

Appendix 2: Behavioral Management of Nonhuman Primates

Introduction:

NIH recognizes the continued need for nonhuman primates in biomedical research and strives to ensure that such use is humane, ethical, and responsible. Federal regulations, international regulations, and professional standards agree that proactive plans to address environmental enhancement, animal well-being, and socialization are necessary and that such needs should be balanced against quality and reproducibility in research (1-8). To meet these objectives, behavioral management programs at NIH must minimally address social grouping, environmental enrichment, any nonhuman primates requiring special attention, as well as the use of restraint devices (when they are necessary to meet research objectives), and any exemptions from participation in the environmental enhancement plan. It is the intent of this document to establish best practices for behavior management programs in the NIH Intramural Research Program (IRP) which go beyond the minimum standards and address the physical and psychological well-being of nonhuman primates. Such plans should include social housing, positive reinforcement training, behavioral assessment and intervention plans, exercise enclosures, and environmental enrichment among other strategies as well as an evaluation stage (4, 9-14).

Behavioral Management Strategies:

Long developmental periods, high intelligence, and complex social structures are common characteristics of all nonhuman primate species and set them apart from most other animal model species (3) ([NIH DVR Enrichment Plan, 2020](#)). The goal of a behavioral management program is to provide the animals with the option and ability to engage in species-typical behavior and promote psychological well-being through the use or application of environmental enrichment (physical, social, nutritional, occupational, and sensory enrichment), social housing, and applying positive reinforcement training techniques to facilitate husbandry, veterinary, and experimental procedures. Providing these options will ultimately address the physical, physiological, and behavioral needs of the nonhuman primates and meet or exceed current professional and veterinary standards of care (13, 15-18).

Social Housing

Nonhuman primates, as social species, should be housed in stable pairs or groups whenever possible unless an exemption is justified based on experimental requirements (as approved by the Animal Care and Use Committee [ACUC]) or veterinary-related concerns (as approved by the Attending Veterinarian) (1, 2). Providing species-typical social housing does not preclude participation in most experimental procedures, in fact, the majority of nonhuman primates held for use in research in the United States are maintained in some form of social housing (19). While it is recognized that not all social animals are socially compatible, there are many strategies available to enhance the odds of success when introducing unfamiliar animals such as partner selection(20, 21), pre-introduction evaluation/temperament testing(22-27), gradual steps introductions(28, 29), introduction in larger enclosures(30), staged introductions for larger groups(31, 32), protected contact or intermittent full contact introductions(33-35), treatment with anxiolytic medication to facilitate introduction(36), interspecies contact(37-39), and behavioral modification training such as cooperative feeding or other strategies to enhance compatibility(40-43). If single housing is required, it should be for the minimum duration necessary. Methods should be explored, if possible, where animals can engage in periodic release into larger enclosures for enhanced structural contact (44) or consider alternative social housing

such as, intermittent housing or protected contact housing . Investigators should also consider the impact of single housing when planning research projects and include details about the social housing paradigm in publications (33, 45-52).

ACUCs should consider the following questions when evaluating the justification for single housing of nonhuman primates due to experimental design (1, 14). Does the Animal Study Proposal (ASP):

- a) describe the course of the experimental portion necessitating single housing and if subsequent re-pairing /group housing is possible?
- b) state a plan and timeline for returning an animal to social housing after the experiment portion requiring single housing ends?
- c) reference working with the behavioral enrichment staff or IC facility veterinarian to employ tools that can provide the single-housed animal with an enhanced environment, maximal cohort exposure, and a quicker return to social housing if it does not interfere with the experiment?
- d) address intermittent periods in the study where social housing may be attempted without interfering with the study?

Physical Enrichment

Physical enrichment for nonhuman primates may include but are not limited to enhancing the animal's physical environment, changing size or complexity of enclosure, cage furniture, manipulanda, visual barriers, varied substrate and forage material, perches, nest boxes, climbing structures, and swings. Additional components of the home cage specifically designed to provide enrichment may include tunnels or grooming contact panels which connect adjacent cages and allow for the expression of species typical behavior (53-55).

Nutritional Enrichment

In their natural environment, nonhuman primates spend a large portion of their day foraging for food. The nutritional enrichment program should include offering novel foods, changing delivery of food, and providing foraging opportunities to increase the time spent conducting these activities. For example, a method to extend foraging time is to provide standard chow in a cage mounted puzzle feeder to slow biscuit consumption (56-59).

Occupational Enrichment

The *Guide for the Care and Use of Laboratory Animals (Guide)* recommends including positive training techniques in husbandry and experimental procedures. The occupational enrichment aspect of a behavioral management program should include positive reinforcement training (PRT). It provides the animals a way to cope with stress, gives them some control, keeps them occupied, promotes exercise and provides mental stimulation (60). Training nonhuman primates through the application of positive reinforcement training may facilitate cooperation in veterinary (61), husbandry (40), and experimental procedures (62). Alternatively, behavioral testing can be seen as a dynamic activity as it provides nonhuman primates opportunities to engage in mentally and physically stimulating procedures outside of the home cage (63).

Sensory Enrichment

Sensory enrichment can be broken down into four categories: visual (television, windows, bubbles, people watching), olfactory (scented sprays, herbs), auditory (radio, people talking to the animals) and tactile (frozen treats, varied nesting, foraging material) (53, 54, 56, 59, 63). Environmental enrichment is one component of an ACUC approved behavioral management program and should be provided in a consistent manner across the animal program. In addition, enrichment programs should be reviewed by the ACUC, researchers, and veterinarian on a regular basis to ensure that they are beneficial to animal well-being and consistent with the goals of animal use(1, 64).

Exemptions

According to the Animal Welfare Regulations (9§CFR 3.81, e), the following exemptions should be considered:

- The attending veterinarian may exempt an individual nonhuman primate from participation in the environment enhancement plan because of its health or condition, or in consideration of its well-being. The basis for exemption must be recorded by the attending veterinarian for each exempted nonhuman primate. Unless the basis for exemption is a permanent condition, the exemption must be reviewed at least every 30 days by the attending veterinarian. (Sect. 3.81 (e)(1)) (2).
- For a research facility, the Committee may exempt an individual nonhuman primate from participation in some or all the otherwise required environment enhancement plans for scientific reasons set forth in the research proposal. The basis of the exemption shall be documented in the approved proposal and must be reviewed at appropriate intervals as determined by the Committee, but not less than annually (Sect.3.81 (e)(2)) (2).
- Records of any exemptions must be maintained by the dealer, exhibitor or research facility and must be made available to USDA officials or officials of any pertinent funding Federal agency upon request. (Sect.3.81 (e)(3)) (2, 56).

Evaluating Behavioral Management Strategies:

Because animal welfare, conceptually, is specific to each individual animal, behavioral management strategies are rarely "one size fits all" with respect to successfully promoting wellbeing across a population. When consulting published strategies and interventions, it is important to remember that variations in facilities, such as size and husbandry practices, as well as characteristics of the animals themselves such as age and temperament, may differentially impact the effectiveness of intervention. The development of a behavioral management program is thus an iterative process and should include periodic evaluation of interventions to ensure that efforts actually positively promote animal welfare. To accomplish this, interventions should have an attainable and quantifiable goal, such as an increase in species-typical behavior, and this should be measured systematically to determine whether the intervention is meeting its goal, at least in some individuals. For example, the SPIDER (Setting Goals, Planning, Implementing, Documenting, Evaluating, and Readjusting) framework has been a widely accepted implementation and evaluation tool for environmental enrichment across captive animal facilities (see Alligood and Leighty, 2015 for review) (65). Not only do evaluations quantify the extent to which interventions work or point towards

directions for improvement but can also serve as "pilot data" for how to customize interventions more efficiently in the future for the facility and animals. For example, previous managers who have evaluated their interventions have found traits such as personality and sex determined success in behavioral training more so than social rank or rearing history (66, 67). Yet, these traits may or may not affect training outcomes similarly across facilities and populations, thus the importance of evaluating interventions for specific populations.

Summary:

Behavioral management strategies for nonhuman primates have been widely adopted across the NIH IRP, the United States, and Europe to address the welfare of nonhuman primates used in biomedical research. Standardized strategies have been applied to a wide range of research situations with varying research goals without adverse results. All NIH programs must have an environmental enrichment plan for nonhuman primates used within their program. Enrichment plans should delineate the standardized approach to be used within the program as well as document the effectiveness of the plan. Programs choosing to go above this minimum must consider the introduction of additional research variables between their animals and animals housed in different facilities and programs. In all situations, the decision regarding whether or not to enhance the microenvironment of nonhuman primates housed in the NIH IRP ultimately rests with the Principal Investigator and the ASP review process in each Institute or Centers' ACUC. Valid reasons for either enhancing or limiting the microenvironment should be provided to the ACUC during initial ASP review.

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Approved – 12/11/2013

Revised- 3/22/2017, 12/19/2019, 12/09/2020, 01/24/2024