NIH Policy Manual

3043-1 - Introduction of Rodents, Rodent Products and Rodent Pathogens from Non-Approved Sources

Issuing Office: OD/OM/ORS/SR/DVR **Phone:** (301) 496-2527

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Transmittal Notice

1. **Explanation of Material Transmitted:** This chapter describes policies and procedures to be followed when rodents, rodent products and rodent pathogens originating from sources other than those Approved Sources through the Division of Veterinary Resources (DVR), Office of Scientific Resources (SR), Office of Research Services (ORS) are introduced into NIH facilities. This chapter has been revised to include linkage to the Online Rodent Import Application (ORIA), and updates to procedures in alignment with the move to online services and data storage for rodent import permits. The flowchart has been updated to include hyperlinks, making it a valuable summary and user friendly. Modifications have been made to clarify the policy applicability.
2. **Filing Instructions:**

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A. Purpose

This manual chapter (MC) establishes policies and procedures (See 3043-1 Flowchart - Introduction of Rodents or Rodent Products from Non-Approved Sources.docx.) designed to prevent the inadvertent introduction of infected rodents, rodent products and rodent pathogens into the National Institutes of Health (NIH) and its holding facilities. Introduction of unwanted pathogens to a defined health status facility can adversely affect the health of the colony and directly or indirectly interfere with critical research programs and the mission of the Institutes or Centers (ICs). In addition, the introduction of unwanted zoonotic agents can pose a health hazard to personnel.

B. Background

The conduct of a vigorous research program requires the movement of animals, their tissues and other rodent products from animal colony to animal colony, both within the NIH and from external sources. This movement creates opportunities for the introduction of unwanted pathogens into established colonies which can have an adverse effect on the animals, research and personnel, resulting in the loss of valuable government resources or pose a human health hazard. For example, Hantaviruses present in some rats and wild rodents, pose a risk to both established rodent colonies and to the humans who come into contact with infected animals.

Current federal regulations pertaining to the movement of laboratory rodents or their products relate mainly to organisms causing disease in humans or domestic livestock. Therefore, it is important for the NIH to supplement these regulations with policies and procedures designed to protect our rodent colonies and research mission. It is the goal of this policy to establish a dynamic balance between the need for animal movement, and the protection of both human health and research critical to the mission of the NIH. **Investigators must not import rodents or rodent products into any animal facility without receiving the appropriate approvals.**

C. Policy

The policies and procedures in this chapter apply when rodents, rodent products, or rodent pathogens for *in vivo* use are introduced into NIH facilities from sources other than those approved through the Division of Veterinary Resources (DVR), Office of Scientific Resources (SR), Office of Research Services (ORS). These policies and procedures apply to all NIH facilities located on the Bethesda campus, any off-campus facility covered under the Association for Assessment and Accreditation of Laboratory Animal Care International's (AAALAC International) accreditation file numbers 000777 and 000401.

This manual chapter is designed to reduce the risk of introducing unwanted pathogens, infectious and zoonotic diseases, into animal facilities and protect the mission of the NIH. Rodents from Non-Approved Sources shall not be introduced into NIH animal facilities or NIH laboratories without prior approval through the ORIA system. In addition, it is the IC's responsibility to ensure that, at a minimum, the IC Animal Program Director (APD), and the DVR Director or delegated NIH Rodent Import Officer (NIH RIO) has knowledge of the introduction of rodents from Non-Approved Sources prior to their introduction. (See 3043-1 Flowchart - Introduction of Rodents or Rodent Products from Non-Approved Sources.docx).

Rodents or rodent products (to be used in rodents) inadvertently infected with Lymphocytic Choriomeningitis Virus (LCMV), Hantaviruses or other assayable zoonotic agents of moderate potential hazard to people are excluded from NIH facilities. With adequate justification, *Exemptions* for research purposes can be issued but must be approved by the IC RIO as well as the NIH Institutional Biosafety Committee (IBC) through the Biosafety Officer (BSO) in the Division of Occupational Health and Safety (DOHS), SR, ORS. The IC RIO maintains copies of approvals. Intentionally infected rodents or rodent products used to

intentionally infect rodents for *in vivo* studies of Lymphocytic Choriomeningitis Virus (LCMV), Hantavirus or other assayable zoonotic agents are exempt (as defined in this chapter) when their use has been approved on an animal study proposal.

Primary responsibility for training of investigators regarding this policy lies with the IC Animal Programs. *The NIH Animal User* and *Principal Investigator* training courses shall contain material to heighten the awareness of the risk associated with rodents and rodent products from zoonotic and rodent specific pathogens both to humans and other animals in the NIH facilities. See Office of Animal Care and Use (OACU).

The IC APD or their delegate is responsible for the disposition of animals harboring infectious agents introduced into their areas of responsibility.

Laboratory principal investigator(s) (PIs) and their laboratory/branch chief(s) are responsible for the handling and disposition of rodent pathogens and products introduced for *in vitro* use into their laboratory. Rodent pathogens and products for *in vitro* use shall be handled in a manner which prevents the inadvertent introduction of the agent(s) or material into other NIH facilities.

D. References

1. Animal Welfare Act (7 U.S.C. 2131 et. seq.), as amended and regulations at 9 C.F.R. Part 1
2. 9 C.F.R. Part 3
3. Public Health Service Act, Sections 361-369 (42 U.S.C. 264-272), as amended, and its implementing regulations at 42 C.F.R. Parts 71.56
4. PHS Policy - PHS Policy on Humane Care and Use of Laboratory Animals, 2015
5. NIH Manual 3040-2, Animal Care and Use in the Intramural Program, 2014 or succeeding revisions
6. The Guide - National Research Council Guide for the Care and Use of Laboratory Animals, 2011
7. CDC Fact Sheet on Embargoed African Rodents and Monkey Pox Virus
8. USDA: Animal and Animal Product Import Information
9. Federation of International Mouse Resources (FIMRe)
10. NIH Manual 1340-1, Permits for Import or Export of Biological Materials, 2014 or succeeding revisions
11. NIH Manual 1743, “Keeping and Destroying Records," Appendix 1, "NIH Records Control Schedule"
12. Biosafety in Microbiological and Biomedical Laboratories. Centers for Disease Control and Prevention/National Institutes of Health, 5th Edition, December 2009
13. Supplement, Guidelines for Biosafety Laboratory Competency, CDC and the Association of Public Health Laboratories, 2011 or succeeding revisions
14. Centers for Disease Control and Prevention, Hantavirus Information Resource Page, CDC - Hantavirus
15. Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International)

16. NIH Delegations of Authority, Program: General, No. 31, NIH Intramural Animal Care and Use Program
17. 49 CFR Chapter 1, Subchapter C-Hazardous Materials Regulations, *requires PIC card to access link*
18. 42 CFR Part 70 – Interstate Quarantine

E. Definitions

1. **Animal Program Director (APD):** A Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine, who is supervised by, and receives delegated program authority from the Scientific Director (per delegated authority via the IC Director from the Institutional Official) for all activities involving animals in an IC, including ensuring compliance with guidelines, policies and regulations such as, this manual chapter, the National Research Council Guide for the Care and Use of Laboratory Animals, 8th ed. (commonly referred to as the Guide), the Public Health Service Policy on Humane Care and Use of Laboratory Animals (PHS Policy-), the Animal Welfare Regulations in the Animal Welfare Act (AWRs); and for maintaining Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) accreditable standards of the Animal Care and Use (ACU) program and facility (ies). The Animal Program Director serves as the "Attending Veterinarian" for the purposes of Animal Welfare Act interpretations. (See MC 3040-2)
2. **APDs' Committee:** A committee established to provide advice and guidance on veterinary issues to the Director, Office of Animal Care and Use. The committee includes the Animal Program Director of each IC. (See MC 3040-2)
3. **Animal Research Advisory Committee (ARAC):** The intramural NIH institutional Animal Research Advisory Committee includes the Chair of each IC Animal Care and Use Committee (ACUC). The Deputy Director for Intramural Research shall appoint the Chair, Executive Secretary and additional members. (See MC 3040-2)
4. **Application:** Refers to NIH Form 2369-1, "Application for Permit to Introduce Rodents," or NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use In Vivo Biological Assessment." The issued permit is valid for new imports of specified rodents, or rodent products or pathogens for a twelve (12) month period. The receiving NIH facility may request updated health status information from the sending institution during this period. The receiving NIH facility will subsequently determine whether to accept or reject the shipment based on the sending facility's current health status. These applications are submitted and filed electronically via the Online Rodent Import Application (ORIA).
5. **Approved Source:** A source of rodents or rodent products that supplies genetically-defined, specific pathogen-free animals to NIH investigators. These sources characteristically meet the barrier production practices, genetic management and monitoring, microbiologic and health surveillance standards; and shipment practices to assure maintenance of health status required or prescribed in/by the DVR-held NIH Animal Procurement Contract. The NIH Rodent Import Officer (NIH RIO) maintains a list of sources that meet the Approved Source criteria. Note: Additional sources not

included in the DVR-held or general animal procurement contract may be available through defined and established relationships with individual ICs. For consideration of a source to be included in the Approved Source list, the NIH RIO and Rodent Import Advisory Subcommittee (RIAS) must first review the documentation of the source's program to provide pathogen-free animals and endorse the program. Sources must then be approved by the APD's committee.

6. **Biological Safety Officer (BSO):** The NIH BSO provides technical advice to Principal Investigators and the Institutional Biosafety Committee (IBC) on research safety procedures. The principal function of the biosafety officer should be to advise the Principal Investigator, the Institutional Biosafety Committee and the lab workers concerning the most appropriate safety practice that would assure the safe conduct of recombinant DNA research and the working with microbiological agents, etiologic agents and their vectors of human disease. The NIH Biosafety Officer serves as the Executive Secretary for the NIH Institutional Biosafety Committee. (The BSO roles and general responsibilities are defined in the NIH Guidelines Section IV-B-3.)
7. **Exemptions:** An exemption from Quarantine for a particular shipment of rodents that do not meet the NIH minimum health standard may be obtained with appropriate justification and approval (See Section C. Policy).
8. **Facility Veterinarian:** A Veterinarian with training or experience in laboratory animal science and medicine, who receives delegated authority from the Animal Program Director responsible for that facility. The Facility Veterinarian has the responsibility and authority to ensure timely adequate veterinary care to all animals housed in the facility. The Facility Veterinarian is responsible for ensuring compliance with all applicable regulations, guidelines and policies, and for maintaining accreditable standards of the ACU program and facility. The Facility Veterinarian has the responsibility and authority to report any issue of non-compliance to the Animal Program Director responsible for that facility and to the supporting and sponsoring IC Animal Care and Use Committees. (See MC 3040-2.)
9. **Isolation Area, Rodent:** A DVR or IC operated containment area for the receipt, housing, husbandry and health testing of rodents **believed to be free of specific rodent pathogens and zoonotic agents**. The design and operation of the area shall ensure the isolation and containment of rodent pathogens and zoonotic agents at the cage level. The physical and procedural attributes of an isolation barrier are similar or identical to that of a quarantine facility/area. The APD of the lead or sponsoring IC, or in the case of a centrally run isolation area, the Director of DVR, is accountable for the adequacy of isolation and containment. The establishment of an isolation area within a shared or central animal holding facility shall have the review and endorsement of the animal facility's user ICs.
10. **Laboratory/Branch Chief(s):** The individuals within a laboratory or branch with responsibility and accountability for the compliance of all established NIH and PHS policies, procedures, and guidelines for the laboratory or branch. This person may also be referred to as the Senior Laboratory Principal Investigator in some ICs.
11. **Minimum Health Standard, NIH:** All rodents introduced into NIH facilities must be shown to be free of Lymphocytic Choriomeningitis Virus (LCMV); and Hantaviruses, as applicable based on local or species risk (See definition for "Non-Approved

Source".) The sending facility must provide assurance and/or evidence that annual testing for the specified agents is performed throughout their facility, or it must be demonstrated (serology or Polymerase Chain Reaction (PCR)) that the specific animals to be shipped are likely free of these agents. Unless approved for scientific study of Ectromelia infection under an animal study protocol, rodent products for use in mice must also be shown to be free of Ectromelia virus. (See Appendix 2 – Guidelines and Procedures, Section II).

12. **NIH Facility:** Any building, structure, laboratory or other facility, whether or not animals are housed or used there. An "animal facility" houses animals.
13. **NIH Institutional Biosafety Committee (IBC):** The IBC provides recommendations to the Director of the NIH or his designee, in matters pertaining to the control of hazards associated with the intramural use of microbiological agents, their vectors, and recombinant DNA. The committee serves as an advisory body to the Division of Occupational Health and Safety (DOHS), SR, ORS.
14. **Non-Approved Source:** A source of rodents or rodent products that does not meet the definition or requirements of an Approved Source. Wild caught rodents or colonies derived from wild caught stock must provide evidence that colonies are free of LCMV and Hantaviruses. If possible, direct testing is the preferred method; however if necessary indirect testing (sentinels) during Quarantine may be used.
15. **Office of Animal Care and Use (OACU)** - The office with authority to act on behalf of the Institutional Official to ensure that NIH programs and facilities for ACU are in compliance with MC 3040-2, the Guide, the PHS Policy and the Animal Welfare Regulations (AWR)s. This authority is exercised by the Director, OACU. (See MC 3040-2.)
16. **Online Rodent Import Application (ORIA):** A web-based application system for submission and management of rodent import permits, including a searchable database, managed by the NIH Rodent Import Officer and maintained by DVR.
17. **Rodent Import Permit:** A permit which verifies approval for the import of **specified rodents or rodent products** from a Non-Approved Source. The permit does **NOT** approve the source for future imports not included on the permit.
18. **Principal Investigator (PI):** A scientist designated by the Laboratory/Branch Chief or the IC Director or Scientific Director responsible for conducting an animal study in compliance with this policy, MC 3040-2, the Guide, the PHS Policy, and the AWRs, and who certifies acceptance of this responsibility by signing the Animal Study Proposal. (See MC 3040-2.)
19. **Quarantine:** A place in which an animal suspected of carrying an infectious agent/rodent pathogen excluded from the receiving NIH facility is kept in confinement while testing is performed. This relates to Quarantine facility/area and to Isolation area for purposes of this policy.
20. **Quarantine Facility/Area, Rodent:** A DVR or IC operated containment facility or area within a facility for the receipt, housing, husbandry and health testing of animals with known, suspected or unknown health status. The design and operation of the facility shall ensure the isolation and containment of rodent pathogens and zoonotic agents at the cage level. The ideal barrier would:

a. Physically separate the quarantine facility from other rodent holding facilities or areas;
b. Use certified Class II Biological Safety Cabinets for cage changing and handling of animals;
c. Have the ability to autoclave contaminated bedding and supplies out of the area;
d. Have the ability to control and limit access to key personnel;
e. Utilize appropriate disposable or dedicated personal protective equipment (PPE) (e.g. jumpsuits, shoe covers, hair covers, gloves, etc.);
f. Have access to shower facilities; and,
g. Have established standard operating procedures for the daily husbandry, testing and disposition of animals.

Because a Quarantine Facility/Area can accept animals with suspect or unknown health status, a break in the physical or procedural barrier poses a significantly higher risk to other nearby colonies, than the risk posed by an Isolation Area which only accepts animals believed to be free of unwanted pathogens or zoonotic agents. Therefore, the establishment of a Quarantine Facility within a shared or central animal holding facility shall have the review and endorsement of the animal facility's user ICs. The APD of the Lead or sponsoring IC, or in the case of a centrally run quarantine facility the Director of DVR, is accountable for verifying the adequacy of isolation and containment, as well as ensuring that the Quarantine Facility is on file with the NIH RIO.

21. **Quarantine Permit Service Office (QPSO):** The QPSO, DOHS assists investigators in obtaining permits that may be required when importing/exporting animals, animal products, etiologic agents, or vectors of human or animal disease. Permits must be coordinated through the QPSO in collaboration with the IC RIO and the NIH RIO.
22. **Rodent:** A mammal of the order Rodentia, including but not limited to mice, rats, guinea pigs, and hamsters.
23. **Rodent Import Officer, NIH (NIH RIO):** A Veterinarian appointed by the Director of the DVR, SR, ORS, with delegated responsibility for activities defined in this policy, including overseeing activities at the DVR operated rodent Quarantine Facilities, and managing the Online Rodent Import Application (ORIA) system. For more information contact OD DVR Rodent Import by e-mail: oddvrrodentimport@mail.nih.gov (NIH Global Directory).
24. **Rodent Import Officer, Institute/Center (IC RIO):** A Veterinarian, the APD of an IC and/or their designee, with responsibility for import activities defined in this policy within their IC.
25. **Rodent Import Advisory Subcommittee (RIAS):** A committee appointed by the APDs to serve in an advisory capacity to the NIH RIO in periodic reviews of this policy. The RIAS shall include at least one scientist member of the Animal Research Advisory Committee (ARAC) for purposes of policy review. The NIH RIO may seek the counsel of the RIAS in reviewing applications for Approved Source status, and to settle disputes involving this policy.

26. **Rodent Products:** Any rodent tissue or derivative directly introduced into a rodent or combined with another product for rodent *in vivo* use. Products include but are not limited to antibodies (polyclonal or monoclonal), body fluids, proteins, embryos, sperm, or cells.
27. **Veterinarian:** A doctor of veterinary medicine; a person qualified and authorized to practice veterinary medicine.
28. **Zoonotic:** A disease that can be transmitted from animals to humans.

F. Responsibilities

1. **Animal Program Director (APD):** The IC Animal Program Director (APD) is responsible for ensuring compliance with this policy, the Guide, the PHS Policy, and the AWRs in the animal program (See MC 3040-2). The APD will serve as or delegate responsibility as the IC Rodent Import Officer for purposes of this policy.
2. **APD's Committee:** The Committee shall be responsible for reviewing veterinary operational issues which affect the overall NIH Animal Care and Use program, including this policy. **Duties of this committee include the periodic review and enforcement of this policy and its procedures.**
3. **Animal Research Advisory Committee (ARAC):** Provides review of revisions to this policy after review by the APD's Committee. Both committees must approve revisions to this policy. Provides a representative to serve on the RIAS when major policy revisions are discussed..
4. **Director, DVR, ORS:** Implements those aspects of this policy relating to the DVR and the NIH RIO.
5. **Facility Veterinarian:** The Facility Veterinarian is responsible for maintaining the health status of rodents in their corresponding animal facilities. Choices of action include:

    a. Approve the animals for entry into their animal facility .
    b. Approve animals for entry into an Isolation Area (minimal risk based on health history).
    c. Approve animals for entry into areas where infectious studies will be performed, such as ABSL3 or Isolation Areas designated for studies of specific infectious agents.
    d. Require the animals to be quarantined with further testing.
    e. Reject the animals for entry into their facility.
    f. Require more information before making a decision.

    In the first four cases (a-d), the Facility Veterinarian approves the import electronically on the ORIA system. In the last two (e and f), the Facility Veterinarian denies approval of the Application electronically. Results will then be routed back to the submitting IC RIO. After animals have completed Quarantine including documenting the testing of their health status on NIH Form 2369-4 "Rodent Quarantine Release" and offer for release, the Facility Veterinarian determines if and when suspect or questionable animals can enter their facility.

6. **IC RIO:** The IC RIO manages this policy within their IC:

    a. Assists the Principal Investigator (PI)/applicant in securing approvals, permits, transportation, etc., related to the introduction of rodents or rodent products into an animal facility or laboratory. The above includes assistance with obtaining health monitoring and husbandry information for review by the Facility veterinarian. This may be aided by using NIH Form 2369-2 "Animal Health Data Request Template."
    b. Reviews and approves or disapproves applications for the introduction of rodents from Non-Approved Sources into NIH IC animal facilities, under their purview (NIH Form 2369-1), for facility or laboratory applications, based on the supportive evidence for absence of LCMV and Hantaviruses (if applicable) and other murine pathogens excluded from their facilities.
    c. Updates the application to list the applicable Facility Veterinarian.
    d. Reviews and approves or disapproves applications for the introduction of rodent products and pathogens (NIH Form 2369-3) into NIH IC animals, under their purview, based on the supportive evidence for the absence of LCMV, Hantaviruses (if applicable), Ectromelia virus, and other murine pathogens excluded from their facilities.
    e. Reviews and approves or disapproves applications for introduction of rodents from Non-Approved Sources into laboratories of an IC.
    f. Provides oversight within their IC to ensure quarantine of animals until such time that data can be generated to verify that the animals are, at a minimum, free of LCMV, and Hantaviruses, as applicable. Forwards data to the NIH RIO.
    g. May suspend an approved Rodent Import Permit if additional evidence suggests a high risk.

7. **IC Scientific Director:** The IC Scientific Director ensures compliance with this policy by intramural staff within his/her IC.
8. **Laboratory/Branch Chief(s):** The Laboratory/Branch Chief has authority to approve importation directly to a laboratory for *in vitro* use, and also oversees the principal investigators in their branch. The IC RIO approves permits for *in vivo* use in the laboratory.
9. **NIH RIO:** The NIH RIO manages this policy for the NIH.

    a. May suspend an approved permit, pending further discussion with the IC RIO, if it is determined that a high risk decision was made. In general a 1-2 business day turnaround time is expected.
    b. Coordinates use of the DVR rodent Quarantine Facilities/Areas.
    c. Sets testing requirements for and offers animals for release from DVR quarantine once testing demonstrates the rodents meet the NIH minimum health standard. NIH Form 2369-4, "Rodent Quarantine Release".
    d. Provides guidance on this policy to IC RIOs and Facility Veterinarians.
    e. Evaluates and approves proposals for import permit Exemptions. Approved Exemptions will be reviewed annually.

f. Maintains the Online Rodent Import Application (ORIA) system which fulfills the following duties:

1. Assigns and applies a Rodent Import Permit number to each approved application.
2. After approval, sends an e-mail notification, which contains a link to the approved permit, to the facility veterinarian, the IC RIO, the requestor, and all other contacts requested on the permit.
3. Maintains an electronic file of approved, pending, and disapproved Rodent Import Permits and the supportive health information.

10. **Office of Animal Care and Use (OACU):** Provides training for investigators and staff working with animals. ***The NIH Animal User*** and ***Principal Investigator*** training courses shall contain material to heighten the awareness of the risk associated with rodents and rodent products from zoonotic and rodent specific pathogens both to humans and other animals in the NIH facilities.
11. **Principal Investigator/Applicant (PI):** Initiates rodent import Application(s) for approval of shipments from Non-Approved Sources for:

a. rodents into NIH laboratories or animal facilities
b. rodent products to be introduced into NIH rodents

1. With the help of the IC RIO, obtains health information and completes documents required at the IC level.
2. Initiates any additional permits/applications which may be required, such as United States Department of Agriculture permits, when necessary (See Appendix 2 – Guidelines and Procedures for additional information).

12. Quarantine Permit Service Office (QPSO): **The QPSO** in the Division of Occupational Health and Safety (DOHS) assists investigators in obtaining any additional permits that may be required when importing/exporting animals, animal products, etiologic agents, or vectors of human or animal disease. Permits must be coordinated through the QPSO in collaboration with the IC RIO and the NIH RIO.
13. Biological Safety Officer (BSO): Provides technical advice to Principal Investigators and the Institutional Biosafety Committee (IBC) on research safety procedures. The principal function of the biosafety officer should be to advise the Principal Investigator, the Institutional Biosafety Committee and the lab workers concerning the most appropriate safety practice that would assure the safe conduct of recombinant DNA research and the working with microbiological agents, etiologic agents and their vectors of human disease. The NIH Biosafety Officer serves as the Executive Secretary for the NIH Institutional Biosafety Committee. (The BSO roles and general responsibilities are defined in the NIH Guidelines Section IV-B-3.)
14. **Rodent Import Advisory Subcommittee (RIAS):** A committee appointed by the APDs, which:

a. Reviews proposed Approved Sources with the NIH RIO for purposes of this policy.
b. Provides mediation for disputes if necessary.
c. Reviews revisions to this Policy (The RIAS shall seek scientific representation by a member of the Animal Research Advisory Committee (ARAC) for major policy revisions).

G. Procedures

The procedures contained in Appendix 2 – Guidelines and Procedures provide specific instructions for submitting applications for import of rodents, rodent products, and rodent pathogens. They include guidance for use of the Online Rodent Import System and supporting documents. Procedures also explain the Quarantine/Isolation facilities, and the role of the Quarantine Permit Service Office as related to this policy.

H. Records Retention and Disposal

All records pertaining to this chapter must be retained and disposed of under the authority of NIH Manual 1743,"Keeping and Destroying Records," Appendix 1, "NIH Records Control Schedules" (as amended). These records must be maintained in accordance with current NIH Records Management and Federal guidelines. Contact your IC Records Liaison or the NIH Records Officer for additional information.

I. Internal Controls

The purpose of this manual chapter is to establish policies and procedures designed to prevent the introduction of infected rodents and rodent products into the NIH which could adversely affect the health of rodents used in research, directly or indirectly interfere with research, or pose a health hazard to personnel.

1. **Office Responsible for Reviewing Internal Controls Relative to this Chapter**: Through this manual chapter, the Director of the Division of Veterinary Resources (DVR), Office of Scientific Resources (SR), Office of Research Services (ORS) is responsible for ensuring that internal controls are implemented and working.
2. **Frequency of Review (in years):**
   Ongoing, with reports of any problems submitted to the Director, Division of Veterinary Resources (DVR), SR, ORS.

   Revisions to the policy are due every three to five years or as needed.
3. **Method of Review:**

   a. The NIH RIO and the IC RIOs review compliance with this policy on an ongoing basis, through review of rodent import applications.

b. DVR will ensure that new APDs receive information regarding this policy and will provide guidance to all users as needed.
c. Questions or concerns are discussed with the NIH RIO and if necessary forwarded to the Director, DVR for appropriate routing and action.
d. The Rodent Import Permits are maintained in a data base managed by DVR which allows review as necessary.
e. If changes to the rodent import policy or procedures are necessary, they will be addressed by the APDs (through the RIAS), and with final scientific approval by the NIH Animal Research Advisory Committee (ARAC). The RIAS shall include a scientist member of the ARAC for purposes of policy review.
f. Triennially, the Intramural ACU program is visited by their accrediting organization, the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) which reviews all aspects of the animal programs.

4. **Review Reports are sent to:**
Director of the Division of Veterinary Resources in ORS as needed. The DVR, Director will inform the APDs Committee and the Deputy Director for Intramural Research (DDIR) of any significant findings.

Appendix 1 - Supporting Information/Documents

1. Flowchart: Introduction of Rodents or Rodent Products from Non-Approved Sources
2. Requirements for Handling Imported Rodent Embryos, Oocytes, Ovaries or Sperm
3. Printable worksheet to assist with data collection for NIH Form 2369-1 "Worksheet for Permit to Introduce Rodents"
4. NIH Form 2369-2 "Animal Health Data Request Template"
5. Printable worksheet to assist with data collection for NIH Form 2369-3 "Worksheet for Rodent Products or Rodent Pathogens for Use In Vivo Biological Assessment"
6. NIH Form 2369-4 "Rodent Quarantine Release"

Appendix 2 - Guidelines and Procedures

I. **Introduction of Rodents from Non-Approved Sources:** See 3043-1 Flowchart for Introduction of Rodents or Rodent Products from Non-Approved Sources

The introduction of rodents from Non-Approved Sources requires submission and approval of the NIH Form 2369-1, "Application for Permit to Introduce Rodents" through the Online Rodent Import Application (ORIA)**:**

A. **Application Submission and Approval:**

***Helpful Tips*:**

The number of animals on the permit should be the total number of animals over the life of the permit (12 months). If multiple shipments are anticipated, the number of

animals in each shipment may be clarified (itemized) in the text box provided for comments. If the original number of animals is found to be insufficient, amendments to adjust the number of animals may be submitted through ORIA later. In situations where quarantine and/or embryo rederivation is likely, applications should be submitted at least 60 calendar days prior to the anticipated date of entry into an NIH animal facility to allow adequate time for diagnostic testing and/or rederivation procedures.

It is particularly important to provide the name, telephone number, and e-mail address of the veterinarian or person responsible for animal health at the source facility in the application form. (Overseas telephone contact is often difficult and expensive; therefore, listing an e-mail address or fax number in the application is recommended.)

It may be helpful to have the NIH Form 2369-2, "Animal Health Data Request Template" at hand when contacting the originating facility; and later, when evaluating documentation of their pathogen monitoring and control program. All information acquired should be attached to the application. If applicable, the testing for Lymphocytic Choriomeningitis Virus (LCMV) and Hantavirus, must have been conducted within the last 12 months. If an exemption to the Quarantine policy is desired, contact the NIH RIO.

Click here for **Instructions: Animals going to a Facility or Laboratory**.
Click here for Accessible Instructions: Animals going to a Facility or Laboratory

1. **The Principal Investigator (PI) or representative must**:

    a. Request a permit for animals going to a facility or laboratory using the Online Rodent Import Application (ORIA) system
    b. Complete all requested information
    c. Attach supporting health information files and submit the application

2. **The IC RIO must**:

    a. Ensure that the imported animals represent a low risk to both personnel and animal colonies from viruses such as, Lymphocytic Choriomeningitis Virus (LCMV) and Hantaviruses by reviewing the application* and ensuring that it contains the following:

        i. the health information required for compliance with the minimum health standard
        ii. name of the Facility Veterinarian of the facility in which the animals are to be imported and/or housed (if necessary, IC RIO will complete this information)
        iii. specify Quarantine/Isolation location (if applicable); this could also be noted by the Facility Veterinarian

        *Applications to introduce rodents into a laboratory for acute studies

(held for less than 12 hours) where no contact with other animals is planned may be approved by the IC RIO directly.

After ensuring required information is correct and complete, the IC RIO approves or disapproves the application. If the application is **approved**, the ORIA system routes it to the Facility Veterinarian of the final location where the animals or tissue will be housed and/or used. If it is **disapproved**, the application is returned to the applicant with an explanation.

3. **The Facility Veterinarian (of the final location where the animals or tissue will be housed and/or used) must:**

   a. review the approved application received through the ORIA system from the IC RIO
   b. review the health information submitted for compliance with the specific facility's requirements (In addition to meeting the minimum health standard, animals destined for an NIH animal facility, must also meet the specific health requirements of the receiving facility.
   c. add or updates the quarantine/isolation location and testing methods (as applicable). (More information on Quarantine/Isolation facilities and procedures below.)
   d. approve or disapprove the application. If disapproved, an explanation for the decision must be included in the application routed back through the IC RIO.

   NOTE: *The ORIA system will assign a Rodent Import Permit number when both the IC RIO and the Facility Veterinarian of the final housing location have approved it. If animals are going to a laboratory, the ORIA system will assign a Rodent Import Permit number when the IC RIO has approved the application.*

B. **Quarantine/Isolation Facilities:**

***Quarantine Facilities*:** The DVR and IC operated rodent Quarantine Facilities are used for rodents entering the NIH from facilities or colonies of unknown or high risk health status.

***Isolation Facilities*:** The DVR, IC, or Shared Facility Isolation Areas may be utilized for rodents entering the NIH from colonies with known, acceptable, low risk health status at the discretion of the IC RIO and facility veterinarian.

An import permit is required to import rodents to these facilities.

1. **Monitoring in Quarantine/Isolation Facilities for Potential Pathogens**:

   NOTE: Direct testing of imported animals provides the best indicator of their health status.

   a. **Test procedures for animals in Quarantine Facilities** are designed to comply with this policy and are performed in accordance with the Quarantine Facility's standard operating procedures. The IC RIO and/or Facility Veterinarian may request direct testing of imported animals, use of direct/contact sentinels, or use of indirect sentinels to test for LCMV and Hantavirus (ex. for rodents not reared under laboratory conditions). All imported animals will be direct tested for endo- and ectoparasites. Animals will be considered for release from Quarantine upon receipt of negative results from tests performed using direct serology for immunocompetent animals, cohabitation with direct sentinels, or polymerase chain reaction (PCR) testing for rodent pathogens and parasites.
   b. **Testing procedures for animals in isolation areas** are designed to comply with this policy and the requirements of the receiving facility. Testing imported animals for endo- and ectoparasites is highly encouraged (at the discretion of the facility veterinarian overseeing the isolation). Additional testing by serology, PCR, or a combination thereof is decided after a thorough review of the health history of the imported animals, the health history of the sending facility, and the specific pathogen-free status of the receiving facility.
   c. **Non-standard testing** will be conducted as requested by the IC RIO and/or the facility veterinarian

2. **Release of Animals from Quarantine/ Isolation Facilities**

   a. The NIH or IC RIO offers animals for release when test results indicate that the animals are free of LCMV and Hantaviruses, if applicable. Release from quarantine is documented using NIH Form 2369-2 "Rodent Quarantine Release." A summary of quarantine test results is provided on this form to the receiving Facility Veterinarian and the IC RIO. IC Quarantine Facilities will provide this report to the NIH RIO. On request, IC isolation sites will provide test results for LCMV and Hantavirus, if applicable, to the NIH RIO. If confirmed test results indicate that the quarantined rodents have unanticipated LCMV, Hantaviruses, or Ectromelia virus, positive animals will either be relocated to an off campus non-NIH holding facility or be immediately euthanized following discussions with the importing institute veterinarian.
   b. The facility veterinarian for the receiving facility must evaluate the health status of the animals in light of that facility's policy. If the rodents have pathogens that are not acceptable at the facility they are slated to enter, the owning IC may elect to find alternative housing and eradicate the

pathogen(s). If the eradication process is conducted in DVR Rederivation/Special Studies facilities, it must be accomplished within a reasonable period of time; reasonable period of time is dependent upon other demands for the use of the Rederivation/Special studies space. If rederivation is used, the procedures should meet the guidelines adopted by the Federation of International Mouse Resources (FIMRe), as modified for rodents. (See "Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm")

3. **Establishment of Quarantine Facilities**

Rodent Quarantine may be conducted at facilities other than DVR Quarantine Facilities. IC Quarantine Facilities must meet the definition of "Quarantine Facility, Rodent." The NIH RIO must first review a written outline of the procedures to be used to protect both rodent colonies and personnel from LCMV, and Hantaviruses if applicable, during the quarantine period and also, if applicable, upon subsequent entry into an NIH facility. Documents must include the location of the facility, standard operating procedures governing policies, procedures and practices of the quarantine, and individual accountable for the site. Unresolved issues between an IC and the NIH RIO shall be brought to the RIAS for resolution.

II. Flowchart - Introduction of Rodent Products and Rodent Pathogens from Non-Approved Sources:

A. Rodent Products and Rodent Pathogens for *In Vitro* Use

Rodent products and rodent pathogens for *in vitro* use **only** (those that never contact reagents, cells, etc., to be used in live rodents) **do not fall under this policy**. However, the senior laboratory Principal Investigator(s) (PI) or laboratory/branch chief(s) must ensure that products for *in vitro* use are handled and disposed of in a manner that: 1) prevents accidental exposure/contamination of personnel or rodents and, 2) prevents the inadvertent introduction of the agent(s) or material into other NIH facilities. *In vitro* experiments utilizing a natural rodent pathogen (e.g. Ectromelia virus, lymphocytic choriomeningitis virus (LCMV), epizootic diarrhea of infant mice virus (EDIM), mouse hepatitis virus (MHV), mouse parvovirus (MPV), murine norovirus (MNV), *Helicobacter*, etc.) must be performed with appropriate caution using biosafety level 2 (BSL2) practices or greater as required for zoonotic agents.

NOTE: The APD and/or the NIH Biosafety Officer (BSO) can assist laboratory personnel in the development of policies and procedures for the safe handling of rodent products and rodent pathogens. In general, rodent pathogens must be handled in a certified biosafety cabinet. All contaminated materials must be disposed as medical pathological waste or be chemically inactivated.

B. **Rodent Products and Rodent Pathogens for *In Vivo* Use:**

Rodent pathogens for *in vivo* use must be described in the Principal Investigator's approved Animal Study Proposal (ASP); and have the concurrence of the facility management where the animals being used are housed prior to the commencement of work.

Rodent products for *in vivo* use must meet the NIH minimum health standard. Their introduction requires the electronic submission and approval of the NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use *In Vivo* Biological Assessment". The following exceptions do not require a permit: 1) products contained in commercially available test kits, 2) reagents that have been produced (e.g. in bacteria) processed (e.g. affinity purified antibodies) in a manner that shall exclude or inactivate all pathogenic agents and, 3) rodent products containing a known pathogen which has been approved on an ASP used to intentionally infect rodents for *in vivo* studies of the pathogen.

1. **Rodent Products: Other than Frozen or Fresh Embryos, Sperm, Oocytes and Ovaries**

    a. The Principal Investigator (PI) should first ensure that the procedures and rodent products, or treated materials to be used *in vivo* are listed on an approved Animal Study Protocol (ASP). If not, they must submit an amendment to add the product.
    b. The PI must complete and submit a NIH Form 2369-3, "Application for Rodent Products or Rodent Pathogens for Use *InVivo* Biological Assessment" to the IC RIO for approval.
    c. Routinely, the IC RIO will request testing of the material using Polymerase Chain Reaction (PCR) or Mouse Antibody Production (MAP)/Rat Antibody Production (RAP)/Hamster Antibody Production (HAP) prior to *in vivo* use, to ensure the products are free from LCMV, Ectromelia virus, Hantaviruses and other agents as required by the designated animal facility. Mouse Antibody Production (MAP)/Rat Antibody Production (RAP)/Hamster Antibody Production (HAP) testing may be used as an initial test, or may be used to verify PCR positive results.
    d. For cells or materials obtained from another NIH PI, investigators may submit test data obtained by their collaborator. Both investigators must certify that the materials have had no further exposure to any rodent products since the provided testing was done.
    e. The IC RIO reviews the application and any testing data, and if approved, the electronic system will route it to the Facility Veterinarian. The Facility Veterinarian reviews it for compliance with facility and room specific exclusion criteria and provides final approval.

f. Rodent products exclusively for *in vivo* use that do not meet the minimum health standard, and are not exempted from the standard due to their research use, must be processed to exclude/and or inactivate the pathogenic agents, the import cancelled; or must be disposed if already introduced at NIH, and the pathogens cannot be excluded or inactivated. If product is processed to exclude or inactivate pathogens, it must be demonstrated free of the pathogen prior to approval. The findings must then be reported to the NIH RIO who will alert the NIH IC RIO(s) and keep a record of the findings on file for a period of 3 years.

2. **Rodent Products: Frozen or Fresh Embryos, Sperm, Oocytes and Ovaries**

   a. The freezing of embryos, sperm, oocytes or ovaries provides no assurance that they are free of horizontally or vertically transmitted pathogens. Therefore, the guidelines from the FIMRe are **required** for all imported frozen or fresh embryos, sperm, oocytes or ovaries brought into the NIH; and are **recommended** for all frozen or fresh embryos, sperm, oocytes or ovaries derived from colonies of unknown or suspect health status being brought into a specific pathogen free facility. The reconstitution of lines from frozen or fresh embryos, sperm, or oocytes derived from colonies of unknown or suspect health status, shall follow the same procedures used for embryo rederivation of lines contaminated with unwanted pathogens. Frozen or fresh imported embryos, or embryos derived from *in vitro* fertilization using imported frozen or fresh sperm, or oocytes must be carefully washed prior to implantation into recipient females. (See "Requirements for Handling Imported Mouse and Rat Embryos, Oocytes, Ovaries or Sperm".)
   b. The reconstitution of lines from frozen or fresh ovaries derived from colonies of unknown or suspect health status shall also be carefully washed prior to implantation. In all cases, recipient female(s) and their offspring shall be held in a rodent isolation area or Quarantine facility until their health status is confirmed by the testing. In the case of transferred embryos, a minimum of one recipient mother from each group of transferred washed embryos shall be tested.

3. **Application Process: Rodent Products and Rodent Pathogens for *In Vivo* Use**

   Submit the application using the ORIA system for NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use In Vivo Biological Assessment".
4. The Quarantine Permit Service Office (QPSO), and the NIH Institutional Biosafety Committee (IBC), should be consulted to determine if additional

permits (such as a USDA or wildlife import permit) are required (for reasons stated below). Assistance in making this determination is available from the NIH Biosafety Officer, DOHS - telephone number 301-496-2960.

Click here for Instructions: Rodent Product or Pathogens for *In Vivo*
Click here for Accessible Instructions: Rodent Product or Pathogens for *In Vivo*

III. **Additional Import and Permit Regulations and Guidelines - Quarantine Permit Service Office**

Several agencies of the United States Government regulate and require permits for the importation, transfer, shipment, or exportation of certain animals, animal products, or etiologic agents or vectors of human or animal diseases. Investigators must work with their IC RIO to determine whether an import permit **other than** a NIH Form 2369-1 "Application for Permit to Introduce Rodents" or NIH Form 2369-3 "Application for Rodent Products or Rodent Pathogens for Use *In Vivo* Biological Assessment", covered by this policy, is required. The IC RIO will coordinate with the NIH RIO and the QPSO to come to a decision regarding the need for additional permits. The QPSO will provide investigators with assistance and appropriate application forms to import, export, or transport regulated materials or animals. Import and Export Permits are also available on-line.

1. The USDA Animal and Plant Health Inspection Service (APHIS) has statutory authority to regulate the importation of any animal-derived or biological material that has been in contact with substances that may be contaminated with pathogens of agricultural importance. For example, USDA permits are required for the importation of monoclonal antibodies, hybridoma cell lines, cell cultures, and other biologic materials that have been in contact with a material of animal origin, such as fetal bovine serum. USDA permit forms and information are available on-line. The website is: www.aphis.usda.gov/permits.
2. The Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC) Etiological Agent Import Permit Program Atlanta, Georgia is responsible for regulations involving the importation into the United States or distribution after importation, of any etiologic agent or any arthropod or other animal host or vector of human disease(See NIH MC 1340-1, "Permits for Import or Export of Biological Materials" and 42 C.F.R. Part 71.54). A DHHS permit must be obtained for importation and/or distribution of these materials. The DOHS NIH Institutional Biosafety Committee (IBC) through the Biosafety Officer (BSO) has been authorized by the CDC to issue DHHS import permits, except those involving African origin rodents, which require special CDC approval (See "CDC Fact Sheet on Embargoed African Rodents and Monkey Pox Virus").

3. Finally, the United States Fish and Wildlife Service (USFWS), United States Department of Interior, has the authority under Federal regulations (50 C.F.R. 23) to control the import and export of all wild caught and threatened or endangered species and specimens from such coming into or leaving the United States. For clarification on these regulations, researchers must contact a biologist in the USFWS at (703) 358-2104.

IV. **Additional Information can be found as follows:**

1. For further information on this policy, contact the NIH RIO by e-mail, Global Directory- OD DVR Rodent Import (oddvrrodentimport@mail.nih.gov) or the applicable IC RIO. For additional information on the importation or transportation of any etiologic agent or host or vector of human or animal diseases, or the importation of wild caught and threatened or endangered species or specimens from such, contact DOHS at 301-496-2960.
2. All Federal requirements for the importation of rodents must be adhered to. Copies of the current requirements can be obtained from the NIH Institutional Biosafety Committee (IBC) through the Biosafety Officer (BSO), the NIH RIO and/or the USDA requirements-website, CDC requirements-Permit Officer, Division of Quarantine in CDC at 404-639-8108, or by referencing 42 CFR, Section 71.54.