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How Should Treatment of Animals Beyond the Lab Factor Into Institutional Review?

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Abstract

Discussions of nonhuman research ethics tend to focus on what we owe nonhuman research subjects in laboratory settings only. But humans make critical decisions about these animals outside the lab, too, during breeding, transportation, and end-of-study protocols. This article reviews extra-lab risks and harms to nonhuman research subjects, focusing on the most commonly and intensively used animals like rodents and fishes, and argues that extra-lab risks and harms merit ethical consideration by researchers and institutional review.

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Beyond the Lab

Discussions of nonhuman research ethics tend to focus only on what we owe nonhuman research subjects in laboratory settings. But humans make critical decisions about these animals beyond the lab, too. We decide how these animals are born, how they live, and how they die. In the United States (US), we make these decisions about many animals each year. According to the US Department of Agriculture, 994 297 animals were held or used at US research facilities in 2021.[1] This figure excludes animals like fishes and rodents bred for research,[2] yet these animals account for the vast majority of research subjects.[3,4] For instance, researchers estimate that rodents account for between 93% to 99% of all US lab mammals, with between 10 to 115 million rodents used annually, depending on the methodology used.[5,6]

This paper surveys 3 contexts beyond the lab in which nonhuman research subjects are potentially vulnerable to harm: breeding, transportation, and end-of-study protocols. Because practices vary across and within species, this paper highlights case studies across species while focusing on some of the most intensively used animals in the US, namely fishes and rodents. It then notes that these impacts merit ethical consideration and institutional review and describes how different moral frameworks for assessing nonhuman subjects research might apply to current practices. It concludes that these practices raise serious ethical concerns and that more comprehensive discussion is needed to fully evaluate these concerns.

Three assumptions inform our analysis. First, we assume that sentient animals—that is, animals capable of consciously experiencing positive and negative states like pleasure and pain—have moral standing—that is, morally matter for their own sakes—and that we should therefore consider their interests when deciding how to treat them.[7,8] Second, we assume that fishes, rodents, and other animals discussed in this paper are sentient.[9,10] Third, we assume that, even if all sentient animals have moral standing, different animals merit different protections insofar as they have different interests and needs.[11,12] While not everyone will agree with these assumptions, our aim is to build upon rather than replicate work defending them.

Breeding

Lab animal breeding facilities create many animals who are not directly used in research, because these animals either are used for breeding or have unwanted characteristics.[13,14] In 2021, US research facilities held, without using, 166 322 animals covered by the Animal Welfare Act (AWA), approximately 17% of all AWA-covered animals held.[1] And since many animals—including fishes and rodents bred for research—are not covered by the AWA, the percentage of animals held and not used might be even higher. In 2017, for example, the European Union (EU) held approximately 14 million "surplus" lab animals, including fishes and rodents. Since the EU used approximately 9.4 million animals in experiments that year, surplus animals accounted for approximately 60% of the total research animal population. In other words, for every 2 animals used in experiments, 3 surplus animals were bred but not used in experiments.[13]

How breeding processes affect lab animals depends on which species and breeding facilities are involved. In general, the conditions in which breeding facilities keep animals and the procedures they use depend partly on anthropocentric concerns such as cost and research goals.[13,15,16] For example, to maximize output, breeding facilities often organize animals into group sizes and compositions that deviate from natural mating and rearing behaviors.[13,15,16] Breeding facilities also handle animals frequently, which can increase stress for animals who are not habituated to frequent handling or moving.[16] And when these facilities create animals with characteristics that make natural reproduction difficult or impossible, they often subject animals to invasive procedures, including ovarian transplants and in vitro fertilization, for breeding.[15]

Additionally, the breeding process often creates animals with harmful characteristics or "phenotypes."[17] For example, research mice and rats can develop atypical social behaviors, impaired locomotion, lethal syndromes, skin and coat disorders, and sensory organ, metabolic, reproductive, neurological, immunological, cardiovascular, hematological, respiratory, digestive, and renal diseases.[17] In the EU, 3.9% of genetically altered animals used in research and testing in 2020 possessed a harmful phenotype (313 937 animals).[18] Additionally, 27.3% of animals used to maintain genetically altered lines in the EU that year had a harmful phenotype (83 163 animals).[18] Since genetic modifications are common in intensively used species like mice and zebrafishes,[18] the number of US lab animals with harmful phenotypes is likely very high as well.

Transportation

Lab animals may be transported variable distances between breeding and research facilities when breeding and research are at different locations as well as between different research facilities.[19] In many cases, lab animals are transported not only between facilities but also between countries. For example, the US imports millions of animals for research annually.[4,20] Importation is the primary way in which US research

facilities obtain certain animals, particularly nonhuman primates (NHPs).[15,21] In fact, research threatens some wild NHP populations by driving up prices for laundered or smuggled wild-caught NHPs, raising questions about risks and harms of research for free-living as well as captive nonhuman populations.[21,22]

Lab animals are transported via ground and air.[23] For example, major US commercial rodent breeders use established land routes, either employing their own truck fleets or contracting with other companies.[19] Lab animals are also transported as air cargo, although many major airlines now refuse to carry animals—particularly NHPs—destined for research.[24,25] Travel durations vary, with most trips lasting a few days.[19] For example, ground transportation for rodents ranges from under 24 hours to multiple days: breeding facilities limit how long rodents can be in shipping containers—usually 5 days—due to welfare concerns.[19,26] International travel can require multiple days in transit and multiweek predeparture quarantines for some animals.[23,27]

Transportation is inherently and acutely stressful for many animals.[28,29,30,31] Indeed, transport stress is so common that many research facilities grant animals time to recover to preserve the apparent validity of scientific results.[19,27,32] Standard transport procedures can also compound this stress. For example, adult zebrafishes are typically denied food for 24 hours before transport, removed from their home tanks, and transported in polyethylene bags with high stocking densities, which, combined with long trip durations, can generate dangerous conditions.[33,34] These and other such procedures expose animals to disease, injury, and environmental extremes—risks that are especially pronounced for immunocompromised animals.[32] Of course, animals face ordinary risks associated with ground or air travel, including delays and crashes, as well.[21,23,26]

End of Study

Following their use in research, animals are typically killed.[35] Humans kill lab animals as part of experimental design, either because experiments are sufficiently painful or because the animals are no longer useful.[36] Humans also kill surplus animals who are no longer useful for breeding or have unwanted characteristics.[14,36,37] Regulatory and institutional guidance on killing lab animals recommends "humane" methods that minimize pain and distress while prioritizing study goals and other anthropocentric interests. For example, the AWA makes exceptions when investigators provide scientific justification for using painful or stressful killing methods,[2] and institutional guidance often does as well.[38,39] Other justifications for killing methods that do not minimize pain or distress include efficiency, convenience, and physical and emotional health and safety of humans.[36,40,41]

Lab animals are killed in numerous ways. According to the American Veterinary Medical Association (AVMA) *Guidelines for the Euthanasia of Animals: 2020 Edition*, "acceptable" methods for killing lab rodents include administering barbiturates or dissociative agents, while methods "acceptable with conditions"—which investigators might prefer on scientific or other anthropocentric grounds—include gassing them with certain chemicals, injecting them with certain chemicals, decapitating them, disarticulating their cervical vertebrae from their skulls, and heating their brains using focused beam microwave radiation.[39,41,42] Several of these methods are controversial, given evidence that they cause pain and distress.[40,41] Physical methods such as cervical dislocation depend on the skill of the human, thereby varying in their animal welfare impacts.[41]

As an alternative, some research organizations offer adoption programs for certain animals, including dogs, cats, and small mammals, and some US states legally require offering adoption when certain research animals are no longer needed.[43,44,45] Adoptions can be mutually beneficial, since they can provide companionship for humans and better lives for former lab animals.[46] Some research facilities also retire animals who cannot be privately adopted, such as NHPs, by partnering with sanctuaries to care for retired animals or potentially establishing their own.[47] True sanctuaries provide animals with excellent care and maximal agency throughout their natural lives in a nonexploitative setting.[48] However, these programs remain limited in the number and diversity of animals adopted or retired and are the exception rather than the rule.[44]

Extra-Lab Risks and Harms

These risks and harms clearly merit ethical consideration and institutional review. In the US, under the AWA, Institutional Animal Care and Use Committees (IACUCs) oversee animal use in research facilities. Generally, IACUCs focus on animal welfare concerns *within* rather than *beyond* research protocols.[49,50,51] For example, investigators may submit transportation plans in some cases, but IACUCs are not required to directly review or approve transportation.[52,53] Similarly, IACUCs review killing methods for alignment with AVMA guidance but do not generally require investigators to justify their decision to kill animals.[51] Comprehensive ethical review of animal research must fill these gaps by considering all risks and harms for sentient animals during breeding, transportation, and end-of-study procedures.

Of course, assessment of these risks and harms depends on which ethical framework one applies. In the US, IACUCs apply the "3 *R*'s" framework, asking whether researchers can *replace* animal subjects with nonanimal methods, *reduce* the number of animal subjects used, or *refine* protocols to minimize pain and distress for animal subjects.[53,54] Expanding this framework to include all relevant impacts would raise the bar for approval in many cases; for instance, reduction would require accounting for the number of lab animals *and* the number of surplus animals, and refinement would require accounting for harms in *and* beyond the lab. However, whether these factors alter the outcome of the institutional review process will depend on other factors as well, including the benefits of scientific research for humans and, arguably, the benefits of existence for some nonhumans.

Moreover, applying ethical frameworks that are more rigorous than the 3 *R*'s to assess beyond-the-lab risks and harms might have additional significance.[55,56,57] For example, Beauchamp and DeGrazia argue that animal research must meet 6 principles of social benefit and animal welfare to be acceptable, including meeting animals' basic needs.[57] These principles might forbid at least some beyond-the-lab practices. Similarly, the second author (J.S.) argues that nonhuman subjects research should embody principles of respect, compassion, and justice.[56] These principles would clearly forbid many beyond-the-lab practices. Moreover, when experimental protocols cause harm to animal subjects, these additional considerations might simply make the impermissibility of such animal research overdetermined. But when experimental protocols are deemed harmless, these additional considerations might make the difference in whether the research is allowed to proceed.

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