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Responsible Conduct of Research: Animal Care Use and Research Ethics

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ABSTRACT

The use of animals in research has played significant roles in improving the quality of health of humans and animals. Despite these benefits, however, animals' use in research has been subjected to oppositions on the basis of ethics and research procedures that inflict distress and compromise the welfare of the animals used. Efforts made by the international communities through laws and policies have clearly shown that research involving experimental animals must be done under acceptable scientific and ethical rules. An ethical justification to use animals in research is that the necessity and scientific significance of the research is not only for the benefit of humans, but also for the animals whose welfare may be compromised by the research. Thus, the importance of using strategies that replace sentient animals with less sentient ones, reduce the number of animals used, refine the environment, husbandry and management of animals and provide adequate veterinary care so as to minimize pain and suffering must be ensured. Ultimately, these enhance the welfare of the animals without compromising the objectives of the research. Overall, these are major issues of ethical concern. The recommendations provided by this review on care and ethics of animals used in research are based on published results and proven high-quality scientific principles that promote the welfare of animals. Finally, these can be used to develop animal care and use programs as well as check the standards of performance of research involving experimental animals.

Keywords: *Animal care, research ethics, animal use in research, husbandry*

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INTRODUCTION

The use of animals in research is considered an essential tool in the progress of science. Animals play a central and essential role in research, testing, and education for continued improvement in the health and welfare of human beings and animals (Dawkins, 2012). Most of the involvement of animals in research is directed towards understanding the mechanisms of vital processes so as to improve prevention, diagnosis and treatment of diseases (Cheluvappa et al., 2010). Animals' use in research has led to significant contributions to increased understanding of biological processes, and have been responsible for many important biomedical discoveries.

However, animals used in research are often subjected to distress, painful procedures, or killing (Belliure et al., 2004). Thus, over the years, the use of animals in research has generated controversial questions in the society. Certain segments of the society and few organizations, particularly in developed countries have opposed their use in research. Consequently, scientists and researchers are continually subjected to confrontations from groups who accuse them of

animal exploitation in research. Ethical questions of whether it is right for humans to subject animals to procedures that may inflict pain and suffering on them and what should be the ideal welfare of animals used in research have been raised (Festing and Wilkinson, 2007). These concerns necessitate a thorough review of ethical issues raised from research involving animals; thus, these can help to establish a unified system of control in regulating the practices of researchers and hence, promote adequate care and welfare of animals used in research.

EFFORTS MADE TO MAINTAIN ANIMAL CARE AND WELFARE IN RESEARCH

Animal welfare is a human responsibility that encompasses all aspects of animal well-being, including proper housing, management, nutrition, disease prevention and treatment, responsible care, humane handling, and, when necessary, humane euthanasia (Council, 2009). Several efforts have been made by different international societies to ensure the welfare and care of animals used in research. Various federal and local laws, regulations, policies and standards have also been established to guide researchers on best practices that would

enhance animal welfare (NIH Guide, 2011). For example, in 1876, the Cruelty to Animals Act was enacted in the United Kingdom, which required the government to license individual scientists who used animals in research. This licensing was intended to address the public's concerns and to ensure that only qualified individuals conducted research in animals (Anderson, 2007). Similarly, in 1985, improved Standards for Laboratory Animals Act, was enacted by the United States Department of Agriculture (USDA). Through this Act, registered research facilities were required to establish an institutional animal care and use committee comprising of veterinarians, practicing scientists, legal practitioners and members of the public and general community (IACUC1) (Anderson, 2007). Such committee has been established in many countries to expand the frontiers of knowledge and ensure excellent conditions for research involving the use of animals in biomedical science. Among other responsibilities, the committee provides oversight and assistance in ensuring compliance to all laws, regulations and policies governing the care and use of animals for research, teaching and testing (NIH Guide, 2011), inspects institution's animal facilities, prepares and submit report on to the institutional officials. Further, it reviews concerns involving the care and use of animals at the institution. Again, it makes recommendations to the institution's officials regarding any aspect of the its animal program, facilities, or personnel training. Importantly, it approves, suggest modifications (to secure approval) or withhold approval of activities related to the care and use of animals.

JUSTIFICATION OF ANIMAL USE IN RESEARCH

Over the years, researchers have justified the use of animals in research mainly by emphasizing their benefits to human health (Kostomitsopoulos and Durasevic, 2010). However, justification for the use animal in research should not be based solely on human benefits, but also on the animals whose welfare may be compromised during the experimentation (Olsson et al., 2007). It is essential for researchers to realize the importance of ethics in their use of animal in research. Importantly, animal use in research is only acceptable when the necessity and scientific significance of the research benefits humans and animals, and the likelihood of its success is clearly stated (Kostomitsopoulos and Durasevic, 2010). Thus, there should be a reasonable expectation that the research will increase knowledge of the process underlying the development, maintenance, control and biological significance of behavior, as well as increase understanding of the species under study. The scientific purpose of the research should be of sufficient potential significance that justifies the use of non-human animals. The reason for choosing a particular animal species must also be justifiable while the procedures of the research must minimize the number of animals to be used. It is essential that the benefit of the research are achieved with minimal negative consequences to the animals. Further, the use of animals in research is acceptable only when its expected benefits is more than the harm and suffering that will be caused to the animals. Ultimately therefore, research protocol that minimizes pain, discomfort

and distress on the animals used, must be engaged to justify the use of the animals.

Over the years, the 3R's concept of Russell and Burch on the reduction, refinement and replacement of animals has become an essential aspect of the design of animal research (Guhad, 2005). The use of animals in research can be acceptable when replacement strategy; which avoids the use of animals or replaces sentient animals such as vertebrate, with less sentient ones such as invertebrate are engaged. These practices have been reported to have a significantly lower potential for pain perception (Wakefield et al., 2002). Similarly, researchers can avoid compromising animal welfare through the reduction strategy; which minimizes the number of animals used or maximizes the information obtained per animal (Nevalainen, 2004). In addition, the use of animals in research is justifiable when researchers apply the refinement strategy; which involves modification of animal husbandry or research protocol so as to minimize pain, suffering and discomfort and enhances the welfare of the animals without compromising the objectives of the research (Lloyd et al., 2008).

GUIDELINES FOR THE ENVIRONMENT, HOUSING AND MANAGEMENT OF ANIMALS USED IN RESEARCH

Appropriate animal housing and design of animal facilities are important factors that contribute to animal well-being, quality of animal research and safety of personnel (Memarzadehet al., 2004). The environment, management and housing facilities can alter physiological process and may affect disease susceptibility of the animals used in research. Hence, an ethical research program is one that utilizes suitable environment, housing and management for the animal species or strains, and takes into consideration their physiological and behavioral needs. The environment and housing facilities must allow the animals to grow, mature, and reproduce normally while providing for their health and well-being. Environmental factors such as temperature, humidity, illumination, noise and gaseous particulate composition of the air which can directly influence the physiological behaviour and well-being of the animals used in research must be properly taken into consideration (Memarzadeh et al., 2004).

Temperature and humidity: For the well-being of animals used in research, it is essential to maintain the body temperature within normal circadian variation. Optimum temperature for normal physiological behavior varies with different animals (Table 1).

Table 1:
Normal thermo-neutral zone (TNZ) for some laboratory animals

Animals	TNZ (°C)	Reference
Mice	26-34	Gordon, 2004
Rat	26-30	Gaskiller et al., 2009
Gerbils	28-32	Gordon 1993
Rabbits	15-20	Gonzalez et al., 1971
Cat and Dog	20-30	NRC, 2011

TNZ- Ambient temperature range where which thermo-regulation occurs without a need to increase metabolic heat loss mechanism

Hence, the need to house each experimental animal within the range of temperature and humidity that minimizes stress and physiological alteration. Exposing experimental animals to wide or extreme temperature and humidity results in changes in their behavior, morphology and physiology, which have negative impact on their well-being and may adversely affect their research performance and outcome of research protocol (Tewksbury et al., 2008; Paaijmans et al., 2013). Some studies have reported negative effect of extreme temperatures and humidity on the performance of experimental animals. For example, in rats, low relative humidity and extreme temperature may lead to ringtail, a condition involving ischemic necrosis of the tail and sometimes toes (Crippa et al., 2000). Similarly, extremely high and low humidity may increase pre weaning mortality in mice (Clough 1982). High relative humidity have also been reported to affect animal's ability to cope with thermal extremes (Hasenau et al. 1993). Husbandry and design of housing facility may affect temperature and relative humidity. Factors that contribute to variation in temperature and humidity including construction material and enrichment devices such as shelters and nesting material; number, age, and size of the animals in each facility must be considered in the selection and maintenance of appropriate temperature for animals used in research. This implies that animals should be provided with adequate resources for thermoregulation (nesting material, shelter) depending on the situation.

Ventilation and Air Quality: Adequate ventilation within the experimental animal facility is necessary to provide sufficient oxygen, stable environment and remove thermal loads caused by the animals, personnel, equipment and particulate contaminants such as airborne pathogens (Bell, 2008). It is important to prevent direct exposure of animals to air moving at high velocity because it affects the rate at which heat and moisture are removed from the animals particularly in neonatal homeotherms which may be hairless and have poorly developed mechanisms for thermoregulatory control. Depending on the species, size, and number of animals involved, provision of about 10 to 15 fresh air changes per hour in animal housing rooms is an acceptable guideline to maintain air quality and well-being of research animals (DiBerardinis et al. 2009). Ventilating animal rooms with recycled air is associated with a high risk, although it might be a means of saving energy. Exhaust air recycled to serve multiple rooms also presents risk of cross contamination because many animal pathogens can be airborne. On the other hand, recycled air from non-animal use areas pose less risk of infection. To maintain the well-being of animals used in research, exhaust air should be well filtered to remove airborne particles before it is recycled (NAFA 1996).

Illumination: Light can affect the physiology, morphology, and behavior of various animals used in research (Azar et al. 2008). Inappropriate photoperiod, photo intensity and poor spectrum quality have been reported as potential photo stressors to animals used in research (Hanifin and Brainard 2007). Factors that influence animals' need of light including; light intensity, wavelength, duration of animal exposure to light, animal's pigmentation, body temperature, hormonal status, age and sex must be considered in establishing

appropriate level of illumination for animals used in research (Olsson et al. 2002). Studies have shown the importance of intrinsically photosensitive retinal ganglion cells for circadian, and neurobehavioral regulation in primates and rodents (Hanifin and Brainard 2007). It has been reported that these cells respond to light wavelengths that differ from other photoreceptors and may influence the type of lighting, light intensity, and wavelength selected for certain types of research. For enhanced well-being of animal used in research, lighting should be diffused throughout the animal holding area to provide sufficient illumination for the animals and permit good housekeeping practices and adequate animal inspection (Brainard 1989).

Photoperiod is a regulator of reproductive behavior in many animal species (Brainard et al. 1986; Cherry 1987); hence, excessive light exposure during the dark cycle should be avoided for animals used in research. For example, some animals such as chickens do not eat in darkness (Apeldoorn et al. 1999); hence, illumination should be limited to a duration that will not alter the purpose of the research or compromise the well-being of the animals. Ultimately therefore, control of duration of exposure to light will help to ensure regular diurnal cycle.

Noise and Vibration: Noise control is an important factor that must be carefully considered in the design of animal housing facility because it affects the well-being of experimental animals and personnel involved with animal research (Willott, 2007). Noise and vibrations have been associated with biochemical and reproductive changes in laboratory animals and can become an uncontrolled variable for research experiments (Carman et al. 2007). Excessive exposure of animals to loud sound has been reported to be of detrimental effect to the animals. For example, eosinopenia, reduced fertility and increased adrenal gland weights in rodents (Rasmussen et al. 2009), and increased blood pressure in nonhuman primates (Peterson et al. 1981) are factors associated with this. The intensity, frequency, rapidity of onset, duration, and vibration potential of the sound and the hearing range, and sound effect susceptibility of the animals must therefore, be considered to identify the potential effect of noise on the animals used in research. The environment and housing facilities should be designed to accommodate animal noise while methods of noise reduction can also be applied. Separation of animal and human areas will also help to minimize noise disturbances to the animals used in research. Effort should be made to separate noisy animals, such as dogs, swine, goats and some birds away from quieter animals, such as rodents, rabbits, and cats. In addition, conducting noise generating activities away from rooms where experimental animals are housed is a useful guideline to reduce the damaging effect of noise on experimental animals. The use of radios, alarms, and other sound generators should also be minimized in housing facilities used for animal research to minimize associated adverse physiologic changes (Baldwin 2007).

PRINCIPLES GUIDING ANIMAL CARE USE AND RESEARCH

Animals used for research purposes should be managed and handled with caution and high sense of responsibility. There

should be the provision of appropriate animal transportation and husbandry directed and performed by qualified persons. These qualified personnel must supervise all conducts of experimentation on living animals to limit the hazards and dangers associated with experimental procedures. Adequate control measures to ensure safety and prevention of contamination through the use of appropriate personal protective equipment (PPE) especially when handling poisonous or infectious agents must be ensured. Further, adherence to standard operating procedures (SOPs) as well as appropriate design of experimental facility are essential.

Prevention of pain

In studies that require the animals to reach a moribund state or die spontaneously as the endpoint of the study, the earliest endpoint possible should be used to prevent pain or distress. Ensuring that drug doses are correct and that the drugs used are not expired. Ensuring that procedures to be performed on the animals are reasonable for that species. Importantly, using appropriate anesthetics and analgesics for potentially painful procedures must be ensured. Further, performing surgeries and procedures aseptically to prevent infection must be ensured. Again, performing only a single major survival surgery on any one animal, whenever possible should be encouraged. Therefore, it must be ascertained that performing appropriate post-surgical care, including thermoregulation and fluid balance are all critical factors that must be considered (Weary *et al.*, 2006).

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