited or were cited only once. They found that 4,440 animals were euthanized for no obvious scientific gain in unpublished studies.<sup>[3]</sup> Unpublished animal studies result in waste of animal life.<sup>[3,19-23]</sup> Öztürk and Ersan<sup>[3]</sup> suggested that publishing even animal studies that did not find significant differences would be helpful to avoid duplication of the same study. There are guidelines such as the Animal Research: Reporting of In vivo Experiments (ARRIVE) guidelines to reduce the unnecessary animal experiments and to overcome the inadequate methodology in animal studies.<sup>[24]</sup> Researchers are expected to comply with the ARRIVE criteria and make the necessary effort to publish the results of animal studies and, therefore, the lives of animals sacrificed in experimental studies are not wasted for nothing.<sup>[3,19,20]</sup> van der Worp et al.<sup>[25]</sup> suggested that the only way to prevent the unreported data in

animal studies was to have a central registry system for animal studies similarly to clinical trial registry systems.

Since animals are known to have similar ability to feel pain and enjoy life as humans, it would be morally unacceptable to treat animals only as 'tools' to advance the knowledge.<sup>[26]</sup> Ignoring the fact that animal subjects are also living beings during experiments may expose them to unnecessary suffering and stress beyond the scientific purpose of the experiment. However, due to the scientific resource provided by animal models, it does not seem possible to expect animal experiments to be terminated all over the world in the near future. Moreover, the US Food and Drug Administration (FDA) usually asks two or more animal tests before approval of human trials.<sup>[20]</sup> In this case, the recurrence of many negative examples that have been reported previously should be prevented by taking more strict measures in centers of animal experiments. Although requirement of ethics committee approval for publication acceptance is applied all over the world, ethics committee approval does not ensure the animal welfare and data reliability.<sup>[12]</sup> When an experimental study is carried out with the approval of the ethics committee, researchers are expected to comply with the 3Rs principles. Since the refinement principle is the most uncertain among these 3Rs principles and can be achieved by various methods and there is no consensus about it, the ethics committee approval of the study, unfortunately, cannot provide definitive proof of animal welfare.

In conclusion, since animals do not have the chance to defend their rights such as humans, there is a need for a supervisor mechanism independent of the researcher to supervise and report whether the welfare principle is actually met in experimental animal studies in the real-life practice. The welfare certificate, in which the welfare of the subjects is supervised during the experiment, would serve as a proof of both the well-being of the subjects and the consequently scientific reliability of the data.<sup>[27]</sup> In this context, the content of the welfare certificate includes the criteria that the researcher is routinely expected to comply with (humane endpoints, appropriate skills and training of researchers to minimize pain and distress experienced by animals, taking measures to reduce pain and distress, improved handling of animals, appropriate living conditions, etc.), but only the researcher's statement is not sufficient, and it should be also audited that the necessary conditions are met with the application

of the evidence-based control mechanism. Audit of adherence to welfare certificate criteria could be checked with regular video records of applications and treatments which were sent to welfare audit organization, and additional spontaneous control visits applied by the welfare experts. Application of a review and publication priority for the animal experiments which have the welfare certificate in addition to the ethical approval certificate would encourage the researchers to achieve this welfare document. In this respect, editors and journals would have an important role and sanction power for the improvement of animal welfare in experiments.<sup>[28]</sup> The achievement of worldwide consensus about the content, the requirements, and the application methods of the welfare certificate should be in the scope of scientists in the near future to reach the more humane and more qualified animal experiments.

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