
**REPORT TO THE SENATE ARMED SERVICES
COMMITTEE AND THE HOUSE OF REPRESENTATIVES
NATIONAL SECURITY COMMITTEE**

on

**Department of Defense
Animal Care and Use Programs 1996**

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LIST OF ACRONYMS

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
AALAS	American Association of Laboratory Animal Science
ACLAM	American College of Laboratory Animal Medicine
APHIS	Animal and Plant Health Inspection Service
ASBREM	Armed Services Biomedical Research Evaluation and Management
AWA	Animal Welfare Act
AWIC	Animal Welfare Information Center
BRD	Biomedical Research Database
CRISP	Computer Retrieval Information of Scientific Projects
DDR&E	Director, Defense Research and Engineering
DoD	Department of Defense
DTIC	Defense Technical Information Center
FDA	Food and Drug Administration
FEDRIP	Federal Research in Progress
FY	Fiscal Year
IACUC	Institutional Animal Care and Use Committee
IG	Inspector General
ILAR	Institute of Laboratory Animal Resources
IRAG	Interagency Regulatory Alternatives Group
JDL	Joint Directors of Laboratories
JTCG	Joint Technology Coordinating Groups
LAM	Laboratory Animal Medicine
MATRIS	Manpower and Training Research Information Services
NIH	National Institutes of Health
NRC	National Research Council
OPRR	Office for the Protection from Research Risks
OSD	Office of the Secretary of Defense
PHS	Public Health Service
PCR	Polymerase Chain Reaction
RDT&E	Research, Development, Test, and Evaluation
S&T	Science and Technology
STO	Science and Technology Objective
TAPSTEM	Training and Personnel Systems Science and Technology Evaluation and Management
USAMRMC	United States Army Medical Research and Materiel Command
USDA	United States Department of Agriculture
VEE	Venezuelan Equine Encephalitis
WRAIR	Walter Reed Army Institute of Research

SECTION I

INTRODUCTION/OVERVIEW

This is the Fiscal Year (FY) 1996 Report to Congress on Department of Defense Animal Care and Use Programs. In addition to a general overview, this report provides a detailed accounting of Department of Defense (DoD) animal use; to include its publicly accessible database, animal care and use oversight procedures, Institutional Animal Care and Use Committees (IACUCs), alternatives to animal use programs, Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) status, and animal use.

The report covers animal research conducted by the DoD including education, training, and testing both in DoD laboratories and by extramural projects funded by the Department for FY96. This report does not include information on animals used by the DoD solely for the purpose of food preparation for human or animal consumption, ceremonial activities, recreation, or the training, care, and use of military working animals.

I.1 REQUIREMENTS FOR USE OF ANIMALS IN THE DoD

Department of Defense use of animals in research, development, education, and training is critical to sustained technological superiority in military operations in defense of our national interests. The DoD's biomedical research, development, test, and evaluation (RDT&E) and training programs that are dependent on animal use ultimately translate into improved military readiness as well as reduction in morbidity and mortality associated with military operations. These programs contribute directly to ensuring that service men and women maximize their capabilities to survive the numerous and various hazards they face around the world. Additionally, many examples of the humanitarian benefits of the DoD investment in animal research that are shared on an international basis improve the quality of life of both humans and animals. Several prime examples of the humanitarian benefits of DoD research efforts

are: the Junin vaccine that has provided critical protection for over 120 thousand individuals in endemic areas of Argentina against the ravages of Argentinian hemorrhagic fever; DoD-developed Venezuelan equine encephalitis (VEE), eastern equine encephalitis, and western equine encephalitis vaccines that have been used to limit and control epidemics of VEE in Venezuela and Colombia in 1995, and to protect occupational workers in vaccine production plants around the world. In addition to being important public health tools, the equine encephalitides vaccines are obviously critical adjuncts to animal health programs around the world.

Biomedical research has benefited greatly from animal use alternatives such as non-living systems, cell and tissue culture, and computer technology. However, complex human organ systems interactions, in addition to environmental factors and confounding variables, necessitate the continued judicious use of animal models in DoD programs. Although many innovative animal use alternatives have been developed and are in use by Department scientists, situations remain in which there are no acceptable non-animal alternatives available. As new advances, technologies and breakthroughs in animal use alternatives occur, the DoD will embrace them whenever possible. The chapter on alternatives in this report gives a full accounting of the aggressive programs and numerous animal use alternatives implemented in DoD laboratories.

Disease remains a major cause of death and disability in military operations and conflicts. During Operations Desert Storm and Restore Hope, outbreaks of respiratory diseases, diarrheal diseases such as shigellosis, and parasitic diseases such as leishmaniasis and malaria, threatened the health and well-being of our troops. Indeed, the DoD is still assessing and addressing concerns over the long-term effects of various environmental, physical, and medical factors associated with the Persian Gulf Conflict. It is obvious that the health

and well-being of military personnel extend far beyond the immediate scope of the battlefield. We have an irrefutable moral obligation to our soldiers, sailors, airmen, and marines to provide the maximum protection and care possible. DoD researchers are committed to accomplishing this goal, and in many cases, animal-based research is the critical underpinning for the fulfillment of that obligation.

The DoD must develop the materiel and technological means to best protect and sustain the health and well-being of service men and women against all threats, and provide the best medical treatment possible to those who become casualties. This responsibility underlies the need for the DoD to conduct research, and to train and educate military health-care providers in the most effective medical management of battlefield casualties. Battlefield health care must very often be provided in an austere, harsh and hostile environment, hours away from a definitive care hospital, unlike medical counterparts found in civilian emergency medicine and trauma management. A domestic, low velocity projectile gunshot patient in a modern civilian shock and trauma center will be supported and resuscitated by a full complement of medical staff with a plentiful supply of oxygen, fluids, medications, surgical intervention and nursing. The combat casualty may be supported by only a single aidman and the medical supplies, experience, and expertise he can carry.

One of the most critical areas requiring DoD animal use is the compelling need to develop vaccines, drugs, and therapies to protect, sustain and treat service men and women during military operations. These research programs are strongly focused on a myriad of militarily relevant diseases and threats, many of which can result in potentially fatal diseases or conditions that have no known treatments, therapies, or cures. Consequently, there are numerous instances, including medical chemical and biological warfare defense, where animal-based studies are particularly critical. Ethical concerns, as well as regulatory requirements of the Food and Drug Administration (FDA), necessitate that candidate vaccines and drugs be safe and efficacious in laboratory animal models prior to initiation of human use protocols whenever possible. The rationale for this is to prevent the fielding and use of ineffective or dangerous treatments. Indeed, during the final stages of

vaccine and drug development, large-scale safety and efficacy testing is usually conducted using human volunteers. However, in the search for understanding and developing protection against many highly lethal agents, human use protocols are simply not possible. Consequently, carefully regulated animal use is absolutely vital to the success of Department biomedical research programs. The ultimate goal is to maximize the survivability of our troops in all situations.

I.2 DoD POLICY GOVERNING ANIMAL RESEARCH

The Department of Defense is committed to full ethical and regulatory compliance for its animal-based biomedical research programs. DoD has been proactive in increasing the fixed infrastructure and span of control necessary to ensure lawful and efficient execution of programs and maximize oversight of diverse and varied missions. The Department has aggressively implemented focused programs and working documents that optimize standardization of animal care and use at the user level. This enhanced standardization and oversight have improved a historically good system, and made it outstanding.

In 1995 the DoD developed and implemented a new directive dealing specifically with animal care and use (DoD Directive 3216.1, "The Use of Animals in DoD Programs," 1995) (Appendix A). This directive strengthens and clarifies requirements for nonaffiliated membership on IACUCs and directs all DoD animal use facilities that maintain animals for research, testing and training to apply for AAALAC accreditation.

The DoD also implemented a Policy Memorandum entitled "Department of Defense (DoD) Policy for Compliance with Federal Regulations and DoD Directives for the Care and Use of Laboratory Animals in DoD-Sponsored Programs" (Appendix B). This 1995 policy letter specifies training requirements for nonaffiliated DoD IACUC members and implements a standard format for animal use protocols (Appendix C), a standard checklist for IACUC inspections (Appendix D), and a standard reporting requirement for all animal use research to support a publicly accessible database (Section II).

All animal research must conform to requirements of the 1966 Animal Welfare Act (P.L. 89-544) as amended in 1976 (P.L. 94-279) and 1985 (P.L. 99-198), as well as the National Research Council *Guide for the Care and Use of Laboratory Animals*, (7th rev. edition, 1996), U.S. Government Principles for Animal Use (1985) (Appendix E), and the requirements of the applicable regulations of the United States Department of Agriculture (USDA).

Although the Animal Welfare Act currently exempts mice and rats in the genera *Mus* and *Rattus*, the DoD has long afforded them, along with all other vertebrates, the same consideration given non-exempt species under the Animal Welfare Act. At the same time, DoD biomedical researchers have aggressively developed novel procedures to replace, reduce, and refine the use of animals during experimentation.

I.3 BENEFITS OF ANIMAL RESEARCH

DoD's laboratories and extramural contractors provide the capability to solve the medical and non-medical problems of the future through the efforts of internationally renowned medical and scientific experts working in state-of-the-art facilities and in the field. The Department conducts or funds research, development, training and evaluation to sustain the operational capabilities of today's servicemen and women. As noted in the previous section many of these programs require the use of animals to meet their mission requirements. These programs result in many benefits for both the military and civilian sector (Table I-1). The military benefits from programs that do research in areas that currently threaten military personnel such as combat trauma, chemical and biological agents, infectious diseases not endemic to the United States, directed energy, and occupationally unique health hazards from military operations and environmental extremes. These research programs focus heavily on the prevention of casualties; these efforts contribute significantly to the readiness and sustainment of the DoD's warfighting capability, and also to a significant reduction in the number of casualties reaching the medical treatment facilities. In addition, the DoD is involved in medical research that directly benefits the civilian population such as research in breast cancer, cardiovascular disease,

Table I-1 Animal Use Benefits

Medical
Preventive medicine
Infectious disease research
FDA safety and efficacy testing prior to use in humans
Vaccine development
Enhanced technical base of medical knowledge
Participation in Phase 2, 3, 4 drug evaluations
Identify new species of bacteria
Identify new antibiotics
Establish potential hazards of military nerve agents to humans
Develop new and improved methods for disease prevention, diagnosis, and treatment
Gulf War illnesses
Breast cancer research
Clinical
Improvement in patient care
Bridging the gap between science and bedside treatment
Better understanding of general anesthetics during surgery
Non-Medical
Development of biosensors
Identification of environmental toxins
Training
Special forces medical training
Advanced trauma life support training
Graduate medical training in surgical techniques
Alternatives
Development of alternatives to replace, reduce and refine the use of animals

trauma care and treatment, respiratory injuries, burns, and specific surgical procedures. A list of specific benefits by research category is shown at Appendix F.

Besides the medical benefits of animal research there are many other non-medical and training benefits. The development of biosensors and the identification of environmental toxins benefit both the military and civilian communities. The DoD has many exceptional medical and scientific educational programs that train both medical personnel and scientists. While these people are in the military, the DoD reaps the benefit of this training; once they leave the military, this benefit is

realized by the civilian community. The development of alternatives to animal use by the DoD provides an extra value to both communities and to animals as they discover ways to reduce or replace the use of animals. Also refinement research results in more humane methods of performing research that is applied in many types of research settings.

I.4 SCOPE OF REPORT

This report provides a comprehensive accounting of DoD biomedical research and animal care and use programs. There are sections that include in-depth discussions of:

- a. Publicly accessible information on Department research (Section II),
- b. Policies and procedures for oversight of Department animal care and use programs (Section III),
- c. AAALAC accreditation for Department animal care and use programs (Section IV),
- d. DoD animal use profiles (Section V), and
- e. DoD initiatives to promote alternative methods that replace, reduce, or refine animal use (Section VI).

I.4.1 Publicly Accessible Information on Animal Use in the DoD

On October 1, 1995, the Department of Defense implemented a publicly accessible database analogous to the National Institutes of Health Computer Retrieval Information of Scientific Projects System. The DoD Biomedical Research Database (BRD) is available online to the public, and is composed of succinct summaries of Department research projects, allowing interested individuals easy access to Department research information. The cost of animal-based research is presented by work unit summary in the BRD. In order to prevent duplication, this information is not presented in this report. More information on accessing the database is presented in Section II.

I.4.2 Oversight of DoD Animal Care and Use Programs

DoD animal use oversight is reviewed in Section III. In general, internal and external oversight provisions for animal research conducted by the DoD are at least as stringent as those for research in any other department of the federal government, and in many ways exceed the standards. As a matter of policy, the DoD abides by the applicable federal regulations pertaining to animal care and use, including provisions for oversight. All DoD facilities and extramural institutions sponsored by the DoD must submit proposals for animal use to an IACUC. The IACUCs review proposed animal protocols to ensure compliance with the Animal Welfare Act, and address concerns of the community. The DoD Directive 3216.1 (1995) establishes oversight requirements that exceed the provisions of the Animal Welfare Act. Each IACUC serves as an independent decision-making body for the institution and establishes policy for the care and use of animals at that facility in accordance with applicable DoD directives, federal law and regulations.

The DoD has developed and implemented a standardized protocol format for use by all of its units (Appendix C). It includes requirements for search of Federal Research in Progress database or an equivalent database to prevent duplication of ongoing federally funded research. The principal investigator must justify the use of animals, including consideration of alternatives, justify the choice of species and the number of subjects, and include a literature search and assurance that the work does not needlessly duplicate prior experimentation. The protocol must specify procedures to be used with animals, methods to avoid or minimize pain, include a literature search for possible alternatives, qualifications of the individuals conducting procedures with animals, and disposition of animals at the termination of the work.

The IACUC ensures that personnel involved in animal-based studies are properly trained and, if necessary, establishes a training program to support the staff. The IACUC inspects facilities and animal

care programs at least twice annually, and prepares a written report including a plan to address deficiencies. It enforces compliance with procedures specified in the protocols by conducting inspections, evaluating and, if necessary, investigating reports of deviation from approved procedures. The IACUC of each facility performs semiannual program reviews of all animal use areas. The DoD 1995 Policy Letter strengthens that process by establishing a standardized semiannual review checklist that outlines the areas required for IACUC review. This guidance is consistent with the recommendations of the DoD Inspector General (IG) report of February 1994 (Appendix G). A formal report of inspection shall be prepared twice annually, noting the use of the checklist, and indicating all major and minor deficiencies, a plan for correction of deficiencies, signatures of IACUC members conducting the inspection, and a statement indicating whether there are or are not minority opinions. Finally, the IACUC serves as an impartial investigator of reports of violations of good animal practices and is empowered to suspend the use of animals for protocols not conducted in accordance with the Animal Welfare Act or institutional policy.

The revised DoD Directive 3216.1 (1995) clarifies composition, membership, and training requirements of the IACUC. The changes address the House Armed Services Committee's request to improve community representation and to appoint animal advocates to the Department's IACUCs, consistent with a recommendation of the IG Report of February 1994. The revised Directive (1995) increases the minimum membership of all DoD IACUCs from three to five. In addition, it specifies that

"there shall be at least one non-scientific member on the IACUC. In addition, there shall be at least one member representing the general community interest who is nonaffiliated with the research facility. The nonaffiliated member and the non-scientific membership can be filled by the same person. To ensure community representation at each meeting and inspection, an alternate to the nonaffiliated member

shall be designated for all IACUCs having a single nonaffiliated membership."

Each DoD IACUC has increased its membership to comply with this Directive.

This Directive exceeds the requirements of the Animal Welfare Act and is further strengthened by the DoD 1995 Policy Letter which requires a minimum of 8 hours of training for new non-affiliated members. In support of this training, the DoD developed a program consisting of a set of topics and recommended resources that may be used by individual IACUCs.

Responsibility for oversight of the Department's science and technology programs rests with the Director, Defense Research and Engineering (DDR&E). Her staff, in conjunction with representatives from the Services, annually review the science and technology efforts to ensure they are fully coordinated and without unnecessary duplication of effort. The preponderance of animal use within the Department occurs in biomedical programs. These activities receive specific oversight from the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee, which was created by congressional direction in 1981. The ASBREM Committee is chaired by the DDR&E and co-chaired by the Assistant Secretary of Defense (Health Affairs). The overall biomedical effort is carefully integrated and reviewed to eliminate unjustified duplication of effort by seven subordinate Joint Technology Coordinating Groups reporting to the co-chairpersons.

I.4.3 Accreditation of DoD Laboratories by AAALAC

Animal use programs in the DoD strive to meet all the requirements of AAALAC. AAALAC accreditation is recognized as the "Gold Standard" for animal care and use programs. DoD Directive 3216.1 (1995) states that all DoD laboratories that maintain animals for use in research, testing or training shall apply for AAALAC accreditation. Currently there are 35 DoD animal facilities worldwide, of these 34 (97%) are accredited.

Over the past 4 years, the DoD has been resolute in pursuing AAALAC accreditation for all of the facilities that use animals in research. This diligence has resulted in a 35% increase in accreditation from 60% in 1993 to 97% today.

I.4.4 DoD Animal Use Profiles by Research Category

A profile of DoD animal use is provided in Section V. In this report, a detailed system was adopted for classifying animal use that includes 8 categories with 23 subcategories: 8 medical research, 4 non-medical research, 3 clinical research, 2 training, and 6 other categories of studies and use. Detailed charts and graphs are included in Section V.

In 1996, the DoD used 318,800 animals, which is a 26% decrease from FY95. Of these, 24,381 (8%) were USDA reportable species as defined in the Animal Welfare Act of 1985. Table I-2 summarizes the major animal use statistics for DoD research. In addition, it should be noted that no animals were used for development or testing of offensive weapons. During the time that the DoD has been reporting animal use to Congress (1993-1996), there has been a 42% decrease in the total number of animals used.

I.4.5 DoD Initiatives to Promote Alternative Methods that Replace, Reduce, and Refine the Use of Animals

Congress requested that the DoD establish aggressive programs to replace, reduce, and refine current use of animals. A review of DoD programs and initiatives to develop and implement alternatives to animal research is reviewed in Section VI. Alternatives are presented by those developed by DoD investigators and the general and specific alternatives implemented by the DoD in 1996.

Animal research is an essential part of the scientific process, but it is only initiated after due consideration of alternatives. The DoD uses a Standard Protocol Format that specifically requires each investigator to consider alternatives to the use of animals and to justify the animal model selected.

Table I-2 Summary of DoD Animal Use Statistics

Total Animal Use by Species	% of Total
Rodents, fish, amphibians and birds	95.47
Rabbits	1.15
Farm animals (i.e., sheep, pigs, cows, horses)	0.97
Dogs, cats, nonhuman primates, marine mammals	0.75
Other	1.66

Percentages may not add up to 100% due to rounding of calculations.

Total Animal Use by Category	% of Use
Medical RDT&E	74.8
Non-Medical RDT&E	12.8
Clinical Investigation	6.26
Adjuncts/Alternatives	3.5
Training & Instructional	2.1
Breeding Stock	< 1
Classified Secret or Above	< 1
Other	< 1
Offensive Weapons Development	0

Percentages may not add up to 100% due to rounding of calculations.

In addition, all protocols that involve unrelieved pain or discomfort require consultation with a veterinarian, and a specific database search for scientifically acceptable alternatives to the proposed method. Each protocol that involves animals in research or training must explain the need for the animal research and defend the choice of species as the most scientifically valid model. Often, economies of time and resources are gained when scientifically valid alternatives to animal use are available. Our review of current animal research reveals that scientists in the DoD have developed or adopted many alternative methods based on

ethical considerations and other inherent benefits. The U.S. Army Medical Research and Materiel Command has established a major objective to develop replacement, reduction, and refinement strategies for the use of animals in research. Table I-3 presents examples of alternatives developed by the Department in FY96 to replace, reduce and refine the use of animals. In addition, the Department sponsors conferences and workshops to promote alternatives to animal research. The DoD sponsors a 5-year grant with the Institute of Laboratory Animal Resources of the National Research Council to develop institutional training materials, education, and publications in support of DoD laboratory animal care and use programs. The IACUC process also includes a strong emphasis on consideration of alternatives in all new protocols.

In conclusion, it is the policy of the DoD that animal utilization will be conducted in full compliance with the Animal Welfare Act and that animals are used in research only when scientifically acceptable alternatives are not available. At the same time, the use of animals in research is essential to protect the health and lives of military personnel; therefore, the DoD will be engaged in biomedical research that involves the use of animals for the foreseeable future.

Table I-3 *Examples of DoD-Developed Alternatives for Replacement, Reduction, and Refinement of the Animals Used in Research*

- The DoD is developing environmental enrichment programs for nonhuman primates and ferrets.
- Artificial human skin is used to study inflammatory responses to heat and medical countermeasures against vesicant agents.
- Investigators have successfully adapted several of the mosquito colonies to membrane feeding.
- Research is being performed to discover/develop cell lines which could replace synaptosomes (and therefore animals) in the study of botulinum toxin.
- DoD investigators have developed an artificial eye with lenses that can mimic the focusing characteristics of the eye.
- The nervous system of the sea slug, *Aplysia californica*, has been developed as a model to study the effect of chemical and toxic agents on the electrical properties of nerve cells.

SECTION II

PUBLICLY ACCESSIBLE INFORMATION ON ANIMAL USE IN THE DoD

II.1 CONGRESSIONAL REQUEST INFORMATION

House Armed Services Committee Report 4301 (1995) requested the Secretary of Defense to "develop a mechanism for providing Congress and interested constituents with timely information... about [Department of Defense (DoD)] animal use programs, projects and activities, both intramural and extramural." In response to this request, and to serve the interest of both the scientific community and general public, the Department has implemented a publicly accessible database called the Department of Defense Biomedical Research Database (BRD). The BRD is a database containing succinct summaries of the Department's research projects involving the use of animals. This database is analogous to the National Institutes of Health (NIH) Computer Retrieval of Information of Scientific Projects (CRISP) System. The CRISP System is a biomedical database containing information on research projects supported by the United States Public Health Service, as well as information on intramural research programs of the NIH and the Food and Drug Administration. The BRD became accessible to the public through the Internet on October 1, 1995. It is located on the Manpower and Training Research Information Services (MATRIS) home page.

II.2 THE FY95 BIOMEDICAL RESEARCH DATABASE

The data in the FY95 BRD were developed from the current work unit summary system of the Defense Technical Information Center (DTIC). DoD organizations performing research, development, test and evaluation (RDT&E) projects are currently mandated to provide annual reports of research to the DTIC. The DTIC maintains these work unit summaries in a database. While the majority of DoD animal use occurs in RDT&E projects, some work is performed in clinical investigations programs that are not mandated to provide work

unit summaries to the DTIC. Therefore, the DoD directed that these non-RDT&E DoD animal research projects develop summaries to be entered into the BRD. The areas of research, testing and training in the FY95 BRD include, but are not limited to, the following: infectious diseases, biological hazards, toxicology, medical chemical defense, medical biological defense, clinical medicine, clinical surgery, physical protection, training, graduate medical education and instruction.

Military activities that house, care, or use animals provided a work unit summary for any animal-based research. The FY95 BRD contained 831 summaries and was made accessible to the public on October 1, 1996. A work unit summary may refer to a single protocol or a series of protocols that are performed in a given category of animal use. The summaries include the following information:

Title: Title of the work unit.

Funding Fiscal Year: The funding for the entire work for a given fiscal year. The funding includes civilian salaries, cost of animals, cost of materials, cost of human-based research, cost of non-animal based research, etc. - all costs related to the work unit except military salaries.

POC/Author: The primary contact (POC) for the work unit is usually the Public Affairs Office.

POC Address: The complete mailing address of the POC.

Performing Organization: The name of the activity where the work is performed.

Objective and Approach: This section is a narrative on the objectives and the approach of the work unit. This narrative provides a general summary of the work.

Indexing Terms (Descriptors): A list of indexing terms or keywords. The keywords

contain "animals" and the term for any animal types which may be used in the work unit (i.e., guinea pigs, rats).

These summaries were compiled into the BRD and organized into a presentation format for the Internet.

II.3 ACCESS AND USE OF THE BIOMEDICAL RESEARCH DATABASE

The BRD can be accessed at:

<http://dticam.dtic.mil/dodbr>

The BRD home page shown in Figure II-1 is a searchable database. To perform a search, enter a specific search topic in the search window and click on Do Search or press Enter. The results of the search will produce a hypertext list of titles (Figure

II-2). To access a particular summary, click on the specific title and the summary will appear (Figure II-3). In addition, a list of all the summaries can be accessed by selecting View all titles.

II.4 FY96 UPDATE OF THE BIOMEDICAL RESEARCH DATABASE

The DoD will make all FY96 work unit summaries of animal use in research, testing, education, and training available to the public this year. All military activities that house, care, and/or use animals have provided summary information on any animal research, testing, education, or training work for the FY96 BRD. The cost of FY96 animal-based research is presented by work unit summary in the BRD. In order to prevent duplication, this information is not presented in this report. These data will become available to the public on October 1, 1997.

Netscape: DoD Biomedical Research

Back Forward Home Reload Images Open Print Find Stop

Location:

What's New? What's Cool? Destinations Net Search People Software

DoD Biomedical Research

Please read this privacy and security notice.

Welcome to the DoD Biomedical Research Database. This database has been developed from biomedical research, testing or training programs being federally funded in FY95. The areas of research, testing and training include, but are not limited to, the following: infectious diseases, biological hazards, toxicology, medical chemical defense, medical biological defense, clinical medicine, clinical surgery, physical protection, training, graduate medical education and instruction. This information will be updated on an annual basis.

For further information related to any of the studies included in this database, please contact the point of contact listed with each reference.

(FAQ) Frequently Asked Questions.

NOTE: You must have a FORM-capable browser to do a search. If you have not used the VMSIndex Search before, please read the search hints.

● View all titles.

Search Topic:



MATRIS

For questions and comments:
email@dticam.dtic.mil
October 1996

1/10 ?

Figure II-1 DoD Biomedical Research Home Page

Netscape: Search all dodbr html files on MATRIS

Go To:

toxicology

There are **31** items found:

1. [Characterization of Metabolites of the Neurotoxicant Trimethylolpropane Phosphate \(TMPP\) \(NAV 223\)](#)
2. [Characterization of the Metabolism, Distribution, and Toxicity of 2,6 Di-t-Butyl-4-Nitrophenol for Purposes of Health Hazard and Risk Assessment for Exposed Submarine Personnel \(NAV 244\)](#)
3. [Describe the Exercise Decrement Associated with Exposure to Intermittent Levels of Oxides of Nitrogen](#)
4. [Determine Toxicological Effects of Aerosol Exposure to Botulinum Toxin](#)
5. [The Effect of Organ Procurement Conditions on Cytochrome P-450 Activities](#)
6. [Evaluation of New Methods to Prevent and Treat Dental Emergencies in Naval Personnel, Effect of Vitamin E Supplementation on Nicotine Associated Periodontal Bone Loss](#)
7. [Evaluation of Various Waste Streams Generated by the Chemical Decontamination of Chemical Agent Identification Sets](#)
8. [Explosives, Propellants, and Nitrates Toxicology](#)
9. [Health Effects of Imbedded Depleted Uranium](#)
10. [Hepatic Toxicity of Perfluorinated Carboxylic Acids and Polychlorotrifluoroethylene: A Nuclear Magnetic Resonance Investigation in ...](#)
11. [Hydrocarbon Remediation Issues](#)
12. [Improved Methods to Evaluate Performance Deficits Induced by Complex Mixtures \(NAV 243\)](#)
13. [In Vitro Approach to Predictive Toxicokinetics](#)
14. [An Interdisciplinary and Alternative Approach to Assess Carcinogenicity of Chlorobenzenes](#)
15. [Molecular Mechanisms of Toxicity](#)
16. [Non-Lethal Measures of Toxicity: Performance Decrements \(NAV 240\)](#)
17. [Perform Preclinical Pharmacodynamic/Pharmacodynamic Studies of New Drugs](#)
18. [Assessment of the Toxicity of SFE, A Fire Extinguishant and Potential Substitute for Ozone Depleting Substances in Environments of Potential Military Interest \(NAV 254,NAV 264\)](#)
19. [Preclinical Toxicology Studies of New Drugs](#)
20. [Predictive Mechanisms of Carcinogenesis of Air Force Chemicals](#)
21. [Screening of Air Force Chemicals](#)
22. [Species Differences in Skin Penetration](#)
23. [Behavioral Assessment of Neurotoxicities Associated with Dideoxynucleoside Administration](#)
24. [Toxicity Test Model R&D](#)
25. [Toxicokinetics of Sulfur Mustard and its DNA-Adducts in the Hairless Guinea Pig and Marmoset-DNA-Adducts as a Measure for Epithelial Damage](#)
26. [Toxicokinetic Modeling of Air Force Chemicals](#)
27. [Toxicological Evaluation of Classified Compound](#)
28. [Toxicology and Human Health Issues](#)
29. [Toxicology of Halon 1301 Replacement](#)
30. [Two-Generation Study in Mink Fed Diisopropyl Methylphosphonate](#)
31. [Blood Preservation by Freeze Drying](#)

Figure II-2 Search Results on Toxicology from the BRD

Netscape: D00BR - Preclinical Toxicology Studies of New Drugs

Back Forward Home Reload Images Open Print Find Stop

Location: <http://dticam.dtic.mil/dodbr/index/dodbr615.html>

What's New? What's Cool? Destinations Net Search People Software

Title: Preclinical Toxicology Studies of New Drugs

FY95 Funding: \$1,277,000

Primary Contact: Public Affairs Office
Organization: Army Medical Research and Materiel Command
Address:
City: Fort Detrick
State: MD
Zip: 21702

Performing Organization: Illinois University
Address:
City: Chicago
State: IL
Zip: 60612

Objective and Approach:

Preclinical toxicology studies designed to provide a comprehensive evaluation of the toxicity potential of selected candidate compounds. The results of the studies on each compound will provide toxicology data needed to file a notice of claimed exemption for an investigational new drug (IND) application for that compound with the U.S. Food and Drug Administration (FDA). This toxicology data is needed before a Phase I clinical trial can be conducted. Longer term and more specific animal toxicity studies are required before clinical trials can be expanded in length of treatment and in number of individuals treated.

Conventional toxicological procedures will be utilized and revised as required to meet U.S. FDA guidelines and regulations.

Indexing Terms:
RA I
toxicology
preclinical
antiparasitic drugs
dogs
rats
lab animals
RA IV
RAII
ID
advance development

Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to the use of animals in research and was reviewed and approved by the Institute's Animal Care and Use Committee.

20% of 2K

Figure II-3 Sample of Publicly Accessible Information

SECTION III

OVERSIGHT OF DoD ANIMAL CARE AND USE PROGRAMS

This section of the Department of Defense (DoD) Report to Congress provides a detailed overview of the formal mechanisms and strategies for providing adequate oversight to the Department's numerous animal care and use programs. For the purposes of this report, research is defined as those congressionally authorized science and technology (S&T)-based activities—Title II, Research, Development, Test and Evaluation—of the Military Departments, and for which funds are appropriated, within program elements 6.1 (Basic Research), 6.2 (Exploratory Development) and 6.3 (Advanced Development).

The mechanisms detailed here show a clear and long-standing commitment by the DoD to manage its biomedical research and clinical programs in a systematic, comprehensive, and effective manner. Individual programs are driven by specific mission requirements, and are subjected to a thorough, stratified review and analysis prior to commitment of funds. The DoD uses animals only when necessary to complete its mission, and in a way that is in full compliance with applicable laws, regulations, and guidelines.

III.1 DETERMINATION OF DoD NEEDS FOR ANIMAL RESEARCH

Determining research needs and research plans is a comprehensive process integrated into DoD's planning, programming and budgeting processes. Integral elements of these processes are the Department's Research and Development Descriptive Summaries submitted to Congress in justification of the annual budget request. These summaries provide the Office of the Secretary of Defense, the Office of Management and Budget, and the Congress with significant detail of every research project's past accomplishments, planned accomplishments, and future plans.

Each DoD research laboratory tailors its organization, staffing, and related infrastructure

within available resources to best meet its S&T mission and to support each Commander's accountability, responsibility, and authority. In October 1995, the Department implemented the use of a comprehensive DoD Standard Protocol Format as a basis to justify and document all proposed animal use (Appendix C). The Standard Protocol Format solicits specific information that ensures a complete and thorough Institutional Animal Care and Use Committee (IACUC) review for all animal use proposals. Although the specific procedural elements and processes of individual protocol review may differ in minor ways from facility to facility, the general submission, review, and approval processes are summarized here.

An investigator develops a research protocol in support of departmental S&T guidance and other supplementing instructions developed within the chain of command, both external and internal to the laboratory. Augmenting the formal S&T coordination and review process is a literature search to verify non-duplication of previous or ongoing research. Previously, this search was performed only on the Defense Technical Information Center (DTIC) database. DTIC maintains a database of ongoing and completed DoD research at the work unit level of detail. The Standard Protocol Format now requires that "a search of Federal Research in Progress (FEDRIP) and DTIC databases or their equivalent is required for DoD-funded research. An additional search of the scientific literature (MEDLINE, GRATEFUL MED, MEDLARS, AWIC, etc.) is highly recommended." Review and certification that this requirement has been met are integral elements of the review and approval process prior to initiation of a research project. If animal use is planned for the intended research, the principal investigator must prepare an animal protocol request for the local IACUC. In addition to the DTIC and FEDRIP search, the Standard Protocol Format requires detailed information regarding results and dates of other on-line database searches (e.g., AWIC, AGRICOLA, CAAT, MEDLINE) that deal with

alternatives to painful procedures. Additional pertinent knowledge and information on the proposed study are gained through review of the scientific literature and participation in scientific meetings, symposia, and workshops detailing other ongoing or completed research.

Since protocols require the utilization of Defense resources, individual protocols are reviewed for factors such as military relevance, necessity, scientific merit, and relative research priority. Such reviews are normally conducted within the laboratory's command-and-control structure and are routinely characterized by the features of peer review systems.

DoD IACUCs carefully review research proposals involving the care and use of animals for numerous factors, including but not limited to ensuring that (a) the study is based on sound scientific principles; (b) the number of animals used is the minimum required to achieve the purpose; (c) the phylogenetically lowest species of animal is selected as the appropriate model; (d) there is appropriate use of analgesics and anesthetics, or if required, there is adequate scientific justification if not used; (e) the research is not unnecessarily duplicative; (f) the personnel conducting the research are qualified by training and experience to conduct the research; and (g) the scientific question to be answered is of sufficient importance to warrant the use of animals. Additionally, detailed information regarding methodology, techniques, schedules, etc., is required, greatly facilitating a comprehensive and thorough review by IACUCs.

III.2 OVERSIGHT OF ANIMAL CARE AND USE PROGRAMS AND FACILITIES

There are three principal vehicles for oversight of animal care and use programs at DoD research facilities: Major DoD Activities and Service Command Staff, the local IACUC, and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

III.2.1 Military Departments

Each Military Department has a component or components responsible for oversight and review of its research facilities and animal care and use

programs. Periodic reviews, site visits, and inspections are conducted formally, and reports are prepared as required.

The Army's ultimate oversight responsibility is divided between two major commands: the U.S. Army Medical Command and the U.S. Army Materiel Command. In the U.S. Army Medical Command, programmatic guidance and site visits are performed by specialty trained laboratory animal medicine (LAM) veterinarians in the Headquarters, U.S. Army Medical Research and Materiel Command, and the U.S. Army Medical Department Center and School (Veterinary Programs Manager). In the U.S. Army Materiel Command, oversight is provided by a specialty trained LAM veterinarian assigned to the U.S. Army Chemical and Biological Defense Command. Ultimate responsibility for laboratory animal care and use programs in the Navy resides in the Office of the Surgeon General of the Navy. Oversight is accomplished by a specialty trained LAM veterinarian assigned to the Naval Medical Research and Development Command, who also serves the Health Services Education and Training Command (Clinical Investigations), and the Inspector General at the Naval Bureau of Medicine and Surgery. Air Force oversight responsibility rests with a specialty trained LAM veterinarian assigned to the HQ, Air Force Medical Operations Agency, Clinical Investigations and Biomedical Research Division, Office of the Air Force Surgeon General, and with the Office of the Director of Medical Inspection, Air Force Inspection Agency.

III.2.2 IACUCs

The backbone of the review procedures for all DoD animal-based research is the IACUC review of the research proposal or protocol. DoD Directive 3216.1 requires all DoD facilities using animals in research to comply with the Animal Welfare Act (AWA). The AWA requires the Chief Executive Officer to appoint an IACUC, qualified through the experience and expertise of its members, to assess the research facility's animal program, facilities, and procedures. The AWA requires that IACUCs have a minimum of three members: an appropriately qualified chairman; at least one member not affiliated with the institution in any way other than as a member of the Committee; and a veterinarian with training or experience in laboratory animal

medicine and science. Each DoD IACUC is currently chaired by an individual with credentials and experience appropriate to the post, typically a senior physician, scientist, or veterinarian. The DoD Directive 3216.1 (1995) (Appendix A) clarifies the composition, membership, and training requirements of the IACUC. This Directive (1995) increases the minimum size of all DoD IACUCs from three to five, which is in concert with the National Institutes of Health (NIH) Office for Protection from Research Risks (OPRR) model. In addition, it specifies that:

"...there shall be at least one non-scientific member on the IACUC. In addition, there shall be at least one member representing the general community interest who is nonaffiliated with the research facility. The nonaffiliated member and the non-scientific membership can be filled by the same person. To ensure community representation at each meeting and inspection, an alternate to the nonaffiliated member shall be designated for all IACUCs having a single nonaffiliated membership."

The diverse backgrounds/professions of the nonaffiliated and alternate nonaffiliated IACUC members are provided in Appendix H. Currently, 28% of the nonaffiliated members are private sector civilians, 48% are civilians employed by the federal government, and 24% are military. In accordance with the Directive, these members represent the community and are not affiliated with the research facility. Full compliance with the Directive 3216.1 has resulted in an increase in the overall number of DoD IACUC members.

This Directive exceeds the requirements of the AWA and is further strengthened by the DoD 1995 Policy Letter (Appendix B) that directs a minimum of 8 hours of training for the new nonaffiliated members. DoD IACUCs implemented these requirements on October 1, 1995. All DoD new non-affiliated IACUC members received at least 8 hours of training to fulfill the requirement.

Each IACUC has at least one Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine who serves as an animal advocate. The U.S. Army Veterinary

Corp's formal postgraduate training program in laboratory animal medicine provides didactic training in IACUC composition, function, and regulatory requirements. This training also prepares them to serve as animal advocates.

It is a proactive Department policy that nonaffiliated members are encouraged to perform unannounced site visits of animal care facilities in addition to full participation in all discussions and votes on all research proposals. At least 20 unannounced visits to Department animal facilities by nonaffiliated members of DoD IACUCs were reported in FY96.

The IACUC has statutory responsibility for reviewing the facility's animal care and use program and inspecting the animal facilities on a semiannual basis. Consequently, at least once every 6 months, each IACUC performs an in-depth review of the animal care and use program and inspects the animal facilities. To facilitate these inspections, the DoD has developed and implemented a standardized semiannual program review checklist that details the requirements of the review. Each DoD IACUC is currently using the new standardized checklist during their semiannual program reviews. The IACUC prepares written reports of its evaluations and submits them to the Institutional Official, usually the facility commander. Reports specifically address compliance with the AWA, and identify any departures from the Act to include an explanation for the departure. The report must distinguish between significant and minor deficiencies and provide a schedule for resolution of deficiencies.

All DoD IACUCs document their meetings and activities, including the results of inspections, complaints, actions, and training. They are empowered to review and investigate concerns involving the care and use of animals at the research facility resulting from complaints received from the public or in-house workers, or from reports of noncompliance received from laboratory personnel. To facilitate the reporting and resolution of complaints or concerns, facilities commonly place signs or notices in high-traffic areas and in animal study areas advising both the public and personnel who work with animals how to contact members of the IACUC, facility commanders, and/or the Inspector General (IG) whenever questions

concerning humane care and treatment of animals arise. DoD facilities have developed a wide variety of proactive and innovative mechanisms to both inform the public on how to contact responsible individuals as well as programs to ensure that those who work with animals are fully apprised of the requirement to provide humane and ethical care (Appendix I). Additionally, IACUCs make recommendations to the Institutional Official regarding any aspect of the research facility's animal program, facility, or personnel training; review and approve, require modification to, or withhold approval of new research protocols involving the use of animals; review and approve, require modification to, or withhold approval of proposed significant changes regarding the care and use of animals in ongoing research protocols; and suspend an activity involving animals when they determine that the activity is not being conducted in accordance with the approved protocol.

III.2.3 AAALAC

AAALAC is a nonprofit organization chartered to promote high quality standards of animal care, use, and welfare through the accreditation process. The AAALAC accreditation process provides scientists and administrators with an independent, rigorous assessment of the organization's animal care and use program. To increase accountability and tracking, a centralized DoD point of contact and database for AAALAC information have been established to enhance monitoring, reporting, and facilitation of the AAALAC accreditation process. An in-depth discussion of the AAALAC accreditation process and a profile of DoD's participation are provided in Section IV.

III.2.4 Training

The DoD provides extensive veterinary and animal care services for DoD facilities. Veterinarians with specialty training in LAM direct programs for animal care and use throughout the Department. They serve as a valuable resource to the research staff and the IACUC to ensure that all research methods and maintenance procedures are consistent with the latest principles of animal medicine, and current interpretations and implementing regulations of the AWA. The DoD sponsors formal post-doctoral training programs

for veterinarians in LAM, including a nationally recognized in-house 4-year residency program culminating in specialty board eligibility for certification in the American College of Laboratory Animal Medicine. Some DoD veterinarians attend various university post-graduate LAM training programs resulting in a masters degree or Ph.D. It is significant that approximately 25% of the current membership of American College of Laboratory Animal Medicine, the veterinary specialty most closely associated with animal welfare and laboratory animal care and use, received either all or part of their training in DoD-sponsored LAM training programs. In August 1995, the DoD began a formal post-graduate Masters of Public Health in Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences. This outstanding program provides the Department with a new source of LAM experts who will significantly enhance animal welfare in our research laboratories.

In addition to veterinarians, the DoD trains animal care specialists (Military Occupation Specialty 91T) to assist in the daily management, care, and treatment of laboratory animals. Over the last 29 years, the DoD has trained over 3,500 animal care specialists. In March 1996, the Division of Veterinary Medicine established the Walter Reed Army Institute of Research (WRAIR) DoD Laboratory Animal Workshop program. Many of the workshops focus on species-specific techniques and handling, while others provide general laboratory animal information required by federal law and other guidelines for the research mission. Successful completion of the workshops fulfill the training requirements for use of those animals in research protocols. The WRAIR DoD Laboratory Animal Workshop schedule is provided in Appendix J. Additionally, DoD research institutions send appropriate staff to a variety of seminars and workshops sponsored by the National Institutes of Health, other federal agencies, and private institutions dedicated to the proper care and use of research animals. The Annual Public Responsibility in Medicine and Research meeting is an outstanding example of this type of training.

The DoD provides detailed informational and instructional material to all members of the IACUC, including nonaffiliated members, to ensure

that each is fully cognizant of the numerous responsibilities of IACUC members under the provisions of the AWA. The DoD Directive 3216.1, "The Use of Animals in DoD Programs," requires new nonaffiliated IACUC members to receive an initial 8 hours of training and continued training for IACUC members, investigators and technicians. This requirement went into effect on October 1, 1995. Although training is an individual institute's responsibility, the DoD has developed a program consisting of a set of topics and recommended resources to support the training requirement (Appendix K). The topics are meant to be general and allow for tailoring of the training to meet the institute's specific needs. The recommended resources are readily available commercially. Formal training on animal care and use issues is provided to all appropriate personnel in Department research laboratories in accordance with the provisions of the AWA. Examples of training or materials currently provided to IACUC members are detailed in Appendix K. One of the examples listed in Appendix K is the Institute of Laboratory Animal Resources (ILAR) publication *Education and Training in the Care and Use of Laboratory Animals*. As one of the major sponsors for this publication, the DoD has established a formal relationship with the National Research Council (NRC), an extension of the National Academy of Sciences. The publication is used as a guide by the DoD and has been translated into five languages. Many countries use this publication as a standard for the care and use of laboratory animals.

III.2.5 Community Visits

Individuals or groups wishing to visit Department facilities need to comply with certain procedural guidelines. All DoD facilities are served by a public affairs office, either at the facility, post, or base. Visits by the public or the press are arranged and coordinated through the appropriate public affairs office. DoD facilities are visited by various special interest groups including community and civic groups; animal welfare or animal advocates, groups, or individuals; dignitaries, academia, and teachers; local, state, and national politicians; congressional members and staff; elementary to post-doctoral students, etc. Consequently, a greatly diversified range of

individuals are constantly visiting and observing the quality of Department facilities.

III.2.6 Office for Protection from Research Risk Oversight

A number of DoD research laboratories participate in the NIH grants process. Institutional compliance with The Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy) is a prerequisite for granting or continuation of NIH intramural and extramural funding. The formal vehicle for compliance with the PHS policy is an "Animal Welfare Assurance" negotiated between individual institutions and the OPRR. The principal references for the negotiation of an OPRR "assurance" are the Health Research Extension Act of 1985 (Public Law 99-158, November 20, 1985, "Animals in Research"), the Animal Welfare Act, and NRC's *Guide for the Care and Use of Laboratory Animals*. Consequently, OPRR provides additional oversight to those laboratories that have negotiated OPRR assurances.

III.2.7 Additional Oversight

Within the DoD, individuals may raise animal welfare concerns. This may be with the IACUC, facility commanders, the IG, or the attending veterinarian. Other means of compliance or concern may be voiced through "Waste, Fraud and Abuse Hotlines," or the formal chain of command. Procedures to enhance and facilitate these mechanisms have been implemented in DoD facilities.

The function of the IACUC and the role of an ombudsman is augmented by the Department's IG. An ombudsman is defined by Webster's dictionary as "a government official charged with investigating citizens' complaints against the government." The Humane Society of the United States, a witness at the April 7, 1992 hearing on The Use of Animals in Research by the Department of Defense before the House Armed Services Committee, offered the ombudsman program at the Massachusetts Institute of Technology as an example of a model program. This program consists of an ombudsman assigned to the university president's office to hear complaints regardless of the nature. These include, but are not

limited to, personnel complaints, sexual harassment, animal welfare, etc. The DoD assigns this responsibility to its IG and respective Inspectors General of the Military Departments. In addition, military bases and large organizations on military bases have their own Inspectors General who fulfill this function. Significantly, IG complaints can be made anonymously, with no requirement to identify oneself in the registering of a complaint. Also of note is the fact that IG investigations are conducted with complete autonomy, and are completely insulated and immune to pressure from the chain of command.

Oversight of extramural (contract) animal-based research is provided for in the revised DoD Directive 3216.1 (1995). It states that

- a. "all extramural research proposals using live animals shall be administratively reviewed by a DoD veterinarian trained or experienced in laboratory animal science and medicine before grant or contract award."
- b. "the most recent USDA inspection reports are provided or obtained for the facility under consideration for a research contract or grant using animals, and that during the term of the award, the most recent USDA inspection reports be reviewed on an annual basis."
- c. "a DoD veterinarian trained or experienced in laboratory animal science and medicine shall conduct an initial site visit to evaluate animal care and use programs at contract facilities conducting DoD-sponsored research using nonhuman primates, marine mammals, dogs, cats, or proposals deemed to warrant review. The initial site visit shall occur within 6 months of when the facility has taken delivery of the animals under DoD contract or grant award. Any facility receiving a DoD-funded grant or contract for animal-based research shall notify the DoD component sponsor and shall have a site inspection within 30 days of notification of loss of AAALAC accreditation for cause, or notification that the facility is under USDA investigation. Site inspections for cause shall evaluate and ensure the

adequacy of animal care and use in DoD-sponsored programs, and provide recommendations to the sponsoring DoD component about continued funding support of the research."

As directed by DoD Directive 3216.1, all nonhuman primate protocols receive an additional centralized review external to the research facility.

III.3 CHAIN OF COMMAND OVER ANIMAL CARE AND USE PROGRAMS

The chain of command is designed to resolve problems at the lowest possible level. It provides control and communication between various components of organizations. Each link in the chain of command is a level of responsibility and authority that extends from the President of the United States, as Commander in Chief, down to the lowest supervisory level. Different levels within the chain have different responsibilities and authority. Each level in the chain is responsible for a lower level and accountable to a higher one. Every individual in the military is part of the chain of command and is accountable to it.

III.4 AVOIDANCE OF UNINTENDED DUPLICATION OF RESEARCH

Both the DoD and the Congress have a long history of concern about the potential for unintended duplication of Defense research. Within the past decade, the Department has initiated significant improvements in its mechanisms for coordination, joint planning and review of its research programs.

In 1981, Congress expressed concerns about the potential for unnecessary duplication of biomedical research among the Military Departments (H.R. 96-1317). This resulted in the DoD proposing an Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee to coordinate biomedical research planning and the conduct of biomedical research among the Military Departments. Congress fully endorsed and built upon this proposal by establishing DoD Lead Agencies for major elements of the biomedical research programs for which there were either no,

or very few, service-unique requirements (H.R. 97-332). For example, the Army was designated the DoD Lead Agency for military infectious disease and combat maxillofacial research while the Navy was designated DoD Lead Agency for preventive and emergency dentistry research. The ASBREM Committee established Joint Technology Coordinating Groups (JTCGs), consisting of directors of biomedical research programs and representatives of biomedical research laboratories, to coordinate all DoD biomedical research planning and execution. The ASBREM Committee process has proven to be highly effective at eliminating unnecessary duplication of biomedical research.

The ASBREM Committee process became the model for joint DoD coordination initiatives. Responsibility for joint coordination, planning, execution and review of the Department's S&T programs was assigned to joint oversight bodies: the Joint Directors of Laboratories (JDL), the ASBREM Committee, the Training and Personnel Systems Science and Technology Evaluation and Management (TAPSTEM) Committee, and the Joint Engineers. The resulting technology area responsibilities are shown in Figure III-1. Joint S&T oversight bodies are assisted in execution of their responsibilities by subordinate S&T coordinating groups that are focused on coordination of specific technology areas. For example, the ASBREM Committee is supported by the JTCGs (Figure III-2) and the JDL is supported by separate technology panels.

In addition to these formal coordination and review processes to eliminate unintended duplication of research, there are a number of less formal mechanisms that provide significant disincentives for research duplication. Competition, both in-house and extramural, for research support is a prominent feature of S&T; each year large numbers of scientifically meritorious research proposals cannot be funded due to shrinking resources and funding shortages. In most cases the professional stature of individual scientists or engineers among their peers is measured in proportion to their individual and original contributions to the scientific literature. There is little if any reward for unnecessarily duplicating the work of others; such actions often have significant negative impacts on how the scientist or engineer is viewed by peers and on the ability to

secure research support. Additionally, within the DoD civilian personnel system, scientists' and engineers' pay grades are determined in part by the level of individual scientific and technological contributions. One outcome of research is publication of a manuscript in a professional journal. A sample listing of journals with DoD animal research publications are at Appendix L. Peer-reviewed journals critique the research during the review process leading to an overall enhancement of the research process as well as validating the scientific merit and necessity of the research. These less formal, relatively unquantifiable, disincentives substantially augment and buttress the Department's formal mechanisms for regulating and avoiding unnecessary research duplication within its S&T programs.

III.5 AVOIDANCE OF UNNECESSARY RESEARCH

The same factors that effectively prevent unwarranted duplication of research are also applied to prevent unnecessary research. Additionally, through Cooperative Research and Development Agreements, the Department has increased its emphasis on leveraging and exploiting for Defense needs S&T investments from other federal agencies, U.S. industry, and academic institutions, as well as from the international scientific community. Past descriptions of Defense S&T "spin-off" have been supplanted by programs intended to "spin-on" accomplishments by others as well as to optimize the dual-use potential of the Defense S&T investment. The foundation of Defense S&T strategy is the application of S&T accomplishments to sustain Defense technological superiority through efficient and responsive modernization of our warfighting capabilities.

III.6 SUMMARY

Biomedical research using animals is highly structured and regulated in the United States, being governed by numerous laws, regulations, and policies. Consequently, the DoD has a number of stratified formal and informal mechanisms for reviewing, regulating, and executing its biomedical research mission and animal care and use programs. Research performed by the DoD is carefully reviewed by various offices, committees, and program managers before it is funded or

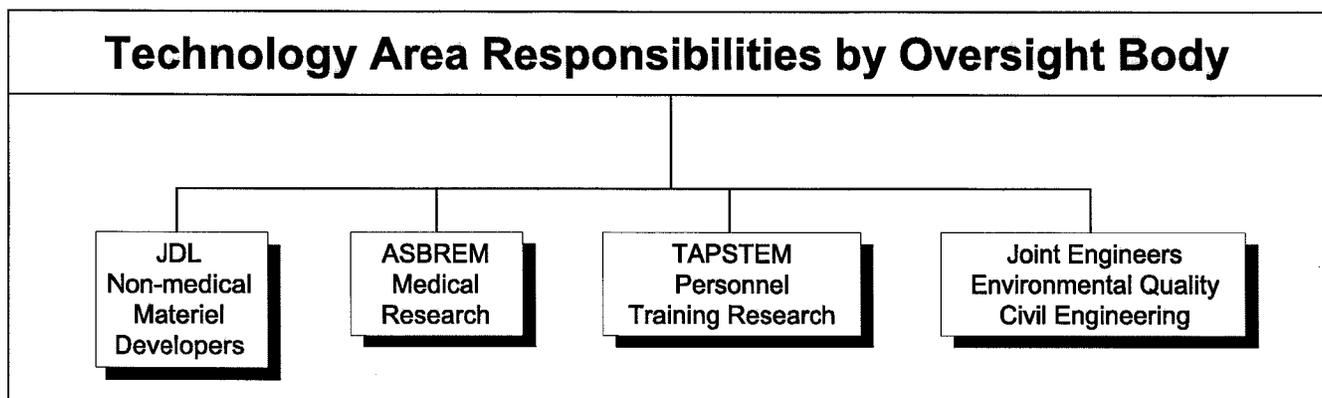


Figure III-1 DoD Technology Area Responsibilities

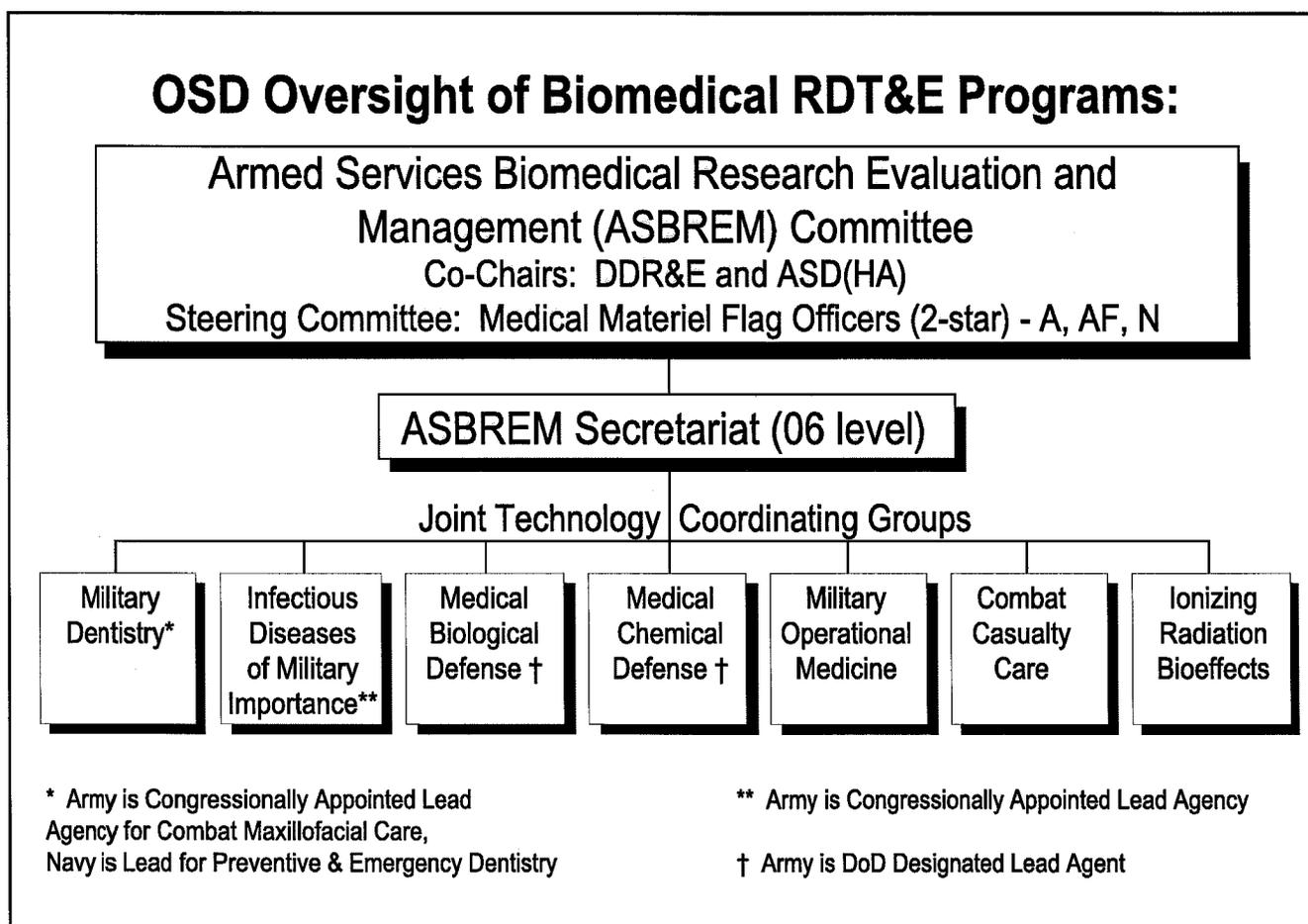


Figure III-2 Structure of ASBREM Committee

implemented. These reviews serve to determine the necessity to the mission, provide oversight of animal care and use, and avoid unnecessary or unintended duplication of research. Over the past decade, the DoD in concert with the Congress has streamlined and greatly improved coordination of its S&T activities to avoid unnecessary duplication and provide a focused program of research responsive to the DoD's unique and wide-ranging needs. Individual IACUCs provide oversight of animal care and use programs and research. Additionally, IACUCs provide training and

information about animal care and use, and ensure the humane use of animals in research. Each DoD facility's IG is an effective means for investigation of concerns about the necessity of animal use, as well as the ethical treatment and humane care of animals used in DoD research. When viewed in its totality, the Department's significant progress and investment in administration, infrastructure, standardization, training, and oversight of animal use are indeed impressive, and can serve as useful models for the rest of the biomedical research community.

SECTION IV

AAALAC ACCREDITATION OF DoD LABORATORIES

The Department of Defense (DoD) recognizes the benefits of accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). With the publication of the Joint Regulation on the Use of Animals in DoD programs, June 1, 1984 (AR 70-18), the DoD implemented more stringent animal care and use requirements than those required by statute. The Joint Regulation established uniform procedures, policies, and responsibilities for the use of animals in the DoD. The DoD has elevated the requirement with the current DoD Directive 3216.1 (1995), which states that "all DoD laboratories that maintain animals for use in research, testing or training shall apply for AAALAC accreditation." The Joint Service Regulation also cites the National Research Council (NRC) publication, *Guide for the Care and Use of Laboratory Animals*, which is the principal document used by AAALAC in its accreditation process. The animal care and husbandry standards and requirements contained in the Guide are designed to provide an environment that ensures proper care and humane treatment are given to all animals used in research, testing, and training. This care requires scientific and professional judgment based on knowledge of the husbandry needs of each species, as well as the special requirements of the research program.

IV.1 AAALAC ACCREDITATION

AAALAC accreditation is widely accepted by the scientific community, and viewed as an extremely desirable feature of the Department's animal care and use programs. The Association is highly respected as an independent organization that evaluates the quality of laboratory animal care and use. Accreditation covers all aspects of animal care to include institutional policies; laboratory animal husbandry; veterinary care; facility physical plant; support facilities; and special areas of breeding colony operations and animal research

involving hazardous agents such as radioactive substances, infectious agents, or toxic chemicals.

The independent and external peer review that is fundamental to continuing AAALAC accreditation is valuable to any program. AAALAC findings highlight program strengths and identify potential weaknesses. Laboratories maintaining accreditation demonstrate a high degree of accountability and program excellence. AAALAC standards stress the appropriate appointment, composition, and empowerment of an Institutional Animal Care and Use Committee (IACUC). This Committee is responsible for monitoring and evaluating all aspects of the institution's program that uses animals for teaching and/or research purposes. IACUC functions are addressed in Section III of this report.

IV.2 DoD PROGRAM REVIEWS

The DoD utilizes external peer review for the evaluation of many of its programs, such as drug screening laboratories, and review of military medical facilities by the Joint Commission for Accreditation of Health Organizations. At the same time, the DoD recognizes the diversity of mission operations and global reach of the military mission. There are situations where external peer reviews are not cost effective due to the remote locale, limited scope of operations, or host nation sovereignty. In these cases, equivalency standards can apply and be effectively monitored. The Joint Service Regulation and Service-conducted inspections of facilities implement the requirements of the Animal Welfare Act and the 1996 NRC *Guide for the Care and Use of Laboratory Animals*.

The DoD is committed to continuing its full participation in the AAALAC accreditation process as the external peer review evaluation method for assessing program compliance with regulations, guidance, and ethical responsibility.

IV.3 DoD AAALAC ACCREDITED PROGRAMS

The number of DoD AAALAC accredited programs that maintain animals for research testing and training has significantly increased over the past 4 years (Figure IV-1). There are 35 DoD animal facilities worldwide that use animals; of these, 34 (97%) are AAALAC accredited. This increase reflects DoD's commitment to accrediting all of its animal care and use programs.

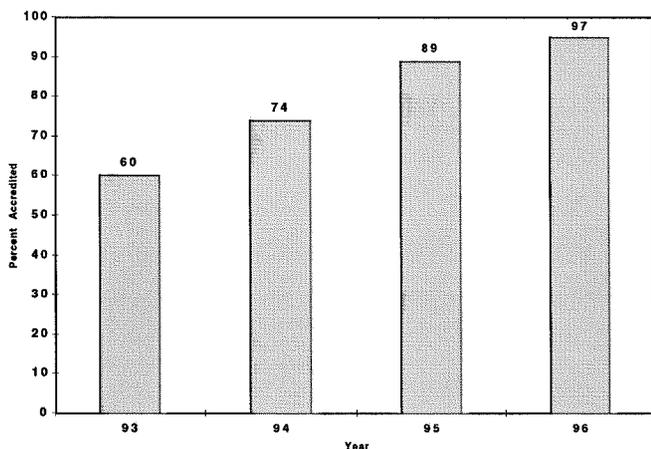


Figure IV-1 DoD AAALAC Accreditation At Time Of Publication of the 93-96 Reports

IV.4 AAALAC ACCREDITATION STATUS FOR U.S. DoD PROGRAMS

There are 31 programs in the United States that maintain animals for research, testing, or training

for the DoD. All of these programs in the U.S., 100% are accredited by AAALAC. In addition, there are four DoD animal use programs that share DoD AAALAC accredited facilities. These programs are small detachments that are assigned to DoD bases and therefore share their animal care and use facilities. Appendix M provides additional information on AAALAC accreditation by program.

IV.5 AAALAC ACCREDITATION STATUS FOR DoD OVERSEAS PROGRAMS

There are four DoD programs using animals outside the United States. In foreign countries, the accreditation process is often complicated by issues of sovereignty; local governments have their own regulations and policies that must be considered. Renegotiation of various agreements may be involved in construction or renovation projects. Despite these and various other impediments, the DoD has raised the standard of excellence in its animal care and use programs by receiving full accreditation in three of its four overseas laboratories. The Naval Medical Research Detachment in Lima, Peru, is the first laboratory in South America, to receive AAALAC accreditation. The Naval Medical Research Unit #2 in Jakarta, Indonesia, is the first DoD laboratory in Southeast Asia to be accredited, and the Naval Medical Research Unit #3 in Cairo, Egypt, is the first laboratory in Africa to be accredited.

SECTION V

DoD ANIMAL USE PROFILES

The information presented in this section provides profiles on the use of animals in various research categories, and the U.S. Department of Agriculture (USDA) pain categories of Department of Defense (DoD) animal-based research, testing and training programs for fiscal year (FY) 1996.

V.1 METHODS

Information was solicited and received from DoD agencies and military commands, organizations, and activities involved in animal care and use programs located both inside and outside of the United States. This included extramural contractors and grantees that performed animal-based research. For the purpose of this reporting requirement, an intramural program represents research performed at a DoD facility and funded by either DoD or non-DoD funds. An extramural program represents research performed by a contractor or grantee that is funded by the DoD.

V.1.1 Animal Use Profiles

The animal use profiles prepared for this report are consistent with the reporting information and data provided to the USDA using Animal and Plant Health Inspection Service (APHIS) Form 7023. In addition, this report contains comprehensive information on all other animals (e.g., mice, rats, birds) used that are not required in reports to the USDA.

For the purposes of this reporting requirement, an animal was defined as any whole nonhuman vertebrate, living or dead, excluding embryos, that was used for research, development, test, and evaluation (RDT&E), clinical investigations, diagnostic procedures, and/or instructional programs. Only live animals or whole dead animals, as defined, that were either on hand in the facility or acquired during FY96 are included. Animal organs, tissues, cells, blood, fluid components, and/or by-products purchased or acquired as such animal/biological components are

not reported. This definition does not include animals used or intended for use as food for consumption by humans or animals, animals used for ceremonial purposes, or military working animals and their training programs.

A single animal was counted only once in determining the number of animals used during the fiscal year for a particular work unit or protocol. This does not refer to the number of times an individual animal is injected, manipulated, handled, or administered medication and/or experimental compounds within a given work unit, protocol, or program. Animals on hand during FY96, but not actually used during the fiscal year, are not included in this number.

V.1.2 Animal Use Categories

All DoD agencies and military commands, organizations, and activities involved in the performance and/or funding of animal care and use programs reported animal work by the category that best describes the general purpose of the animal use. If these categories did not describe the animal use within a particular work effort, the animal was placed under the Other category. The 8 general categories and 23 specific subcategories are listed in Table V-1. In-depth information on specific activities performed within a subcategory is presented in Appendix N. The medical research categories correspond to the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee's Joint Technology Coordinating Group Medical Research Areas. Non-medical categories consist of RDT&E programs performed outside the ASBREM Committee medical oversight. Clinical Investigations studies were performed under the auspices of the Assistant Secretary of Defense for Health Affairs and the military services medical departments through Major Force Program 8 funding. These studies were usually in support of graduate medical education training programs located at the major military medical centers.

Table V-1 Animal Use Categories

MEDICAL (M)
M1: Military Dentistry
M2: Infectious Diseases
M3: Medical Chemical Defense
M4: Medical Biological Defense
M5: Human Systems Technology
M6: Combat Casualty Care
M7: Ionizing Radiation
M8: Other Medical RDT&E
NON-MEDICAL (N)
N1: Physical Protection
N2: Physical Detection
N3: Offensive Weapons Testing
N4: Other Non-Medical RDT&E
CLINICAL INVESTIGATIONS (C)
C1: Clinical Medicine
C2: Clinical Surgery
C3: Other Clinical Investigations
TRAINING/INSTRUCTIONAL (T)
T1: Training, Education, and/or Instruction for Personnel
T2: Other Training/Instruction
ADJUNCTS/ALTERNATIVES TO ANIMAL STUDIES (A)
A1: Adjuncts to Animal Use Research
A2: Alternatives to Animal Investigation
A3: Other Alternatives/Adjuncts
CLASSIFIED SECRET OR ABOVE STUDIES (S): Classified secret or above studies on animals
ANIMAL BREEDING STOCK (B): Animals maintained for breeding
OTHER ANIMAL USE CATEGORIES (O): Other animal use purposes

are those that are usually conducted on humans without anesthesia or analgesia. Examples include most blood-sampling techniques (excluding intracardiac and periorbital blood sampling), injections and tattooing.

The animals reported in Column D of the USDA report are those that experience pain in which appropriate anesthetics, analgesic or tranquilizing drugs were used. Examples include anesthesia for surgical procedures or catheter placement, and analgesia during recovery from surgery.

The animals reported in Column E of the USDA report are those that experience more than slight or momentary pain or distress that cannot be alleviated by drugs. Examples of procedures where drugs were not used because they would have adversely affected the procedures, results or interpretation of the research, or tests include some infectious disease studies and some toxicology studies.

All procedures that involve animals in Columns D or E are extensively reviewed during the protocol approval process. A veterinarian with experience and/or training in laboratory animal medicine must review all procedures that could cause pain and distress in animals. In addition, the primary investigator must write a justification for all

V.1.3 USDA Pain Categories

The USDA requires that all institutions using any regulated animal for research, testing, training, or experimentation register with the USDA as a research facility and submit an annual report. This annual report presents the number of regulated animals used and the type of pain, if any, the animals were exposed to.

The USDA has developed three pain categories for its reporting requirement (Table V-2). All animals herein reported are assigned to one of the three USDA pain categories; this includes animals that are not regulated by the USDA. The USDA requires that any reporting facility that uses procedures producing unalleviated pain or distress file an explanation of the procedures with its annual APHIS report.

The animals reported in Column C of the USDA report are those used in procedures that are not painful. Procedures performed on these animals

Table V-2 USDA Pain Categories
(USDA APHIS Form 7023)

USDA COLUMN C Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.
USDA COLUMN D Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.
USDA COLUMN E Number of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.

procedures for animals in Columns D and E. The DoD standard protocol states, "Procedures causing more than transient or slight pain that are unalleviated, must be justified on a scientific basis in writing by the primary investigator. The pain must continue for only the necessary period of time dictated by the experiment, and then be alleviated, or the animal humanely euthanized." Moreover, the primary investigator must sign an assurance statement that alternative procedures are not available, and the Institutional Animal Care and Use Committee must review and approve all procedures before the study begins.

V.2 RESULTS/DISCUSSION

V.2.1 General Results

There was a total of 318,800 animals used in FY96 which is a 26% decrease from FY95 and a 42% decrease from FY93 (Figure V-1). The Animal Welfare Act of 1985 defines animals as "any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, rabbit, or such other warmblooded animal, as the Secretary may determine..." Therefore, only 8% (24,381) of the animals used by the DoD in FY96 are considered USDA reportable species.

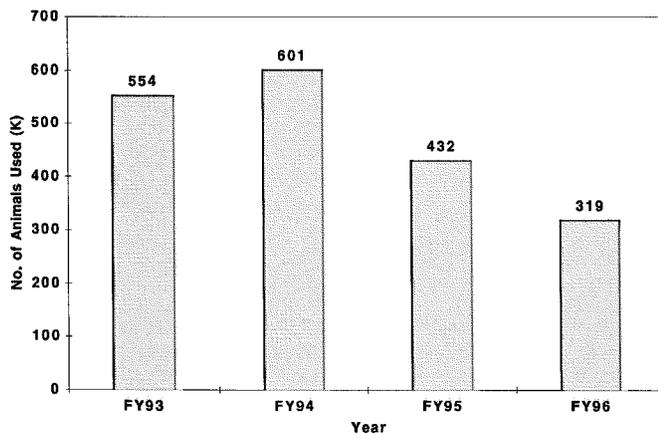


Figure V-1 DoD Animal Use by Year

In FY96, 180,155 animals were used in intramural research programs and 138,645 were used in extramural grants or contracts (Figure V-2). There was a 21% and 32% decrease in FY96 intramural and extramural animal use, respectively. The decreased use of animals by extramural programs (64,709) accounts for 57% of the total FY96 decrease. By their very nature, extramural research

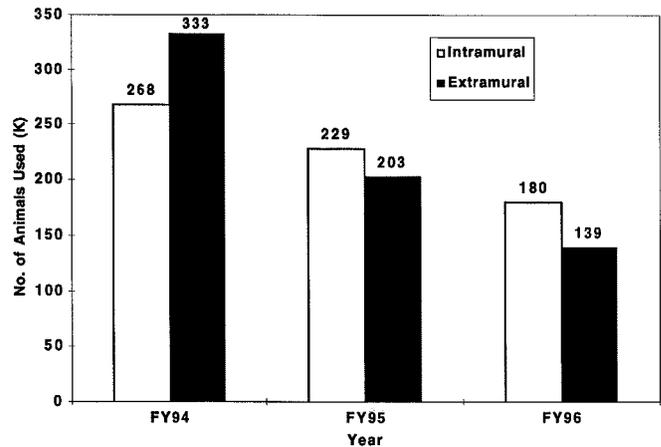


Figure V-2 Intramural/Extramural Animal Use by Year

programs have the greatest fluctuation in the number of animals used from year to year. Each year a different number of contracts are granted to perform extramural research. Many of these do not use animals at all; others only use animals during a portion of the proposed project (e.g., third year of project); and others use animals throughout the entire project. In addition, the level of funding for extramural programs varies from year to year thereby changing the total number of extramural projects. Some extramural research programs are congressionally mandated such as the Breast Cancer Research Program in which funding is dependent on yearly congressional appropriations. Therefore, changes in the number of animals used by the DoD extramural research programs can fluctuate significantly from year to year. The intramural programs have less variation in their use of animals because they have a continuous mission and ongoing research in specific areas. Consequently, any decrease in the number of animals used is most likely a result of the use of alternatives to animal use, a decrease in the number of research projects, or a decrease in intramural funding.

V.2.2 Animal Use by Service

Information concerning total DoD use of animals by each service is presented in Figure V-3. Figures V-4 and V-5 show the intramural and extramural animal use by service, respectively.

In FY96, the Army used 73% of the DoD total animal use, 59% of the intramural animals and 90% of extramural animals. The Army had a 28% decrease (88,582) in the number of animals used in

TOTAL = 318,800

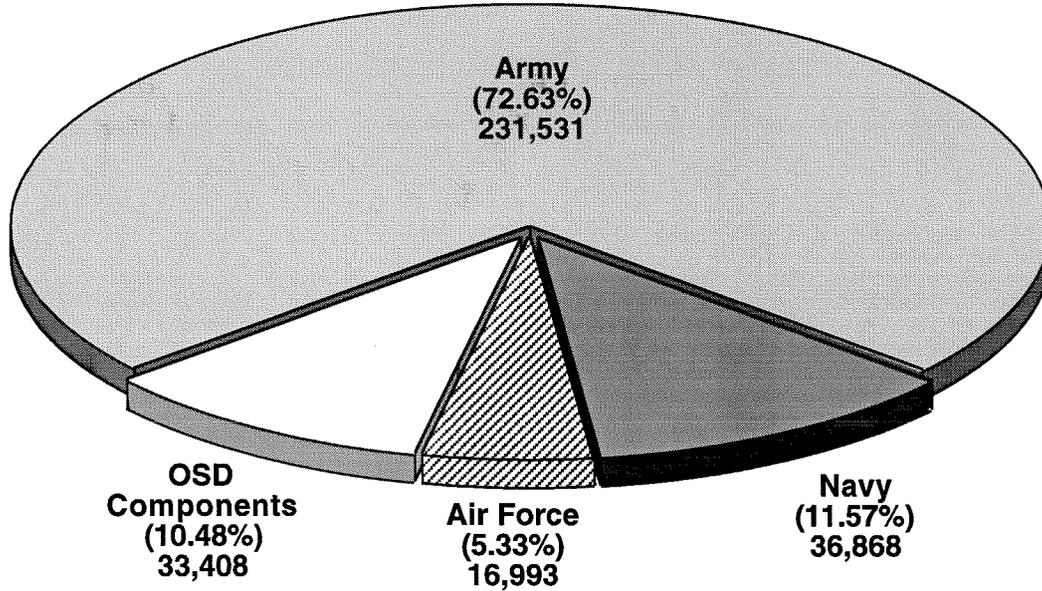


Figure V-3 DoD Intramural and Extramural Animal Use by Service for FY96

TOTAL = 180,155

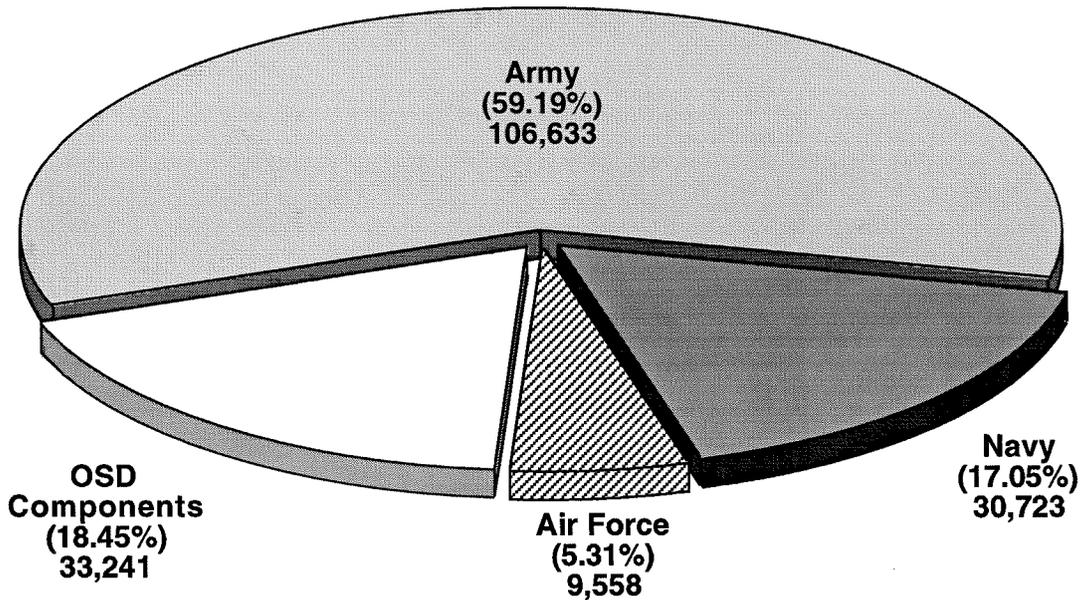


Figure V-4 DoD Intramural Animal Use by Service for FY96

Percentages may not add up to 100% due to rounding of calculations

TOTAL = 138,645

Percentages
may not add
up to 100%
due to
rounding of
calculations

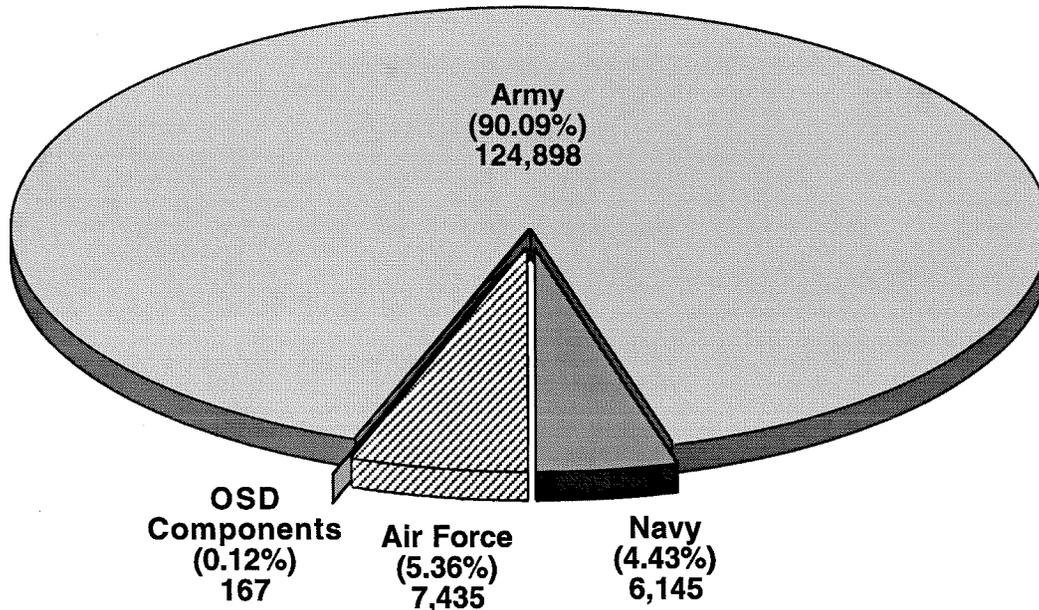


Figure V-5 DoD Extramural Animal Use by Service for FY96

FY96. The majority of this decrease was in extramural animal use (62,169). The U.S. Army Medical Research and Materiel Command is the congressionally mandated Lead Agency for infectious disease and combat dentistry research and the DoD Executive Agent for medical chemical and medical biological defense and nutrition studies. In addition, the Army has an ongoing responsibility to manage the congressionally mandated Breast, Prostate, and Ovarian Cancer Research Programs.

The Navy used 12% of the DoD total animal use, 17% of the intramural animals and 4% of extramural animals. In FY96, the Navy decreased the number of animals used in research by 27% (13,599). Most of this decrease (11,419) was in the Navy's intramural research projects.

The Air Force used 5% of the DoD total animal use and 5% of the intramural and extramural animals respectively. The Air Force had a slight increase in extramural animal use (651). There was a significant decrease in intramural animal use (1,235) resulting in an overall decrease in the number of animals used in research by 584 animals (3%) in FY96.

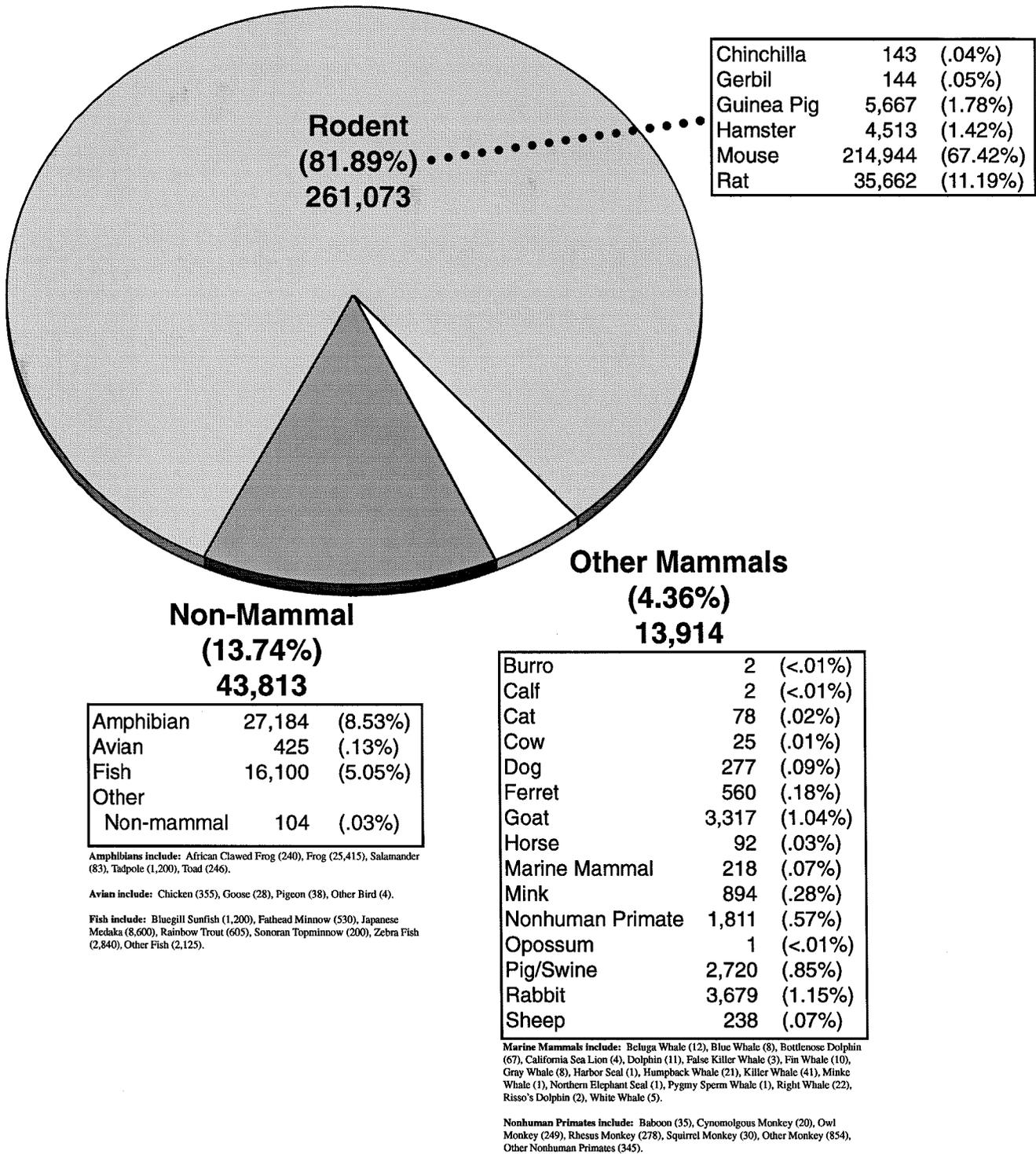
The Office of the Secretary of Defense (OSD) components are the Uniformed Services University of the Health Sciences, Defense Advanced Research Projects Agency, Armed Forces Radiobiology Research Institute, and Armed Forces Institute of Pathology. OSD components used 10% of the DoD total animal use, 18% of the total intramural animals and less than 1% of total extramural animals. There was a 24% decrease (10,314) in the use of animals for the OSD components in FY96. Ninety percent of this decrease (9,303) was in OSD components intramural programs.

V.2.3 Animal Use by Species

DoD animal use by species is presented in Figure V-6. Figures V-7 and V-8 represent the intramural and extramural animal use by species for FY96. The majority (96%) of animals used by the DoD, both intramurally and extramurally, were rodents, birds, amphibians, reptiles and fish.

The numbers of nonhuman primates, dogs and cats continued to decrease in FY96 (Figure V-9). In FY96 there was a decrease in the use of nonhuman primates (247), dogs (263) and cats (33).

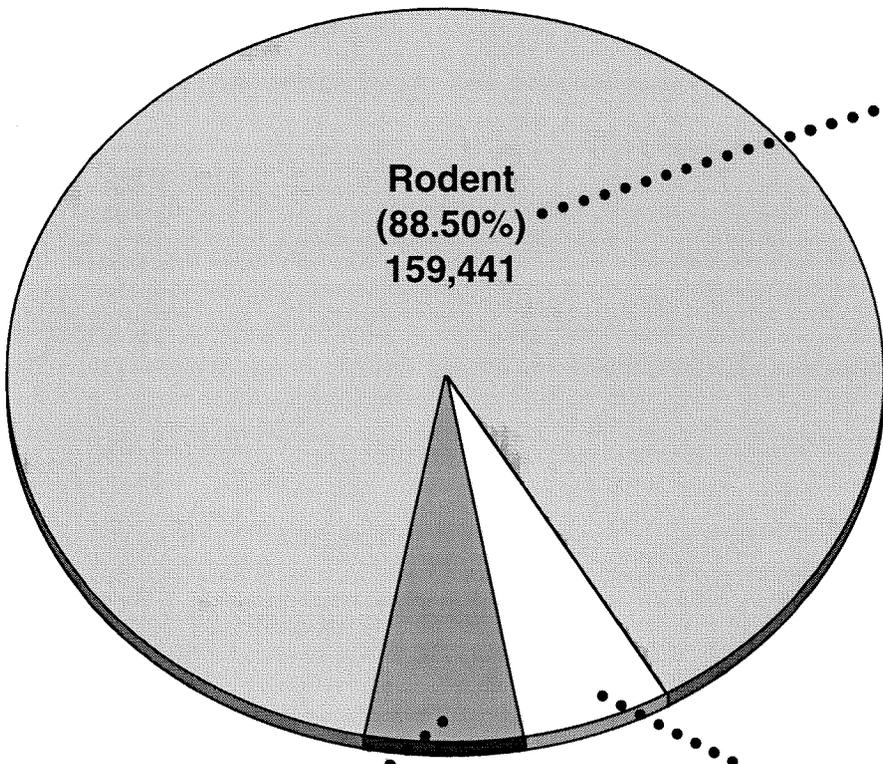
TOTAL = 318,800



Percentages may not add up to 100% due to rounding of calculations

Figure V-6 DoD Intramural and Extramural Animal Use by Species for FY96

TOTAL = 180,155



Chinchilla	143	(.08%)
Gerbil	130	(.07%)
Guinea Pig	4,210	(2.34%)
Hamster	3,033	(1.68%)
Mouse	127,122	(70.56%)
Rat	24,803	(13.77%)

**Non-Mammal
(6.07%)
10,941**

Amphibian	1,616	(.9%)
Avian	115	(.06%)
Fish	9,175	(5.09%)
Other		
Non-mammal	35	(.02%)

Amphibians include: African Clawed Frog (90), Frog (187), Salamander (83), Tadpole (1,200), Toad (56).

Avian include: Chicken (45), Goose (28), Pigeon (38), Other Bird (4).

Fish include: Bluegill Sunfish (1,200), Japanese Medaka (6,600), Other fish (1,375).

**Other Mammals
(5.42%)
9,773**

Burro	2	(<.01%)
Calf	2	(<.01%)
Cat	55	(.03%)
Dog	252	(.14%)
Ferret	310	(.17%)
Goat	3,296	(1.83%)
Horse	70	(.04%)
Lamb	1	(<.01%)
Marine Mammal	67	(.04%)
Nonhuman Primate	1,122	(.62%)
Opossum	1	(<.01%)
Pig/Swine	2,120	(1.18%)
Rabbit	2,323	(1.29%)
Sheep	152	(.08%)

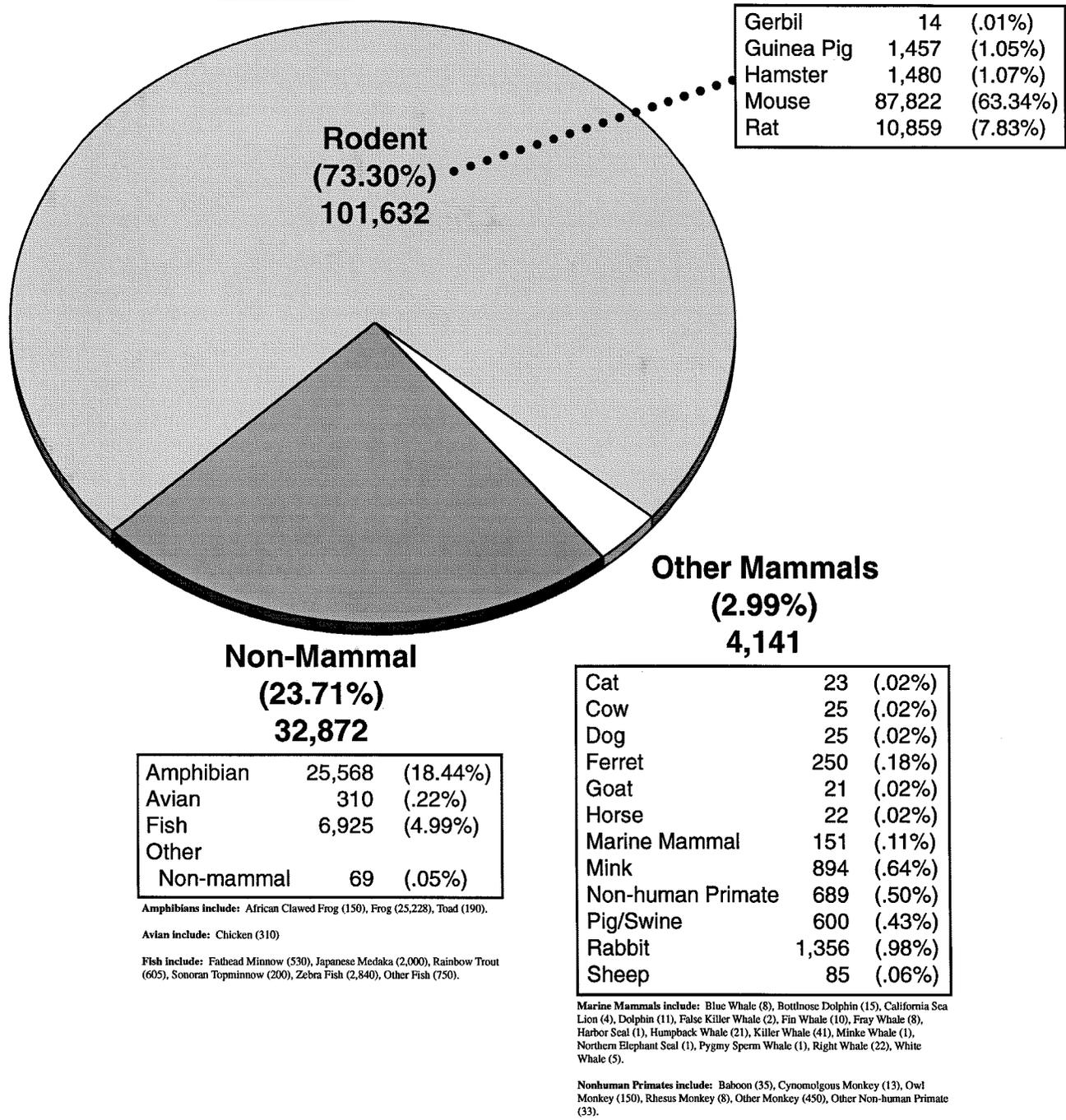
Marine Mammals include: Beluga Whale (12), Bottlenose Dolphin (52), False Killer Whale (1), Risso's Dolphin (2).

Nonhuman Primates include: Aotus Monkey (99), Cynomolgous Monkey (7), Rhesus Monkey (270), Squirrel Monkey (30), Other Monkey (404), Other Nonhuman Primates (312).

Percentages may not add up to 100% due to rounding of calculations

Figure V-7 DoD Intramural Animal Use by Species for FY96

TOTAL = 138,645



Percentages may not add up to 100% due to rounding of calculations

Figure V-8 DoD Extramural Animal Use by Species for FY96

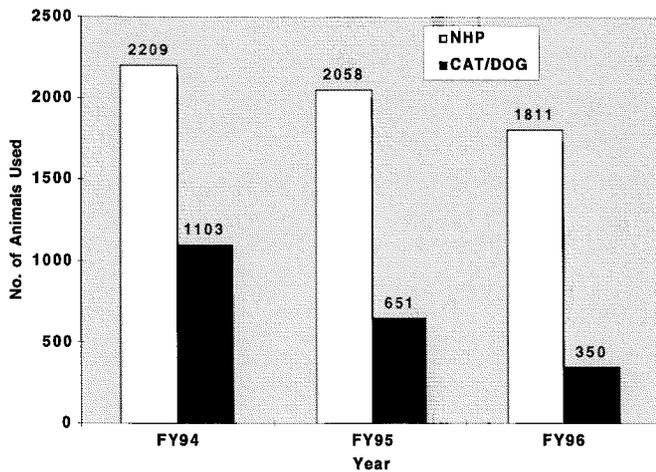


Figure V-9 Use of Nonhuman Primates, Dogs, and Cats by Year

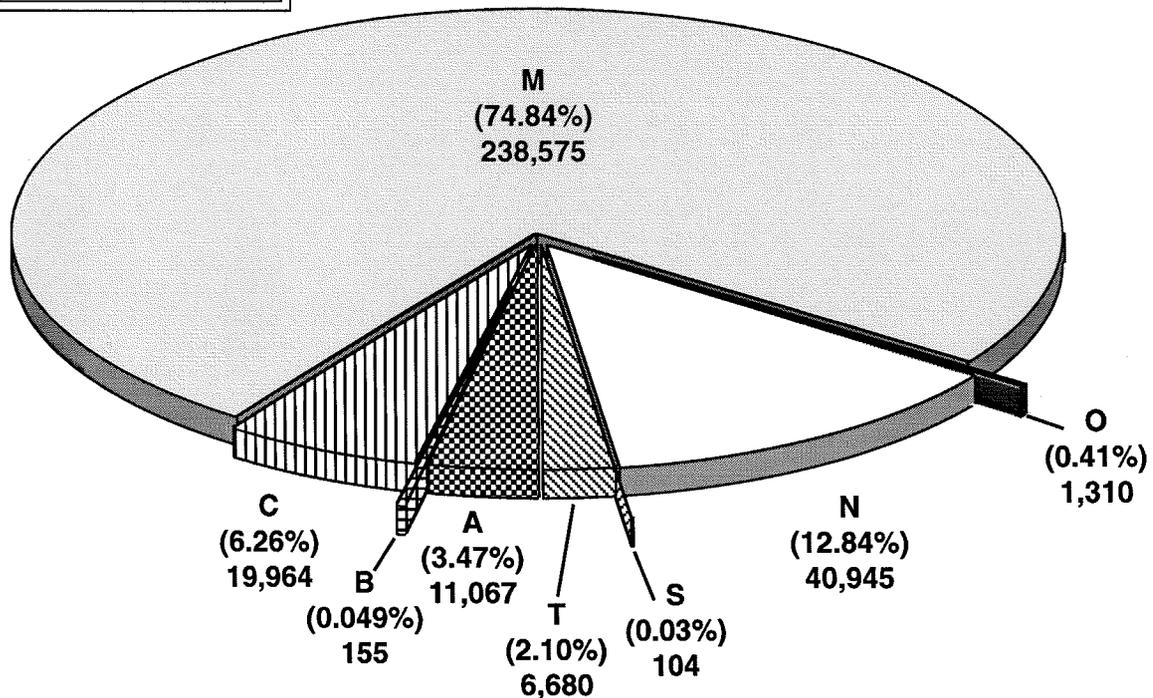
Since FY94, there has been a 18% decrease (398) in the use of nonhuman primates and a 68% decrease (753) in the use of companion animals for research in the Department of Defense. This illustrates the Department's continuing commitment to reducing the use of specific species in research.

V.2.4 Animal Use by Category

Total animal use in the DoD by category is presented in Figure V-10, with the intramural and extramural breakouts in Figures V-11 and V-12, respectively.

The DoD has a critical and challenging mission: to discover, design and develop military medical countermeasures against threats to the health and survivability of military personnel. In order to meet this mission, 75% of the animals used by the DoD

TOTAL = 318,800



A: Adjuncts/Alternatives to Animal Studies, B: Animal Breeding Stock, C: Clinical Investigations, M: Medical RDT&E, N: Non-Medical RDT&E, O: Other Animal Use, S: Classified Secret or above, T: Training & Instructional.

Percentages may not add up to 100% due to rounding of calculations

Figure V-10 DoD Intramural and Extramural Animal Use by Category for FY96

TOTAL = 180,155

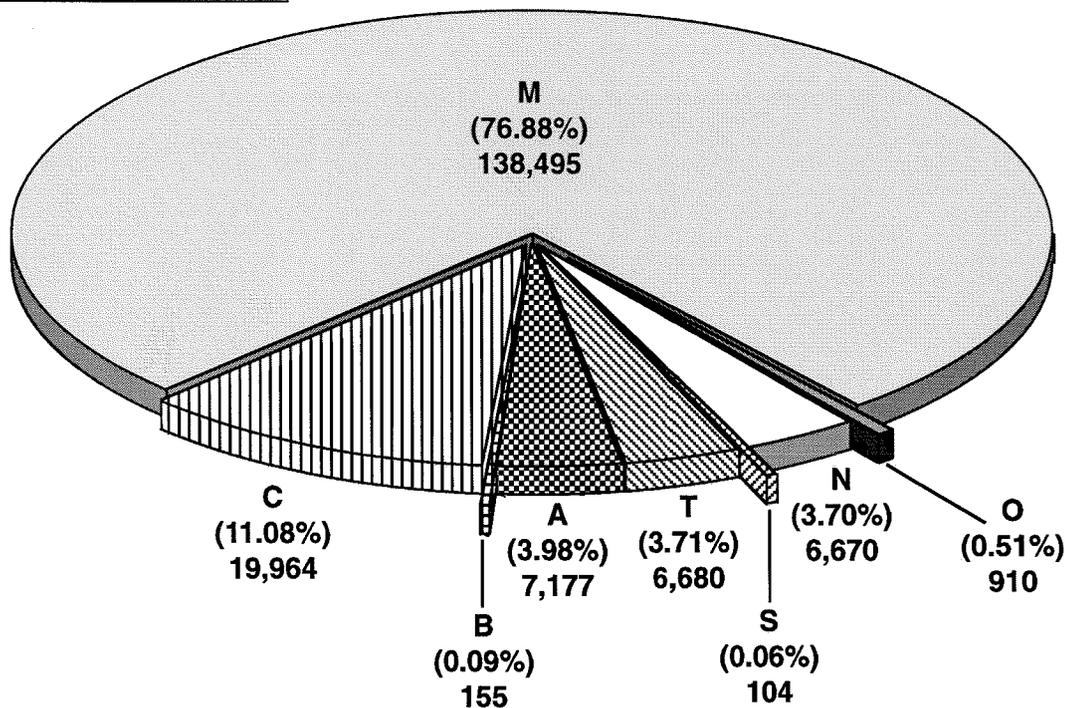


Figure V-11 DoD Intramural Animal Use by Category for FY96

TOTAL = 138,645

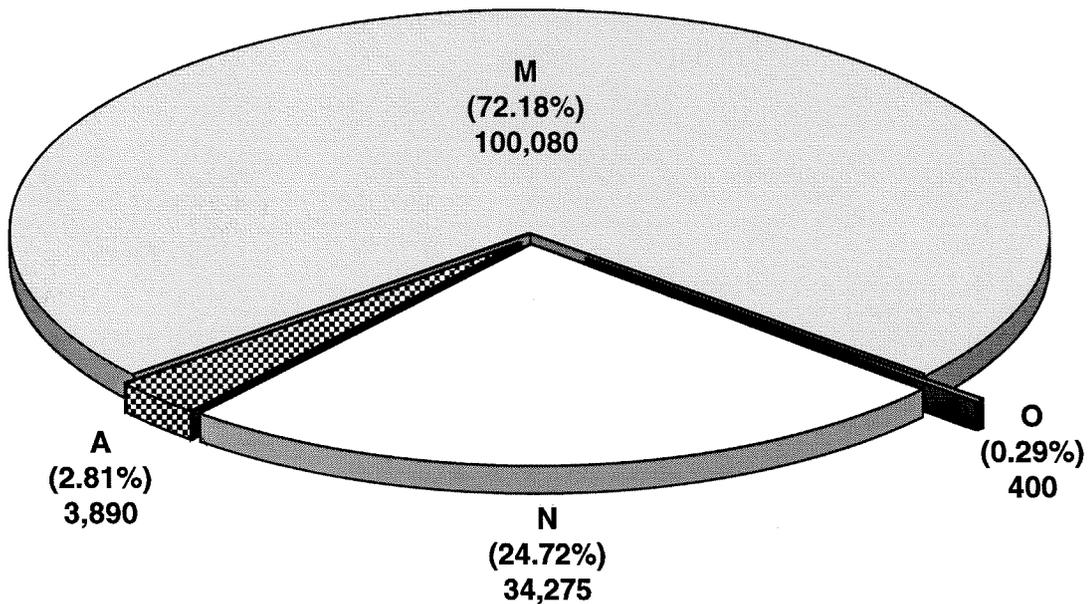


Figure V-12 DoD Extramural Animal Use by Category for FY96

A: Adjuncts/Alternatives to Animal Studies, B: Animal Breeding Stock, C: Clinical Investigations, M: Medical RDT&E, N: Non-Medical RDT&E, O: Other Animal Use, S: Classified Secret or above, T: Training & Instructional.

Percentages may not add up to 100% due to rounding of calculations

in FY96 were in medical research. Thirty-seven percent (87,527) of animals used in medical research were in the area of infectious diseases (M2) and were primarily rodents (99%) (Appendix O). The primary thrust of this research is the development of preventive measures against infectious disease through discovery, design, and development of prophylactic, therapeutic, and treatment drugs for relevant diseases. The biological defense research program (M4) used 30% (72,105) of the medical research animals. Medical biological defense develops, demonstrates and fields new vaccines, drugs and diagnostic kits for the prevention, treatment and diagnosis of biological warfare agents. This research program protects the armed forces from the consequences of exposure to biological warfare agents and enhances their survivability. M8 (Other Medical Research) accounted for 12% of the total medical research category (Figure V-13a). The congressionally directed Breast Cancer Research Program used 73.1% of M8 animals (20,803) (Figure V-13b), which accounts for 9% of the animals used in medical research and 7% of the total DoD animals use. This type of program can cause fluctuations in the total number of animals used from year to year depending on congressional funding levels and direction. Other areas of research within M8 are shown in Figure V-13b.

Clinical research accounted for 6% of the animals used by the DoD in FY96. Studies in this category address clinical medicine and surgical problems for the treatment of both diseases and combat casualties. Ninety-one percent of the animals used in clinical research were used in

clinical medicine studies. While many of these conditions are unique to the military, several are not. Specific types of clinical studies are listed in Appendix N.

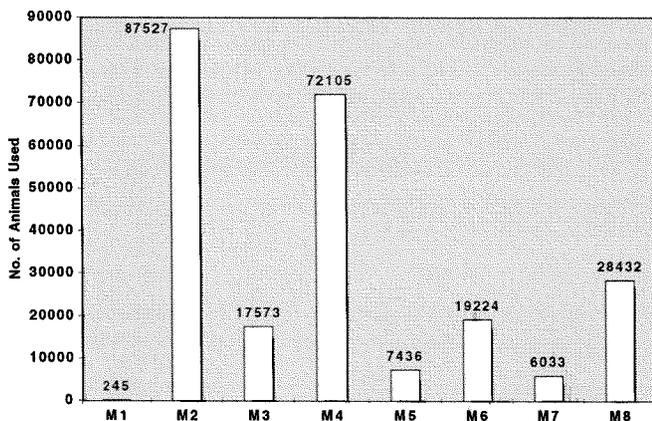
Two percent of the animals used were in the training, education and instruction of personnel. Training and instruction are basically for animal technicians and medical personnel (Appendix N). There was a 12% decrease (874) in animals used in this category in FY96. Breeding stock, classified studies and other studies accounted for less than 1% of the DoD's total animal use in FY96.

Non-medical RDT&E animal use accounted for only 13% of the total animal use in FY96. Research in the area of alternatives to the use of animals was 3% of the total animal use for FY96. Research in this category illustrates the Department's continuing initiatives to promote research to develop alternatives to reduce, replace and refine the use of animals in DoD research. No animals were used for offensive weapons testing during FY96.

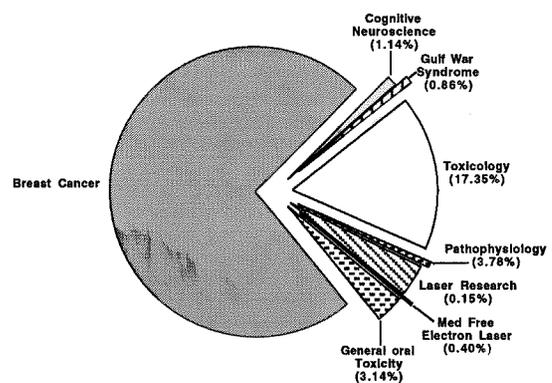
V.2.5 Animal Use by USDA Pain Category

Total animal use in the DoD by USDA pain category is presented in Figure V-14, with the intramural and extramural breakouts in Figures V-15 and V-16, respectively.

Most research (~82%) in the DoD was not painful to the animals involved. In the majority of



(a) Total Medical Research



(b) Other Medical Research

Figure V-13 Animal Use in Medical Research

TOTAL = 318,800

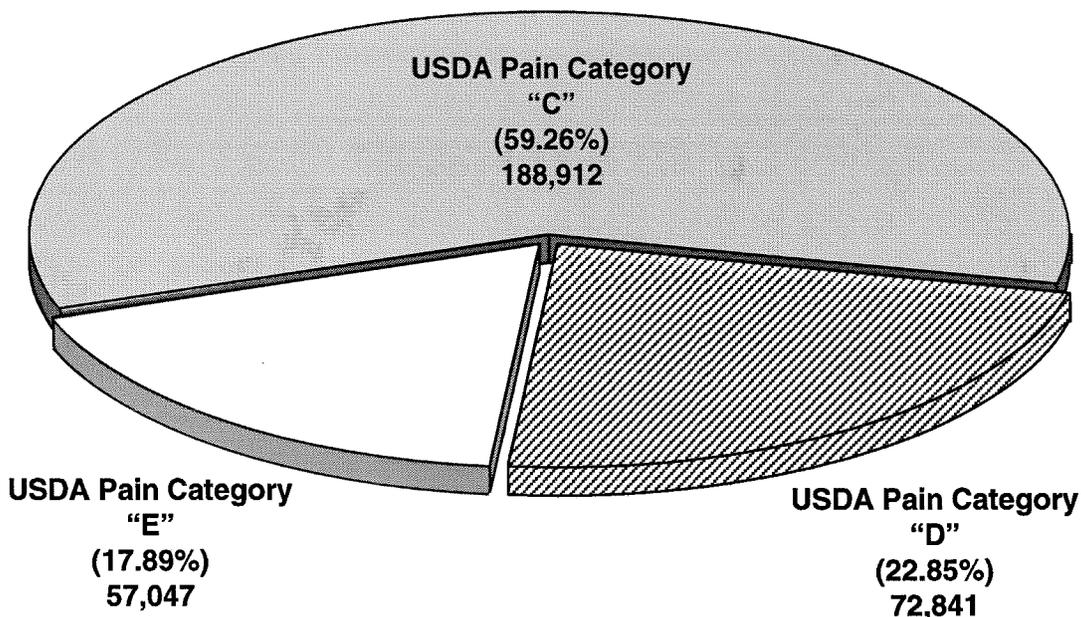


Figure V-14 DoD Intramural and Extramural Animal Use by USDA Pain Category for FY96

TOTAL = 180,155

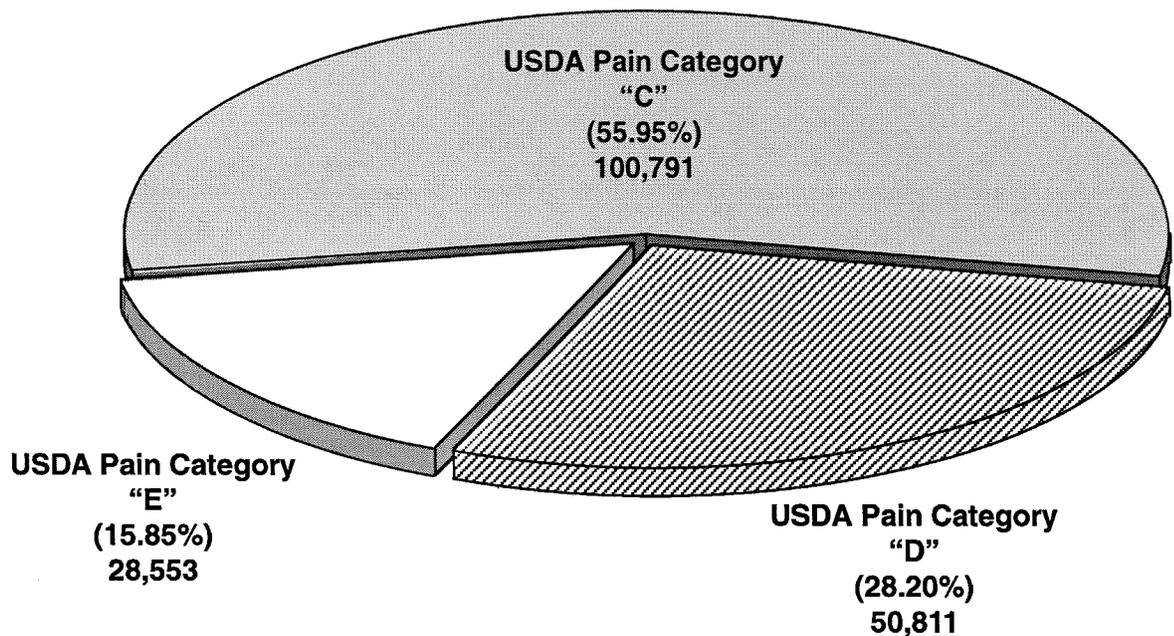


Figure V-15 DoD Intramural Animal Use by USDA Pain Category FY96

Percentages may not add up to 100% due to rounding of calculations

TOTAL = 138,645

Percentages may not add up to 100% due to rounding of calculations

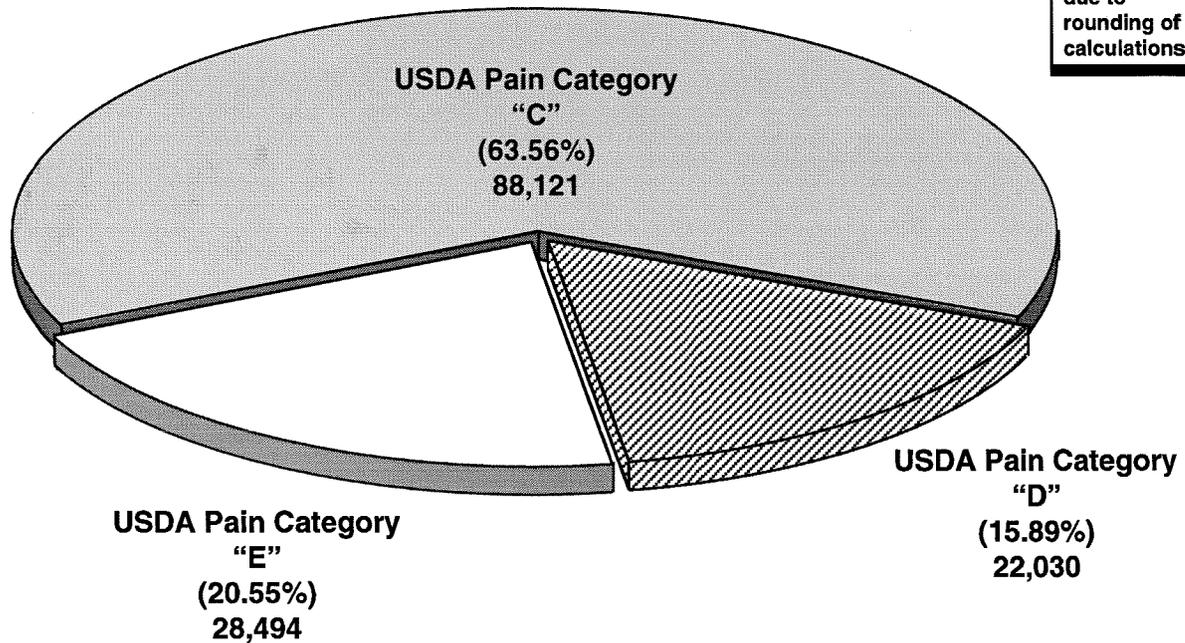


Figure V-16 DoD Extramural Animal Use by USDA Pain Category FY96

the cases (59%), the animals were not exposed to or involved in any painful procedures. In 23% of the cases, animals were given anesthesia or pain-relieving drugs during procedures that could have involved some pain or distress to the animals. In 18% of the animals used, anesthetics or analgesics were not used because they would have interfered with the results of experiments. Most (97%) of the animals used in painful experiments (where reducing the pain or distress would have interfered with the results) were rodents. Less than 1% of the animals in USDA Pain Category E were other mammals and approximately 2% were non-mammals. Animals reported in USDA Pain Category E were used in medical, non-medical, clinical, and secret research studies. There were no animals subjected to unalleviated pain during training or alternatives research studies.

The DoD clearly has a most diverse, unique, and demanding R&D mission. The modern battlefield is a hostile and dangerous environment with extraordinary potential for exposure to lethal

or debilitating conventional weapons, exotic endemic diseases, biological and chemical agents, nuclear blast and radiation, directed energy sources, and complex and dangerous equipment. In addition, a host of adverse environmental conditions, such as cold, heat, high and low pressure, and G-forces are threats to the service men and women. The DoD must provide acceptable protection against these threats and many others. The animals reported in USDA Category E were used in research designed to find ways to protect service men and women from the threats they encounter daily. Note that in most of these studies the distress level is minor such as in heat stress or gastrointestinal distress after being exposed to G-forces. This critical research is often reliant upon animal models for vaccine and efficacious countermeasure development. Research of this kind is not commonly done elsewhere in the government, academic, or private sectors and therefore is the sole purview of the DoD. Also, a large portion of these studies are driven by federal requirements, particularly those of the Food and Drug Administration.

SECTION VI

DoD INITIATIVES TO PROMOTE ALTERNATIVE METHODS THAT REPLACE, REDUCE AND REFINES THE USE OF ANIMALS

Alternatives, as articulated in *The Principles of Humane Experimental Technique* (Russell and Burch, 1959), are defined as methods that **Replace, Reduce and Refine** the use of animals. In addition to these *Three Rs*, the Department of Defense (DoD) advocates a fourth *R*, "Responsibility," for implementing these alternative methods.

Replacement

The replacement alternative addresses supplanting animal use with non-living systems, analytical assays, cell-culture systems, and with animals that are lower on the phylogenetic scale. Additionally, human subjects are used when experimental drugs and other procedures progress to human trials. Such trials are conducted in accordance with Title 32, U.S. Code of Federal Regulations, Section 219, "Protection of Human Subjects in DoD-Sponsored Research."

Reduction

Decreasing the numbers of animals used through the use of statistical or innovative design strategies, while preserving the scientific integrity of the biological model, is a major emphasis of the reduction alternative to animal use.

Refinement

The refinement alternative for animal use addresses the need to ensure that the maximum humane use of each animal is obtained through proper protocol design and efficient utilization of animals, or through the modification of the experimental design to reduce the ethical cost associated with the study.

Responsibility

The DoD has taken responsibility for implementing animal use alternatives. This commitment illustrates the DoD's initiative toward utilization and development of alternatives to animal use.

Department policy with regard to animal alternatives is promulgated in DoD Directive 3216.1 which directs that "it is DoD policy that... alternatives to animal species should be used if they produce scientifically satisfactory results..." This policy is implemented in the Joint Service Regulation on the Use of Animals in DoD Programs, which delegates responsibility to the local commander for utilization of alternatives to animals.

To illustrate the Department's initiatives to promote these *Four Rs*, a description of such initiatives within DoD's research laboratories and medical treatment centers is provided. The following list is not all inclusive, as the number of specific examples of implementing alternative methods that can be documented for DoD's research projects is large. Rather, it illustrates the scope, diversity, and spirit of DoD's *Four Rs* initiatives. This section will demonstrate a broad-based movement toward the use of biotechnology and other innovative adjuncts to replace and reduce animal use as well as refinement in methods used in essential animal studies.

VI.1 DoD DEVELOPMENT OF ANIMAL USE ALTERNATIVES

A review of the 1996 DoD research reveals that nine DoD facilities were actively involved in the development of alternatives to animal use. These developments occur through both research specifically designed to produce alternatives and by research to improve experimental techniques. Whenever possible, DoD investigators attempt to develop state-of-the-art, scientifically relevant and reliable experimental procedures that can be performed without the use of animals. In addition, in cases where the animal models cannot be completely replaced, investigators work diligently to develop refinement techniques to reduce any stress placed on the animal during both experimental procedures and daily living. Examples of alternatives developed by DoD

investigators in 1996 are listed below. This is only a sample of the many alternatives developed this year.

Replacement:

- Research on cellular mediators of tissue damage has lead to cell tissue culture techniques to develop interventions that support endothelial cell functions under harsh conditions. This model can be employed to identify the most beneficial interventions, within a class of treatment modalities, for further study at the animal level.
- Artificial human skin is used to study inflammatory responses to heat and medical countermeasures against vesicant agents
- In the safety testing of wideband microwave pulse, investigators are developing models of wideband interaction with human tissue so that energy deposition may be calculated by computer rather than measured in living animals.
- DoD investigators have developed an artificial eye with lenses that can mimic the focusing characteristics of the eye. Investigators can now expose this eye to various thresholds of laser exposures, and then validate their assumptions with a rhesus eye if needed.
- The DoD is working on the development of a sensitive polymerase chain reaction (PCR) technique to detect *C. burnetii* in clinical specimens that will eliminate the need to detect the microorganism using experimental animals.
- Research is being performed to develop cell lines that could replace synaptosomes (and therefore animals) in the study of botulinum toxin.
- Investigators have successfully adapted several mosquito colonies to membrane feeding. Since the technique has been fully adopted, animals are not exposed directly to mosquitoes. Mosquitoes have been fed

with human blood without any negative effect on reproduction rate. Attempts are being made to use expired human blood from either Indonesian Red Cross or U.S. Military blood banks.

- The DoD has developed a non-mammalian chemical metabolism test system utilizing the Japanese medaka minnow, which is less expensive to propagate and can be exposed to very controlled toxicant atmospheres. Research has shown that minnows metabolize the most common groundwater contaminant in a manner qualitatively similar to the human. These characterized metabolic steps indicate that toxicity data from the medaka are relevant to the human.
- A single, pedicle axial-patterned tubed skin flap which maintains metabolic and vascular functions *in vitro* has been developed. This allows chemical exposure and invasive sampling to be conducted without intact, live animals.
- A functional bilayer recording system has been developed to evaluate liposome formulations for their ability to facilitate fusion with biological and artificial lipid membranes. This lipid bilayer system is also utilized to study the effect of biological toxins on neurotransmitters.
- The nervous system of the sea slug, *Aplysia californica*, has been developed as a model to study the effect of chemical and toxic agents on the electrical properties of nerve cells.
- Developed realistic computer models of nervous systems.

Reduction:

- DoD investigators are developing anatomical computer models of experimental animals to use in computer codes to calculate where and how much microwave energy is absorbed in experimental animals when exposed to radio frequency (RF) fields. This capability

will reduce the number of experimental animals needed for RF dosimetry measurements.

- Shigella vaccine guinea pigs model has been developed and is currently being validated by DoD researchers. This model will drastically reduce or eliminate the need for tests in nonhuman primates.
- Development of *in vitro* primary mouse hepatocyte isolation technique and culture conditions will reduce the use of mice to obtain cells for metabolism studies.
- The Department's research on confocal microscopy methods in toxicology developed methods to detect cytotoxic endpoints using *in vitro* cultured cells as opposed to whole animal exposure. *In vitro* cultured cells coupled with the latest in morphometric analysis will lead to the development of cytotoxicity screens and will decrease the numbers of animals required for *in vivo* studies.
- Primary rat hepatocyte isolation and culture developed by DoD has yielded cell densities from a single rat equivalent to 200 to 300 whole animals (assuming 1 million cells/culture dish = 1 whole rat). Use of smaller culture dishes will enhance animal use reduction. This *in vitro* system has resulted in substantial animal use reduction.
- The DoD has developed a Bayes Theory estimator for the statistic that captures the difference between the disease rate in an exposed group when compared to a control group. This new estimator appears to reduce the number of animals or humans needed in a test by up to 25%.

Refinement:

The DoD is developing environmental enrichment programs for nonhuman primates. They are currently evaluating food and television preference and a token reward system.

- The DoD has developed telemetric implants for measuring core temperature that reduces the stress during heat acclimatization, and improves quantity and quality of data.
- DoD investigators have developed and maintained highly enriched environments for ferrets used in surgery study.

In addition to alternatives currently developed by the DoD, there are several projects that are in development. For example, efforts funded by the Defense Advanced Research Projects Agency (DARPA) are creating simulated leg and organ wounds using virtual reality (VR), holographic imaging, and haptic feed-back devices to replace the use of animals in medical instruction for Special Operational Forces Medics and other DoD medical personnel. Virtual Reality and Holographic Imaging will provide new dimensions in the medical training necessary for the high degree of proficiency required by Special Operational Forces Medics. Direct video networking and improved modeling with holographic techniques will be available to "induce" trauma upon simulated human beings. Additionally, telepresence will not only provide real time imagery for training but will be capable of being transmitted into a remote or denied area to assist medical personnel in treatment of complicated illness or trauma. In some scenarios, remote telepresence can become a physician extender enhancing the treatment provided. It can be used in an evacuation role, providing needed information to the receiving medical facility. Enabling them to conduct preliminary triage and ensuring that the proper specialists are on hand to receive and treat casualties.

VI.2 DoD IMPLEMENTATION OF ANIMAL USE ALTERNATIVES

DoD research protocols strive to minimize the number of animals used to accomplish the program mission and goals. This is accomplished by the implementation of both general and specific alternatives. General alternatives are those that are frequently implemented in DoD facilities.

Specific alternatives are those that may be specific to both a research protocol and/or facility. Approximately 50% of all FY96 animal use projects reported that they were implementing alternative methods to the use of animals. During the review of protocols by the Institutional Animal Care and Use Committee (IACUC), investigators are specifically asked to present information indicating that "Reduction, Refinement, and Replacement" have been addressed in the animal study. Implementation of these alternatives reduces, replaces and refines the Department's use of animals in research.

The following examples are a representative listing of general alternative methodologies commonly practiced in DoD facilities:

Replacement:

- During the review process all potential methods of adequately answering the research objective are reviewed prior to the use of an animal model.
- The evaluation process also considers the selection of a particular animal type; species lower on the phylogenetic scale are considered and used if its selection permits attainment of the research objectives.

Reduction:

- All animal use protocols are subject to review by a biostatistician, who addresses the animal used, study design, statistical evaluation packages and ensures that the minimum number of animals will be used to meet the specific scientific objectives.
- When possible, protocols make use of a repeated measures design and each animal as its own control, thereby reducing the number of animals necessary for a particular study.
- Collaboration between DoD investigators allows for a single animal to be used in multiple training and research procedures resulting in an overall reduction in the number of animals used.

- Training sessions are designed to use the highest student-to-animal ratio that is practical.

Refinement:

- Moribund animals are humanely euthanized to prevent unnecessary pain or distress.
- Utilization of the environmental enrichment strategy, animals are housed in social settings (i.e., pairs or groups) in an enriched environment (e.g., nestboxes, toys).
- Pilot studies are used to refine techniques and define the animal model.

Specific alternatives implemented by the DoD in FY96 were categorized as a subset of replacement, reduction or refinement and are shown in Table VI-1. These categories illustrate the broad-based

Table VI-1 Alternatives Categories

Replacement:

- Non-mammalian species or species lower in the phylogenetic scale
- Biochemical/physical methods
- Computer simulations
- Discarded tissue from other laboratories or re-use of animals
- Other species replace companion animals

Reduction:

- Substitution of another species
- Substitution of computer simulations or other technologies
- Sharing animals between research investigations

Refinement:

- Reduce pain
- Reduce distress
- Research models and animal alternatives

spectrum of alternatives to be implemented by the DoD. Since over 400 alternatives were implemented by the DoD this year, it is impossible to present all of them in this report, a representative listing of the specific alternatives is presented in Appendix P.

In addition to the implementation of alternatives, the DoD has established policies specific to the refinement of animal use. For example Walter Reed Army Institute of Research (WRAIR) has established a policy that mandates

consideration for environmental enrichment for research animals. This policy allows for flexibility and creativity for improving conditions of laboratory animals.

VI.3 DoD INITIATIVES TO PROMOTE ANIMAL ALTERNATIVES

The DoD has established a variety of initiatives and targeted programs that are currently in place to promote alternative methods that will refine, reduce and replace the use of animals. These programs are designed to target individual and institutional awareness by providing educational opportunities, professional training and fiscal resources toward implementing the *Four Rs* approach to animal use.

VI.3.1 Science and Technology Objectives to Reduce Reliance on Animal Research

The Department of Defense continues to seek alternatives to animal use through an Army Science and Technology Objective (STO) initiated in FY 1993 and continuing through FY 2001 entitled *Reduced Reliance on Human and Animal Subjects of Research and Improving Experimental Conditions Using Animals*. The objectives of the program are to develop technologies to incrementally reduce future reliance on animals in research by 25% using FY91 as a base year, and to introduce a minimum of one improvement (methodology or technology) per year in experimental protocols using animals. The U.S. Army Medical Research and Materiel Command (USAMRMC) budgeted approximately \$534,000 in FY96 for this objective which is available to support alternatives to animal use research. Recent accomplishments are:

- Tumor cell screening test, based on a National Institutes of Health (NIH) model, for animal toxicity testing

- Development of computer-modeled structural mutants of various toxins for screening as medical countermeasures
- Evaluation of *in vitro* organ slice methods to replace animal testing for toxicity
- The HeLa cell, a human epithelial tumor line, has been established as a useful proliferating cell model in sulfur mustard (HD) studies
- Living "TESTSKIN" (the commercial human skin equivalent) cellular model is used to elucidate the biochemical mechanisms responsible for HD-induced pathology
- An *in vitro* model of human epidermis formulated with gelled Type I collagen and normal human epidermal keratinocytes was developed to bridge the information gap between monolayers of cells and *in vivo* models utilized in HD vesicant research

The DoD research laboratories manage diverse research program in the development of alternative toxicity assessment methods in collaboration with the National Institute of Environmental Health Sciences, academic institutions and the private sector. Accomplishments in this program have included the development of a new non-mammalian development toxicity model, the establishment of a cooperative research and development agreement on new non-mammalian toxicity models with Colorado State University, and representing the Department of Defense on the Interagency Coordinating Committee on the Validation of Alternative Methods in toxicity testing.

The Army STO structure provides guidance, means, and high visibility to major Army technology initiatives. The Department of Army, in coordination with the Director of Defense Research and Engineering, Office of the Secretary of Defense, publishes the *Army Science and Technology Master Plan* as guidance to Army laboratories and research, development and engineering centers and to non-Army organizations

supporting the Army science and technology base.

VI.3.2 DoD Sponsored Conferences and Workshops on Alternatives to Animal Use

The DoD promotes responsibility for alternatives to animal use by sponsoring major meetings and conferences on the subject. Every 2 years the DoD sponsors an international meeting at Aberdeen Proving Ground on Alternatives to Animal Testing (Table VI-2).

Table VI-2 DoD Sponsored Alternatives

Date	Title
1990	DoD Initiatives in Alternatives to Animal Testing
1992	Current Concepts and Approaches on Animal Test Alternatives
24-26 May 1994	Alternatives in the Assessment of Toxicity: Theory and Practice
12-14 June 1996	Biennial International Symposium on Alternatives in the Assessment of Toxicity Issues, Progress and Opportunities

The 1992 meeting had 35 scientific platform sessions and 22 scientific poster presentations. This international symposium was attended by nearly 300 military and civilian scientists from four countries. Proceedings of the 1992 symposium are available through the Defense Technical Information Center (DTIC). In addition, in 1994 a book edited by Dr. Harry Salem entitled "Animal Test Alternatives" was published by Marcel Dekker, Inc., which included chapters prepared by most of the presenters at this symposium. The 1994 meeting had 26 scientific platform sessions, including one by Dr. Martin Stephens of the Humane Society of the United States, and 45 scientific poster presentations. This meeting was attended by over 330 military and civilian scientists from seven countries. The proceedings and a monograph based on this successful symposium are available through

DTIC. The book "Advances in Animal Alternatives for Safety and Efficacy Testing" has been published by Taylor and Francis. Both of these symposiums were praised as a success by Dr. Martin Stephens of the Humane Society of the United States (Appendix P). The 1996 conference was coordinated with the Scientists Center for Animal Welfare who hold their meeting 10-11 June 1996 to present Animal Welfare and Toxicology/Safety Studies: Current Issues and Trends for the Next Century. The DoD will sponsor another symposium on alternatives to animal use in the spring of 1998.

VI.3.3 National Research Council, Institute of Laboratory Animal Resources, Educational Programs

The DoD's priority and continuing commitment to promoting individual and institutional responsibility for alternatives to animal use are reflected in continuing financial support of the Institute of Laboratory Animal Resources (ILAR) educational program of the National Research Council. The principal thrust of the ILAR grant is development of institutional training materials, educational courses and publications in support of the Department's laboratory animal care and use programs. This ILAR information is used in various military research facilities as an important adjunct to existing investigator training and technical education programs on animal care and use. The ILAR information and programs have generated strong animal alternative provisions for both civilian and military-specific research opportunities. The Department has funded this work since 1987 through two 5-year ILAR grants (DAMD17-87-G-7021 and DAMD17-93-J-3016). Committing diminishing research funds to maintain this important collaboration, annual DoD funding for this ILAR program is in excess of \$100,000.

VI.3.4 DoD's Participation in Other Federal Alternatives Programs

DoD is also represented on the Interagency Regulatory Alternatives Group (IRAG) which planned and presented a "Workshop on Updating Eye Irritation Test Methods" in 1991 and held another workshop on Dermal Testing held at the

American College of Toxicology, in November 1995. The DoD representative on the IRAG (Dr. Harry Salem) received the FDA's Group Recognition Award for his outstanding contributions to the IRAG (Appendix R).

The National Institutes of Health Revitalization Act of 1993 (Public Law No. 103-43, Section 1301) directed the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH) to establish an Applied Toxicological Research and Testing Program which represents the NIEHS' component of the National Toxicology Program. The Act further directed the NIEHS to "(a) establish criteria for the validation and regulatory acceptance of alternative testing methods, and (b) recommend a process through which scientifically validated alternative methods can be accepted for regulatory use." To fulfill this mandate, an ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (ICC-VAM) (the Committee) was established in 1994 by NIEHS to develop a report recommending criteria and processes for validation and regulatory acceptance of toxicological testing methods that would be useful to Federal agencies and the scientific community. The Department of Defense participated in this effort that resulted in a report on the validation and regulatory acceptance of toxicological test methods.

Presentations have also been made on alternatives to the Board of Scientific Councilors of the National Toxicology Program of the National Institute of Environmental Health Sciences (NTP-NIEHS), Board of Scientific Councilors of the Food and Drug Administration and Cancer Etiology Group at the National Cancer Institute.

VI.3.5 Institutional Animal Care and Use Committee Emphasis

Title 9 (Animals and Animal Products), Subchapter A (Animal Welfare), Parts 1-4 of the Code of Federal Regulations has specific provisions for addressing the issue of alternatives during the research animal protocol review process. The DoD has been a leader in forming lawfully constituted and functioning IACUCs at its biomedical research facilities. Accordingly, DoD IACUCs consider alternatives to the proposed use of animals as an important review consideration. All DoD programs

use a Standardized IACUC Protocol Format for animal use proposals, which requires that non-animal alternatives be considered. It states that "No study using animals should be considered prior to the elimination of all reasonable possibilities that the question might be adequately answered using other than animal means." Investigators must provide information on the animal model being proposed and justification for the selected species. The Standard Protocol Format states that "investigators should use the least sentient species that will permit the attainment of research objectives." In addition, the investigators are required to provide a short description of the features of the proposal that may qualify the study as one that refines, reduces or replaces the use of animals. The DoD 1995 Policy letter requires that extramural contractor proposals utilizing animals in research, testing or training include all the information contained in the DoD Standard Protocol Format, thereby requiring them to also provide the alternatives information.

VI.3.6 Veterinary Staff Expertise and Assistance Visits

The major biomedical research commands of the Military Departments each have credentialed laboratory animal medicine (LAM) veterinarians serving in key staff positions. More than 30 board-certified specialists of the American College of Laboratory Animal Medicine (ACLAM) currently serve in the DoD. In addition to being advisors to commanders on issues related to animal welfare and alternatives to animal use, these veterinarians provide oversight and structure to the command's animal care and use programs. These officers also make periodic staff assistance visits to subordinate facilities that use animals and evaluate each laboratory animal care and use program. Consideration of the use of alternatives is reviewed on these staff assistance visits. Another important responsibility of the LAM veterinarian is to review extramural animal use protocols, ensuring that alternatives to animal use and personnel training issues have been addressed.

VI.3.7 Professional Veterinary Training in LAM

The individuals who are specialty trained in veterinary LAM provide expertise in DoD

biomedical research institutions which strongly correlates to effective animal use alternatives programs. This is especially true in the critical area of refinements. The DoD has long been a leader in training veterinarians in the field of LAM, the biomedical and veterinary specialty most closely associated with laboratory animal welfare and laboratory animal care and use programs. Many of the nationally prominent leaders of several laboratory animal associations were formally trained in, or closely associated with, DoD LAM training programs. Examples are the President-elect and several past presidents of ACLAM, the President and several past presidents of the American Association of Laboratory Animal Science (AALAS), and several past presidents and the current Secretary-Treasurer of the American Society of Laboratory Animal Practitioners. This traditional DoD strength in LAM expertise strongly enhances both animal care and use and animal alternatives programs. Greater than 25% of all ACLAM boarded specialists in the U.S. received some or all of their LAM training in DoD LAM training programs.

VI.3.8 AALAS Technician and Laboratory Animal Science Training

There are a number of DoD research facilities that sponsor formal training programs leading to certification of animal care and research personnel as AALAS laboratory animal technicians. This specialized training is offered to both government and non-government animal technicians. It is an important mechanism for ensuring highly qualified animal care and research technicians in Defense laboratories. Individual DoD institutions have sponsored formal seminars for research personnel where experts from the National Agricultural Library, Animal Welfare Information Center explain in detail the resources available for exploring various animal alternatives in the laboratory. The WRAIR sponsors laboratory animal workshops that provide comprehensive technical training available to all DoD personnel on animal use and related issues. Improving the technical expertise of laboratory animal technicians and investigators is a significant refinement element for the use of animals in the laboratory. These workshops are available to all DoD and NIH laboratories. As an example, the workshop on the use of rodents is offered 14 times per year. In and the WRAIR

workshop curriculum include formal training and information on alternatives to animal use. In addition, WRAIR offers quarterly a workshop on ethical and administrative issues relating to animal use. The AALAS technicians' course curriculum

VI.4 SUMMARY

Each year new techniques and capabilities improve the handling, treatment, and use of animals in research and testing, and potentially reduce the need for animals in those same endeavors. In FY96, there was ample evidence of the DoD's aggressive pursuit to develop alternatives to replace, reduce and refine the use of animals, for example, USAMRMC's STO on reducing reliance on animals for research and improving experimental conditions using animals, and the developed alternative shown in Section VI.1. In addition to these developmental efforts, animal use data for FY96 indicate the widespread implementation of validated alternatives. Rats and mice continue to replace nonhuman primates and other mammals higher on the phylogenetic scale in vaccine and drug development efforts. These and other examples of the development and implementation of alternatives have translated into reductions in the overall use of animals higher on the phylogenetic scale (see Section V). Animal use alternatives including refinement, reduction, and replacement constitute key initiatives in the biomedical research, testing, education, and training programs of the Department of Defense. The number of large animals used by the military departments over the past decade has been significantly reduced, and some large species are rarely used at all. Dogs, cats, nonhuman primates, and marine mammals collectively now represent less than 0.7% of the total animals used in research by the DoD.

SECTION VII

GLOSSARY

Adjuvant: An agent mixed in a vaccine to enhance the immunological protection afforded.

Alternatives to Animal Use: For purposes of this assessment, "alternatives" are defined as encompassing any subjects, protocols, or technologies that replace the use of laboratory animals altogether; reduce the number of animals required; or refine existing procedures or techniques so as to minimize the level of stress endured by the animal. These technologies involve the continued, but modified, use of animals; use of living systems; use of chemical and physical systems; and use of computers.

Analgesic: An agent that relieves pain without causing loss of consciousness.

Anesthetic: An agent that causes loss of the sensation of pain. Anesthetics may be classified as topical, local, or general.

Animal: For purposes of this assessment excluding embryos, animal is defined as any nonhuman member of five classes of vertebrates: mammals, birds, reptiles, amphibians, and fish. Within this group, two kinds of animals can be distinguished, warm-blooded animals (mammals and birds) and cold-blooded animals (reptiles, amphibians, and fish). Under this definition, invertebrates are not included.

Animal Use: The use of animals for research purposes. Three aspects of animal use are addressed in this assessment: behavioral and biomedical research; testing products for toxicity; and education of students at all levels. This assessment does not cover animal use for food and fiber; animal use to obtain biological products; or animal use for sport, entertainment, or companionship.

Animal Welfare Act: This act, passed in 1966 and amended in 1970, 1976, and 1985, was originally an endeavor to stop traffic in stolen animals that were being shipped across State lines and sold to

research laboratories. Amendments to the act have expanded its scope to include housing, feeding, transportation, and other aspects of animal care; however, the act bars regulation of the conduct of research and testing by USDA. Animals covered by the act, as currently enforced, are dogs, cats, hamsters, rabbits, guinea pigs, nonhuman primates, and marine mammals.

Antibody: Proactive proteins produced by lymphocytes (type of white blood cell) that can specifically bind foreign substances.

Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC): A voluntary private organization that, by Fall 1996, provided accreditation for 615 institutions. AAALAC accreditation is based on the provisions of the NRC *Guide for the Care and Use of Laboratory Animals*, and is recognized by the Public Health Service.

Biological Model: A surrogate or substitute for a process or organ of interest to an investigator. Animals or alternatives can serve as biological models.

Biomedical Research: A branch of research devoted to the understanding of life processes and the application of this knowledge to serve humans and animals. A major user of animals, biomedical research affects human health and the health care industry. It is instrumental in the development of medical products such as drugs and medical devices, and in the development of services such as surgical and diagnostic techniques. Biomedical research covers a broad spectrum of disciplines, such as anatomy, biochemistry, biology, endocrinology, genetics, immunology, nutrition, oncology, and toxicology.

Blast Overpressure: The concussion that results when weapons such as artillery pieces are fired. Soldiers firing these weapons can be severely injured by the local pressure effects resulting from

weapon use. Blast overpressure occurs when soldiers are fired upon also, i.e., the shock wave from enemy weapon fire/blast.

Carcinogen: An agent or process that significantly increases the incidence of abnormal, invasive, or uncontrolled cell growth in a population. Carcinogens fall into three classes: chemicals, viruses, and ionizing radiation. A variety of screening assays have been developed to detect chemical carcinogens, including the *Salmonella*-mediated mutagenesis assay (Ames test), the sister chromatid exchange assay, and traditional laboratory animal toxicity tests.

Carcinogenesis: The process by which a change to a cell occurs that leads to cancer.

Cell Culture: Growth in the laboratory of cells isolated from multicellular organisms. Each culture is usually of one type. Cell culture may provide a promising alternative to animal experimentation, for example, in the testing of mutagenicity, and may also become a useful adjunct in repeated-dose toxicity testing.

Computer Simulations: The use of specially devised computer programs to simulate cells, tissues, fluids, organs, and organ systems for research purposes: to develop mathematical models and algorithms for use in toxicity testing, and to simulate experiments traditionally done with animals for educational purposes.

Distress: Usually the production of pain, anxiety, or fear. However, distress can also occur in the absence of pain. For example, an animal struggling in a restraint device may be free from pain, but may be in distress. Distress can be eased with tranquilizers.

Education: The aspect of education dealt with in this assessment is the use of animals and alternatives in the teaching of life sciences to health professionals and preprofessionals, and research scientists.

Ex vivo: Outside the living body: denoting removal of an organ, tissue or cells.

Guidelines for Animal Care and Use: Various organizations outside the Federal Government have

adopted their own guidelines -- e.g., the American Psychological Association's *Guidelines for Ethical Conduct in the Care and Use of Animals*, which is comprehensive and has been endorsed by FASEB; the American Physiological Society's *Guiding Principles in the Care and Use of Animals*; and the American Veterinary Medical Association's *Animal Welfare Guiding Principles*. For federal guidelines, see Interagency Research Animal Committee, *NRC Guide for the Care and Use of Laboratory Animals*, and *PHS Policy*.

Institute of Laboratory Animal Resources (ILAR): A component of the National Research Council, ILAR performs periodic surveys on the use of laboratory animals.

Institutional Animal Care and Use Committee (IACUC): An institutional committee that reviews research proposals and oversees housing and routine care of animals. The committee's membership generally includes the institution's attending veterinarian, a representative of the institution's administration, users of research animals, and one or more nonscientist and lay member.

Invertebrate: Any nonplant organism without a spinal column, e.g., worms, insects, and crustaceans. Invertebrates account for 90 percent of the Earth's nonplant species. For the purposes of this assessment, invertebrates are not considered to be animals.

In vitro: Literally, in glass; pertaining to a biological process or reaction taking place in an artificial environment, usually a laboratory. Human and animal cells, tissues, and organs can be cultured *in vitro*. *In vitro* testing may hold some promising alternatives to animal testing, e.g., in testing for eye irritation and mutagenicity.

In vivo: Literally, in the living; pertaining to a biological process or reaction taking place in a living cell or organism.

Macrophage: A white blood cell that is very active in inflammatory responses and in engulfing foreign objects such as bacteria.

National Research Council's *Guide for the Care and Use of Laboratory Animals*: Revised in 1996,

the *Guide* details standards for animal care, maintenance, and housing. It is used by many animal research facilities, both within and outside the Federal Government. AAALAC and PHS also use it when assessing research facilities for accreditation.

Organ Culture: The attempt to isolate and maintain animal or human organs in *in vitro* culture. Long-term culture of whole organs is not generally feasible, but they can be sustained in cultures for short periods (hours or days).

Pain: Discomfort resulting from injury or disease. Pain can also be psychosomatic, the product of emotional stress. Pain can be induced by mechanical, thermal, electrical, or chemical stimuli, and it can be relieved by analgesics or anesthetics.

Polymerase Chain Reaction: A molecular biological system in which pieces of genetic material can be synthesized in large amounts *in vitro*. This material can be used in diagnostic testing, genetic studies, or for a large number of molecular biological purposes.

Protocol: The written plan of a scientific experiment or treatment.

Public Health Service Policy on Humane Care and Use of Laboratory Animals: Revised in 1985, the Policy applies to PHS-supported activities involving animals (including those of NIH). It relied on the NIH *Guide for the Care and Use of Laboratory Animals* (1985), and uses institutional committees for the assessment of programs and maintenance of records.

Reduction: Considered an alternative to animal use when fewer animals are used in research and education through changed practices, sharing of animals, or better design of experimental protocols.

Refinement: An alternative to animal use by better use and modification of existing procedures so that animals are subject to less pain and distress. Examples of such refinements are the administration of anesthetics and tranquilizers, humane destruction, and the use of noninvasive imaging techniques.

Replacement: An alternative to animal use, replacing methods using animals with those that do not. Examples include the use of a placenta instead of a whole animal for microsurgical training, the use of cell cultures instead of mice and rats, the use of non-living systems, and the use of computer programs.

Research Facility: Under the Animal Welfare Act, any individual, institution, organization, or postsecondary school that uses or intends to use live animals in research, tests, or experiments. Facilities that receive no federal support for experimental work and that either purchase animals only within their own state or that maintain their own breeding colonies are not considered research facilities under the act.

Testing: Standardized procedures that have been demonstrated to predict certain health effects in humans and animals. Testing involves the frequent repetition of well-defined procedures with measurement of standardized biological endpoints. A given test may be used to evaluate many different substances and use many animals. Testing is used to establish the efficacy, safety, and toxicity of substances and procedures.

Tissue Culture: The maintenance *in vitro* of isolated pieces of a living organism. The various cell types are still arranged as they were in the original organism and their differential functions are intact.

Toxicity Testing: The testing of substances for toxicity in order to establish conditions for their safe use. There are now more than 50,000 chemicals on the market and 500 to 1,000 new ones are introduced each year.

Vesicant: A chemical agent that causes burns and tissue destruction both internally and externally.

Veterinary Medicine: The science and art of prevention, cure and/or alleviation of disease and injury in animals. Veterinary medicine includes the management of animal care and use programs.

SECTION VIII

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