NATIONAL ENVIRONMENTAL RESPIRATORY CENTER

QUALITY MANAGEMENT PLAN

September 2003

Lovelace Respiratory Research Institute
2425 Ridgecrest Dr. SE
Albuquerque, NM 87108

QUALITY MANAGEMENT PLAN APPROVAL
NATIONAL ENVIRONMENTAL RESPIRATORY CENTER

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Appendices A, B, C, D, and E are available via link on the LRRI QA Home Page

EXECUTIVE SUMMARY

The National Environmental Respiratory Center (NERC) is a laboratory research program jointly sponsored by government and industry to improve our understanding of the roles of individual air contaminants to the health effects associated statistically and experimentally with complex air pollution atmospheres. The strategy of the Center is to create, and then analyze, a composition-concentration-response database created by conducting a series of individual inhalation studies of complex exposure atmospheres having different, but overlapping, compositions. Common source emissions are used for the atmospheres. Except for the composition of the exposure atmospheres, the protocols for the individual studies are identical. Data from each study comprise "layers" in a combined database, which will be analyzed to determine the relative contributions of individual air contaminant species, and their combinations, to the health effects. The consistency of methods and quality of the data are absolutely critical to the success of the program.

To help fulfill the mission of NERC and to ensure maximization of the performance of the Center and the reliability of the resulting information, it is the policy of the Center to establish, maintain and implement an effective Quality Management Plan (QMP) that complies with applicable EPA quality requirements for environmental programs and is consistent with the Lovelace Respiratory Research Institute (LRRI) QMP. The NERC QMP describes the overall strategy for a total quality system using ten quality elements. Additional documents, including research protocols, standard operating procedures (SOPs), and policies relevant to quality assurance are developed as applicable for specific projects and work tasks.

The NERC will be managed as one of the research programs of LRRI, which has a longstanding commitment to quality in both research and research support operations. NERC will be managed by LRRI, within the LRRI research management structure. NERC research will be performed principally by the LRRI scientific and technical staff, with the involvement of other scientists as needed to accomplish the research strategy of the Center. Achieving and continuously improving quality is the responsibility of all personnel. Both NERC and LRRI management are committed to integrating quality requirements and performance standards into daily work, to providing properly qualified individuals to perform the work, and to ensuring adequate training, resources, and administrative support to meet Center quality objectives.

1.0 QUALITY SYSTEM MANAGEMENT AND ORGANIZATION

1.1 Program Quality Policy

Quality excellence is an integral part of the research and research administration and support operations of NERC. It is NERC policy to develop, implement, and maintain a comprehensive quality assurance program to establish and cultivate principles that integrate a quality culture into daily work and to provide definitions for quality that ensure consistent understanding and communication. It is the policy of NERC to conduct research operations, analysis of data, and interpretation and reporting of results in a manner that withstands rigorous scrutiny and thus supports use of its results as a foundation for high-level regulatory and technological decision making. Moreover, it is the policy of NERC to manage quality in a manner consistent with the high standards of quality maintained by LRRI and within the specific guidelines of the LRRI Quality Management Plan, LRRI Policy No. 601 "Research Quality Assurance," and LRRI Policy No. 704 "Scientific Misconduct in Research," attached as Appendices A, B, and C, respectively.

1.2 Program Organizational Structure and Communication

1.2.1 Organization

The management structure of the NERC program is depicted in Figure 1. The NERC Director has overall responsibility for the program and is accountable to the External Scientific Advisory Committee (ESAC) and sponsors. The Director is primarily responsible for financial resources, planning, organization, and direction. The Director is ultimately responsible for the progress of the Center and for program quality. The Director approves the Quality Management Plan (QMP), research protocols, SOPs related to data management, and publications.

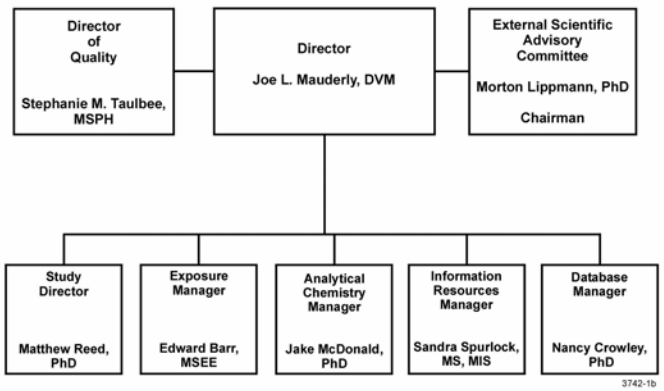

Figure 1: NERC Management

The ESAC is an independent advisory group that is integral to management of the Center. The ESAC worked with the Center Director to develop the Center's fundamental strategy and guide the development of the program. The ESAC is explicitly vested by Center management with approval authority for major strategic and experimental decisions. ESAC members are selected for their expertise and breadth of perspective, and although opportunity is given to sponsors to comment on appointments, the ESAC is not a representative body of the sponsors. Explicit accountability to the ESAC provides NERC management with a level of independence from the diverse and sometimes conflicting agendas and views of the sponsors. Sponsors are kept fully informed on NERC operations and preliminary results, and their advice is sought in all major decisions; however, the only ultimate recourse of the sponsors in influencing Center direction lies in their support of, or withdrawal of support from, the Center.

NERC quality assurance operations are managed within the LRRI quality structure. The LRRI Director of Quality manages the LRRI Quality Assurance Unit (QAU) and reports directly to the LRRI President/CEO. The Director of Quality and the other LRRI quality assurance staff are independent from the conduct of research. The Director of Quality is responsible for the oversight of NERC quality assurance procedures, including auditing, and approves the NERC QMP. The Director of Quality provides audit reports and other quality-related information to the NERC Director and to LRRI Management.

The NERC Study Director is responsible for developing protocols and coordinating the day-to-day research operations and data flow.

The NERC Exposure Manager is responsible for the conduct of inhalation exposures.

The NERC Analytical Chemistry Manager is responsible for the analysis of the composition of the exposure atmospheres, both for measurements performed in-house and for scientific management of external contracts.

The NERC Information Resources Manager is responsible for the contents of the NERC Web Site and maintaining the web-based literature citation database.

The NERC Database Manager is responsible for the structure and maintenance of the database that serves as the repository for NERC results. The Database Manager is responsible for movements of data sets into the interim and final databases, for working with investigators to

ensure adequate documentation of data, and for making data sets available to the public upon approval by the NERC Director.

Because NERC functions as one of the research programs of LRRI, its research operations are conducted within the LRRI line management framework. The LRRI organizational chart is presented in Figure 2.

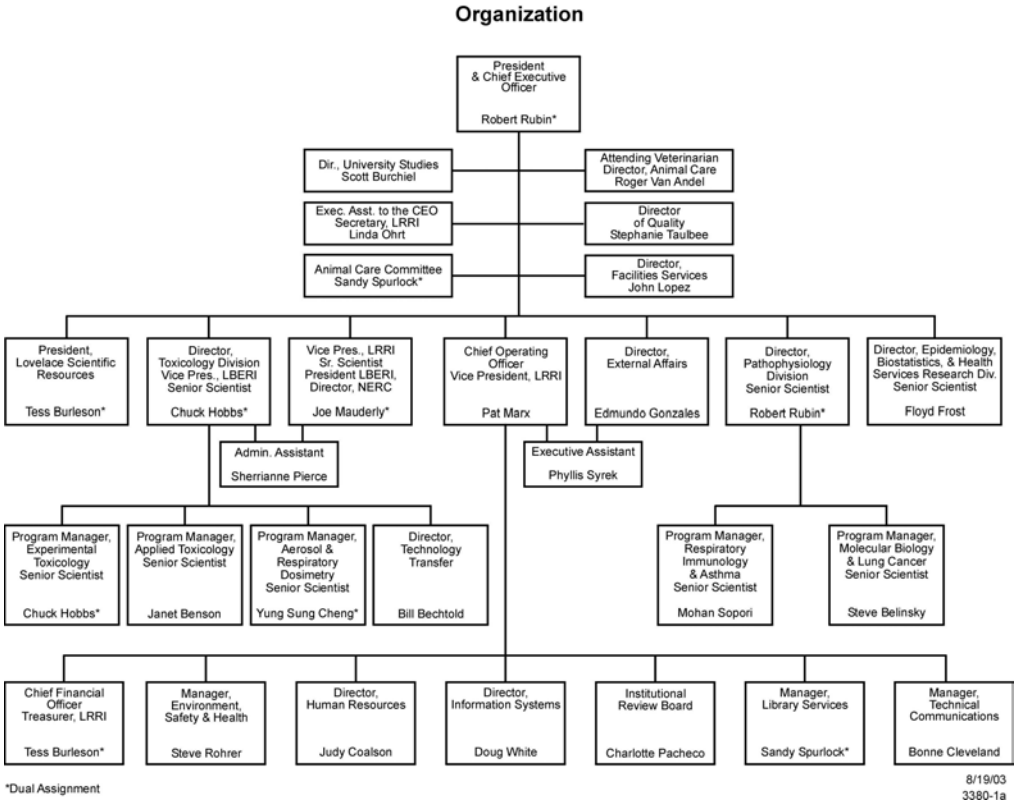

Figure 2: LRRI Organizational Chart

The LRRI President/CEO, under the guidance and oversight of the LRRI Board of Directors, is responsible for LRRI policy and for all research and administrative operations. The President/CEO approves the NERC QMP and has ultimate responsibility for its implementation. The LRRI Director of Quality, Attending Veterinarian/Director of Animal Care, Chief Operating Officer, and Director of Facilities Services all report to the President/CEO.

The Director of Quality is responsible for administering the LRRI QMP. The LRRI Quality Assurance Unit (QAU) conducts quality audits; reviews and approves quality assurance project plans, research proposals, research protocols, and SOPs; provides central indexing of research protocols, laboratory notebooks, and SOPs; and coordinates archiving services for research study records. For regulated safety and efficacy studies, the QAU assures management

and sponsors that studies are conducted in compliance with U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCP) or U.S. Environmental Protection Agency (EPA) Good Laboratory Practice (GLP) regulations. The QAU maintains a master schedule of studies and maintains the central data archives as defined in GLP regulations.

The Attending Veterinarian/Director of Animal Care is responsible for the care and maintenance of laboratory animals and for ensuring that LRRI animal facilities meet requirements set forth by the U.S. Department of Agriculture (USDA), by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International), and by the Public Health Service. The Attending Veterinarian/Director of Animal Care coordinates the activities of the Institutional Animal Care and Use Committee (IACUC) that reviews documents (e.g., research proposals, protocols, and procedures) that describe the use of laboratory animals to ensure compliance with the USDA regulations and Public Health Service policy.

The Director of Facilities Services is responsible for the design and construction of new or remodeled facilities, maintenance of existing facilities, facilities services, facilities security, and the design and fabrication of unique research equipment and systems fabricated in-house. The Facilities Services organization determines performance specifications and design criteria, reviews drawings, maintains a central file for facility drawings and facilities equipment maintenance, and conducts design review and construction inspection associated with the above functions.

As a Vice President of LRRI, the NERC Director also reports directly to the President/CEO, ensuring top management attention to the Center.

The research staff reports to the President/CEO through the Directors of Toxicology and Pathophysiology. These directors are responsible for research line management, including development and use of the controlling documents (proposals, research protocols, SOPs), technical training, animal care quality and compliance with applicable animal use requirements, record keeping, data collection processes, instrumentation, calibration, and reporting of research results. The NERC Study Director, Exposure Manager, and Analytical Chemistry Manager report to the Director of Toxicology.

Other support activities report to the President/CEO through the Vice President/Chief Operating Officer, who is responsible for providing quality administrative and research support services performed in compliance with applicable federal, state, and local requirements.

The Chief Financial Officer (CFO) is responsible for the financial management expertise and processes required to operate efficiently and in compliance with all applicable regulations. This organization prepares budgets, processes payroll and related payroll reports, provides timely payment of supplies and services, and allocates costs of in-house and indirect services. The organization provides monthly detailed accounts of NERC financial resources, expenditures, and commitments to research managers. The CFO is responsible for the Grants and Contracts Office, which is responsible for pre-award and post-award activities related to grants and contracts. The CFO also is responsible for the Procurement and Property Unit, which is responsible for purchasing supplies, equipment, and services (including construction and architect-engineering services), as well as receiving, handling, storing, and shipping activities. This organization reviews purchase requisitions to ensure that they are completed properly and that the user's and quality specifications adequately describe the item or services requested. In addition, this organization receives and stores expendable supplies, identifies and controls capital equipment items using a property numbering system, maintains an equipment database, and prepares materials for shipping out of the Institute.

The Environment Safety & Health (ES&H) Manager is responsible for employee occupational health and safety, environmental compliance and monitoring, hazardous material controls, industrial safety, fire protection, and hazardous waste management. The ES&H organization reviews processes (construction design, equipment specifications, chemical use, chemical purchase requisitions, and work permits) and conducts training. This organization has authority to suspend any ongoing operation where hazard to personnel or the environment necessitates.

The Director of Human Resources is responsible for recruiting personnel, coordinating performance reviews of all employees on no less than an annual basis, and managing other personnel-related issues.

The Director of Information Systems is responsible for computer services including obtaining and managing all computer-related resources (e.g., hardware, software, and data

communications and personal computers). The NERC Database Manager reports to the Director of Information Systems.

The Library Services Manager is responsible for meeting information needs for research and administrative staff, including maintaining on-site and electronic library collections and services, providing interlibrary loans, providing training in the use of on-line and Internet information sources, performing searches of on-line and Internet databases, providing records management, and maintaining institutional archives. The NERC Information Resources Manager is also the LRRI Library Services Manager.

The Technical Communications Unit (TCU) Manager is responsible for producing written and graphical technical information products for the open literature and public presentation. The LRRI TCU provides editorial review of manuscripts and reports as part of the rigorous in-house review process. This organization provides graphic design and production, photography, desk-top publishing, word processing services, document conversion between systems and software, and a central indexing for manuscripts, publications, and presentations.

1.2.2 Communication

NERC quality objectives, policies, and procedures are communicated in writing to investigators, who are responsible for ensuring that their subordinate staff are aware of necessary information and conduct research in accordance with the objectives. Meetings of NERC investigators and key support staff are held periodically for planning and coordination purposes and when other issues arise. E-mailed messages are used frequently to communicate with all key personnel.

NERC research is conducted under formalized protocols, which are reviewed and approved by the ESAC; co-investigators; NERC management; and LRRI QAU, Animal Care, and ES&H personnel. The protocols, which describe methods and list SOPs, are distributed to all investigators, who are responsible for ensuring that their subordinate staff are aware of, trained on, and follow the protocols and SOPs.

NERC progress and preliminary and final results are communicated to the ESAC and sponsors at an annual meeting and in scientific presentations. The ultimate communication of NERC findings is publication in peer-reviewed literature.

LRRI quality objectives, policies, and procedures are communicated to LRRI research and support staff through dissemination of the LRRI QMP (Appendix A), formalized policies (e.g., Appendices B and C), memoranda, and employee meetings. Formalized policies are available to employees on the LRRI Intranet (LRRINET), and all employees are required to sign acknowledgement of reading and agreement to comply with certain policies, including Scientific Misconduct in Research (Appendix C).

Results of quality assurance audits of study data are presented to the NERC Director and LRRI Management in writing, as well as to the cognizant investigators. Actions to remedy findings are tracked, and data sets must be audited by the QAU before being considered final and moved into the final database.

1.3 Technical Activities

The technical activities of the NERC program comprise the conduct of multiple identically designed studies of adverse health effects in rodents exposed daily for up to six months by inhalation to physically and chemically complex atmospheres consisting of multiple dilutions of common source emissions (such as engine emissions, wood smoke, road dust, tobacco smoke, and cooking fumes). Animal "models" consisting of different ages, genders, and strains of mice and rats are exposed for different times, varying by the health outcome being measured. The exposure atmospheres are characterized at a high level of detail. Numerous physiological, cellular, biochemical, and histological health outcomes are measured. Results are analyzed statistically to determine exposure-response relationships for the health endpoints within studies; comparisons are made among exposures (studies); and the combined data from all studies are analyzed to determine composition-response relationships that extend across pollutant mixtures. In addition, a searchable, publicly available database of literature citations relevant to NERC exposures and health outcomes is maintained.

1.4 Communicating the Program's Quality System

Communications are discussed above in Section 1.2.2.

1.5 Resources

The development and refinement of NERC quality assurance processes, data audits, reports, and tracking of corrective actions and training are managed within the LRRI QAU. These functions are provided by LRRI and supported largely through the federally approved indirect cost rate applied to NERC (and other LRRI research) expenditures. A small amount of

quality assurance personnel time for specific NERC-related tasks is budgeted directly from Center funds and supported jointly by all sponsors. Research personnel time for quality control activities, training, protocol and SOP development, and associated costs are charged directly to NERC as research costs.

1.6 Authority to Stop Work for Safety and Quality Considerations

The LRRI President/CEO has authority to stop work for any reason, including safety, quality, animal care, research misconduct, under-financing, or other concerns. The NERC Director also has authority to stop work across the program or the work of individual investigators for those reasons or for underperformance. The LRRI Director of Quality does not have direct authority to stop work, but has the responsibility to inform and advise the NERC Director, and ultimately the LRRI President/CEO, about quality concerns. Such concerns may include evidence of improper or insufficient quality procedures, evidence of lack of sufficient attention to quality, or evidence of research processes yielding data that are unverifiable. The LRRI ES&H Manager has authority to stop work immediately for safety concerns. The LRRI Attending Veterinarian/Director of Animal Care has authority to stop animal research for inappropriate or unsafe use of animals. The ESAC has authority to advise NERC management to stop work, or to not initiate a particular effort, for scientific or strategic reasons.

1.7 Management Assessment of Quality System Adequacy

NERC quality assurance systems and specific actions and policies are topics for review at the annual meeting of the NERC ESAC and sponsors.

Quality operations in general, and current developmental activities and issues of the LRRI QAU are reviewed at the bi-weekly meeting of the LRRI Senior Management Group, which includes LRRI top administrative and research managers (i.e., most of those on the organization chart in Figure 2).

Certain aspects of NERC quality operations, such as experimental schedules, status of audits, data flow, and experimental difficulties are reviewed in a weekly meeting together with reviews of all other LRRI projects involving inhalation exposures. This facilitates awareness of issues in “real time” and timely corrective actions.

NERC quality assurance operations benefit greatly from the fact that some of LRRI’s research is conducted in accordance with GLP quality assurance requirements. The need to

conduct research in compliance with FDA GCP or EPA GLP regulations, and the periodic agency and sponsor reviews of LRRI quality operations that such work entails, result in continuous improvement of quality operations in accordance with the highest industry standards. Although NERC research is not conducted in complete accordance with GLP requirements, it is conducted in the "spirit of GLP" and incorporates most of the protocol, SOP, sample handling and analysis, exposure characterization, data handling, animal care, safety, data auditing, and archiving practices used in GLP studies. The need for capability to comply with GLP requirements, the conduct of NERC research by the same staff and in the same facilities as GLP research, and the periodic stringent quality reviews engendered by the conduct of GLP work ensures strong attention to quality issues and drives continuous development and review of LRRI quality assurance operations.

2.0 QUALITY SYSTEM AND DESCRIPTION

2.1 Quality System Elements

NERC quality goals and systems are described in this **QMP**, which by reference and because most NERC research is conducted at LRRI, incorporates the LRRI QMP (Appendix A). All NERC research is conducted within formalized, approved protocols. Research processes are described in either the protocols or in SOPs. Individual investigators maintain procedures for, and records of, equipment maintenance and equipment and process validation.

NERC data are managed and communicated in accordance with the NERC Data Policy and NERC Data Management SOP (both documents are attached as Appendices D and E, respectively). These documents describe levels and steps of data management processes and records, including laboratory records and official laboratory notebooks, electronic data files, quality control checks performed by investigators, the interim database for pre-audited data, quality assurance data audits performed independently by the QAU, corrective actions to reconcile discrepancies identified by audits, the final database for post-audit QA-approved data that may be analyzed and reported as final, and the public database for elements of the final database released for public access.

2.2 Quality Management Plan Reviews and Revisions

The NERC QMP is reviewed annually by the NERC Director, the LRRI Director of Quality, and the NERC Study Director for adequacy of quality systems and for currency in describing current organizational structure and quality processes.

3.0 PERSONNEL QUALIFICATION AND TRAINING

3.1 Personnel Training and Qualification Procedures

It is the policy of LRRI that all employees have training appropriate for their job. Qualifications and training requirements are determined by function, both by Institute policy and by line management on a case-by-case basis. Training encompasses new employee orientation on safety issues and Institute policies, "on-the-job" training for specific tasks by demonstration of tasks and coaching followed by demonstration of competence by the trainee, attendance at classroom lectures and demonstrations, reading SOPs followed by signed statements that the SOPs have been read and understood, and attendance at external courses or workshops. A list of current SOPs is maintained on LRRINET. Line management determines the SOPs relevant to each job and to each research protocol.

3.2 Formal Qualifications and Certifications for Specialized Activities

Most positions require certain pre-existing academic or experience qualifications. Specialized formal qualifications and certifications are required for certain functions. The NERC Study Director is required to be a Diplomate of the American Board of Toxicology and to have previous experience as a director of complex, multidisciplinary animal studies. The NERC Pathologist is required to be a Diplomate of the American Board of Veterinary Pathology and experienced in anatomic pathology of the respiratory system. The LRRI Attending Veterinarian is required to be a Diplomate of the American College of Laboratory Animal Medicine. The QAU is required to contain a Certified Records Manager and a Registered Quality Assurance Professional-Good Laboratory Practices. The ES&H organization contains individuals with certifications in health physics and industrial hygiene.

3.3 Training Documentation

Training is documented formally, and training records for all personnel are maintained in an electronic database by the QAU. The database is updated continuously as training is documented. The training record of each employee is reviewed no less often than during the annual performance review. Hardcopy files of credentials and special training also are maintained in the employee personnel files.

3.4 Evidence of Personnel Job Proficiency

Line management is responsible for ensuring that subordinates are trained for their assigned tasks and responsibilities, and that acceptable proficiency is maintained. Training

records indicate whether or not employees have reviewed pertinent SOPs or received other training as specific procedures change. Supervisors are responsible for continuously monitoring general and task-specific proficiency. Findings resulting from quality control checks and quality assurance audits are a source of evidence for a lack of proficiency. The performance of all employees is reviewed formally no less than annually.

3.5 Re-Training

Re-training is conducted both on a periodic recurring basis and as needed on a case-by-case basis. Employees in relevant job functions receive recurrent training in safety and animal operations. Line management is responsible for determining the need for re-training for specific tasks or procedures on the basis of: 1) evidence of lack of proficiency; 2) length of time since the task or procedure was last performed; or 3) changes in the task since it was last performed. The latter pertains especially to SOPs, which are both reviewed bi-annually and updated as necessary when procedures change. Employees are notified of procedure changes via e-mail.

4.0 PROCUREMENT OF ITEMS AND SERVICES RELATED TO TECHNICAL ACTIVITIES

4.1 Procurement Planning and Control

The Accounting and Procurement Units are responsible for ensuring that controls are in place to assure compliance with applicable legal and federal acquisition regulations. Submission of a purchase requisition by research or support staff users initiates procurement documentation. A review of procurement documents for commercially obtained items and services is made by the requester or designated person who has adequate technical understanding of the scope of work to ensure that specified quality assurance requirements have been met.

Only the Procurement Unit has authority to purchase major items and services. This organization identifies qualified suppliers and ensures that these suppliers provide acceptable items and services that meet established quality requirements. As appropriate, suppliers are required to provide material safety data sheets and adequate operating and maintenance instructions. Other factors to be considered in the procurement, acceptance, use, and disposal life cycle are: 1) the hazard or volume of the item requested, 2) shelf life, 3) rotation of stock, 4) suspect/counterfeit parts, and 5) disposal and recycle issues.

All purchase requisitions are required to include the accounting code indicating the project or cost center to be charged. The Accounting Unit is responsible for ensuring that charges are allocated properly and for documenting expenses.

4.2 Procurement Technical and Quality Requirements

Technical and quality requirements for most procurements are specified by the requestor of the procurement action. Both technical and quality requirements are included in the purchase requisition as appropriate. The Procurement Unit is responsible for working with functional organizations (e.g., Facilities Services, QAU) to identify technical and quality requirements of large procurements and contracts.

4.3 Procurement Document Specification of Verifying Supplier's Conformance

The Procurement Manager is responsible for ensuring that, when appropriate, purchase orders and contracts issued to vendors contain information noting how the supplier's conformance to specifications will be verified, including specific procedures for acceptance inspection and testing. Line management defines work processes and other circumstances that require formal inspection and acceptance testing according to specific institutional or other requirements.

4.4 Procurement Document Review

The Procurement Manager, reporting to the Chief Financial Officer, is responsible for ensuring that all procurement documents are appropriately reviewed.

4.5 Review of Changed Procurement Documents

The Procurement Manager is responsible for ensuring that all changes to procurement requests or documents receive the same review and approval as the original and that all changes are verified as meeting technical and quality requirements.

4.6 Review of Procured Items and Services

Procurement and property management staff inspect incoming equipment and supply items upon receipt and verify that the items match descriptions in the purchase order. The requestor of supplies and services is ultimately responsible for reviewing compliance of the items or services received with specifications, or non-specified standards of quality and performance, before items are placed into use. The Procurement Unit is responsible for verifying with the requestor that large or complex items or services meet criteria specified in the procurement action.

5.0 DOCUMENTS AND RECORDS

5.1 Records Management Procedures

A study file is maintained for each NERC study, including the protocol and documentation of animal movements and identification, exposures, characterization of the exposure atmosphere, and evaluations of effects. Raw data and other experimental records are maintained by individual investigators in official laboratory notebooks. Final data are retained in the NERC electronic database, as described in Appendices D and E.

The records management program is administered by the QAU. Processes are in place to ensure that records are protected and scheduled for review of disposition and retention. For federally funded contracts, the General Records Schedules approved by National Archives and Records Administration or agency-specific record schedules are used. Records for federal cooperative agreements are retained for a minimum of three years after closeout of the agreement. All NERC study files are retained at least through the end of the program, which is beyond the three-year time for the earlier studies.

5.2 Document Control

Changes to documents are reviewed and modified by the same functional organization that originated the original document. Documents and records are reviewed for conformance to quality system requirements and approved by authorized personnel before general use. Each organization ensures that competent personnel prepare documents and that documents are reviewed within each organization for technical accuracy. Documents are approved by authorized personnel for release and are distributed to and used at locations where the activity is performed. Document control includes ensuring that revised documents receive the same measure of control as the originals.

NERC policy documents and reports are approved by the NERC Director and are controlled by the TCU. NERC research protocols are reviewed by the investigators, the NERC Director, and the ESAC, and are approved by the NERC Director for technical and scientific merit and by the QAU for quality requirements. Research SOPs are approved by LRRI research Division Directors after compilation and review by investigators and technical staff. Protocols and SOPS are controlled by the QAU. Research results (abstracts, reports, and manuscripts) documents are reviewed by the co-authoring investigators and by the NERC Director for technical and scientific merit and for editorial content by the TCU. Abstracts and manuscripts

are controlled by the TCU. Administration and support operations plans, procedures, manuals are approved by the LRRI Chief Operating Officer and are controlled by the functional organization that originated the document(s).

The positions within each organizational group designated to issue documents are identified in SOPs. Internal distribution of selected documents is documented in a distribution list maintained with each document. When receipted acknowledgements are required (e.g., some ES&H documents), the requirements are documented in specific organizational procedures.

6.0 COMPUTER HARDWARE AND SOFTWARE

6.1 Conformance to User and EPA Requirements

6.1.1 Hardware

Information technology infrastructure is designed to be compatible between the two campuses (LRRI North and LRRI South) and is based on HP Pro Curve technology. Hardware and firmware allow the use of virtual local area networks (VLANs) that provide enhanced network security for data collection and data segregation. Both campuses are configured and managed under a single network domain. The campuses are connected by a secure encrypted microwave bridge that provides high-speed data connectivity. Each campus has an independent network while sharing resources and components between campuses. Both campuses have individual compliant domain controllers, SQL servers for data collection and storage, general file servers, and share a common data/system backup system. Compliant data backup servers perform file/database replication between both campuses as a safeguard against system outages and to enhance the data recovery processes. Most applications supporting both campuses are based on thin client technology and are supported with clustered web servers. The servers manage data jointly and are located at each campus, allowing for redundancy and independent operations if communication is lost between the campuses.

The LRRI North Campus provides a gateway to the Internet for both campuses, which affects e-mail and Internet access in the event communications between the campuses is disrupted. System routers are configured with modems to automatically provide an alternate connection to the Internet at the North Campus in the event of a lost communications link between the campuses. Network security requires secure desktops, and the network is protected from the Internet by a firewall that restricts protocol traffic and manages relevant Internet security.

6.1.1.1 Hardware Management

Hardware installation, configuration, and retirement are managed using a network management SOP that mandates processes to control and approve changes that ensure that hardware changes are adequately documented. Hardware/firmware updates are managed using the same procedures to ensure control and compatibility of network hardware.

Each component on the network receives a quality review, and a file system is established for each piece of hardware to assist in managing the components' configuration and qualified state. These files contain configuration records for each network hardware component.

6.1.2 Software Development

Written requirements are created before software is developed. These requirements are approved by the primary users of the system. The approved requirements are placed in a change tracking system, so all changes are documented, and all versions are available. Databases and the change tracking system files are backed up nightly. A set of the backups are placed off-site for storage. Data access is controlled through the use of a login and password for each user. The login determines what data the user can view, edit, or delete.

6.2 Configuration Testing

The software is tested to the requirements in accordance with a system test plan. This initial testing is documented in an automated system. The test documentation includes the individual conducting the testing, the version that was tested, and the results of the tests. The system is then released for beta testing by the end users. All requested changes are documented in an automated system and tracked from initiation through resolution, which includes retest of the changed portions of the system.

6.3 Configuration Change Assessment

Requested software changes are documented in an automated change control system. The change control system documents the steps taken to make the change. The documentation includes an assessment of the change, who made the change, to what software, and the amount of time for the change. The testing of the change is documented, and then the change is released. Changes to database data are managed through a process that includes documentation of the data, insertion of the data into the database, and a formal review of the original data and the data in the database by the QAU. Documentation is maintained that describes each original file and the results of each quality assurance audit of the data.

6.4 Re-Testing and Re-Documentation

Each version of the software is tracked in a version control system. This system allows checking in and out of code and documentation and tracks all changes made to code and documentation from initial creation through the current version. It also tracks the date and time the code and documentation are checked in and the person who made the changes.

6.5 Scientific Data Management

Scientific data capture, processing, and management to ensure data validity, integrity, and security is a managed process. Each study is reviewed for the best processing and handling practices for its data. LRRI employs a robust and secure information infrastructure to accommodate data management that is compliant with acceptable industry practice and customer requirements. Whenever possible, study data are captured over a secure network and written directly to a compliant Microsoft structured query language (SQL) database. The database provides a full audit trail for the data, security from routine backups of data, deployment of secure VLANs, designed redundancy through replication of SQL database servers, and analytical capabilities that do not alter the raw data. If it is determined data can not be captured over the network for writing directly to a secure database, SOPs and quality processes are designed to ensure the integrity and compliance of the data processes. Attributes that contribute to the compliant management of scientific data are:

- Desktop security is reviewed and either operating systems access restrictions are applied or other security procedures are imposed such as secure computer enclosures or SOPs written to cover potential breaches in security.
- VLANs are established that restrict access to network components and isolated network traffic to enhance data security and integrity.
- Exposure data are collected using Lab View Professional®, which allows development, testing, and management of specific data collection applications.
- Lab View tools also are configured to allow the simultaneous writing of data to local collection computers and to compliant databases.

- Databases are backed up using a centralized backup system that accommodates the full backup of databases daily.
- Analysis tools can be developed allowing direct extraction of data from the database while maintaining the integrity of the raw data.

7.0 PROJECT PLANNING

7.1 Planning and Documenting the Generation, Acquisition, and Use of Environmental Data

Because NERC is a laboratory research program, "environmental" data per se are not collected in the program. The complex animal exposure atmospheres generated from common source emissions are characterized to a high level of detail (i.e., equivalent to the detail employed in detailed environmental monitoring, such as the Supersites program, source characterization, and source apportionment). The goal is to contribute a complete physical-chemical speciation of the exposures to the NERC database to facilitate analyses of relationships between composition and health response. The level of speciation was planned by NERC management and the ESAC at the beginning of the program and will remain constant for each of the exposure atmospheres (studies) to facilitate: 1) direct comparisons among studies and 2) analysis of the combined database as a single data set generated by constant methods. The generation and acquisition of these data are described in the study protocols. The general use of the data is described in the Center's strategy and protocols; the specific statistical analytical techniques are selected as the work progresses.

Other data termed "environmental data" are collected to manage and document the conditions under which animals are housed. These data include temperature, humidity, light cycle, and room ventilation rates. The generation, acquisition, and review of these data are described in animal care SOPs. These data are not maintained as NERC "products," but rather are used on an hourly and daily basis to manage animal care operations.

7.2 Identifying and Documenting Type and Quality of Environmental Data Needed

The type and quality of data needed to adequately characterize NERC exposures are described in the study protocols and in analytical and data management SOPs referenced in the protocols.

7.3 Including Key Users, Customers, and Technical Staff in Planning

NERC studies are planned with multiple layers of involvement and approval. The sequence of studies is discussed between NERC management and the ESAC, and is approved by the ESAC. Upon approval to proceed with planning a study, NERC management collects information by discussion with external individuals having relevant experience, seeks external expert advice through consultations and workshops, and works with internal investigator and technical staff to develop a proposed strategy for generating the exposure atmosphere and conducting exposures. The general strategy is discussed with the ESAC and sponsors, typically at the annual ESAC/sponsor meeting, and consensus is reached on the approach. NERC management and investigators then develop the draft study protocol.

7.4 Reviewing and Approving Planning Documents

In addition to the reviews and approvals described in the preceding sections, an Annual Progress Report and written reports of planning workshops are provided to the ESAC and sponsors for review and comment.

NERC study protocols and SOPs are written and reviewed by investigator and technical staff in relevant functional organizations. The NERC Director and ESAC review and approve protocols, which also are sent to sponsor representatives for review and comment. NERC protocols also receive QAU review and LRRI top management review and approval. SOPs are reviewed and approved by managers of functional units.

8.0 IMPLEMENTATION OF WORK PROCESSES

8.1 Implementation of Work According to Planning Documents

All NERC research is conducted according to the study protocols. Upon approval of NERC study protocols, work proceeds immediately at a pace determined by both technical challenges and funding.

8.2 Standard Operating Procedures Documentation

As described above in Sections 1.2.2, 2.1, 3.4, and 5.2, NERC research and LRRI administrative and research support activities are conducted largely according to formalized SOPs that are developed by functional units, approved by line management, and available to all employees in an electronic database maintained on the LRRINET. SOPs are reviewed and either retired, re-approved as written, or updated and approved at no greater than two-year intervals. NERC study procedures not documented in SOPs are described in the study protocols.

9.0 PROJECT ASSESSMENT AND RESPONSE

9.1 Planning Project Assessments

Progress in the NERC program is evaluated continuously by NERC management, and assessment discussions between the NERC Director and Study Director occur on at least a weekly basis.

Two pre-planned, formalized assessment activities occur annually. An annual Progress Report is developed by NERC management and provided to the ESAC and all sponsors each spring. An annual meeting of NERC management and investigators with the ESAC and sponsor representatives is held annually, usually in the late spring or early summer.

Individual sponsors also conduct assessments of a nature and at times of their choosing. These include site visits and requests for presentations at the sponsor location.

9.2 Assessment Planning and Procedures

Quality assessments are described in preceding sections. Some program assessments are planned to occur on a regular, continuously recurring basis. Other assessments occur as issues arise.

The NERC Director attends weekly meetings of LRRI investigators and key technical support staff involved in inhalation exposure studies, and the status of NERC studies and related issues are discussed along with those of other studies. In a weekly meeting, the NERC Director and Study Director review current issues and the status of movement of data into the interim database, through quality assurance audits, and into the final database, and the status of statistical analyses.

The principal high-level program assessment is provided by the ESAC. Progress, difficulties encountered, findings, and plans are reviewed in detail with the ESAC and sponsors at the annual meeting, following development of the Annual Progress Report. This is accomplished through written materials, oral presentations, and discussions, and includes questions and advice from sponsors as well as the ESAC. Other external experts are sometimes brought to the meeting to advise on specific issues.

Other information is disseminated to the ESAC and sponsors throughout the year, including workshop reports, updates on progress, findings, and difficulties, and pre-publication copies of all papers and published abstracts.

9.3 Assessment Personnel Qualifications

The NERC Director has considerable experience in research management at the laboratory, project, and institutional levels, and is qualified to assess day-to-day and strategic progress.

The ESAC is comprised of senior clinicians and air quality, health, and statistical experts and policy analysts selected for their credentials as both producers and users of research data. ESAC members also have considerable experience at the science-policy interface and are thus well qualified to judge not only the progress of the program but also the ultimate utility of the results. Sponsors select representatives among their organizations best qualified to judge progress and provide advice, and most are senior managers with doctoral-level technical expertise.

9.4 Assessor Responsibility and Authority to Stop Work

Authority to stop work is described above in Section 1.6.

9.5 Assessment Documentation, Reporting, and Review

The ESAC issues a written letter report to the NERC Director following each annual meeting. The report contains the ESAC's summary assessment of the program, decisions regarding specific issues, and recommendations for future work. Copies of the ESAC report are provided to all NERC investigators and sponsors and to LRRI top management.

9.6 Assessment Responses and Follow-Up Action

The NERC Director, in consultation with other NERC managers and investigators as necessary, develops a formal, written, point-by-point response to the annual ESAC report. The response is included in the next Annual Progress Report, which is disseminated to the ESAC and sponsors. Responses to the previous year's guidance also are reviewed by the NERC Director during the introductory portion of each annual meeting.

It is the responsibility of the NERC Director to ensure that follow-up actions are taken and that the ESAC's guidance is implemented effectively.

10.0 ASSESSMENT AND VERIFICATION OF DATA USABILITY

10.1 Assessing, Verifying, and Qualifying Data

This section is interpreted as applying to data collected in the environment (e.g., ambient air quality data). The NERC program does not involve the collection, modeling, interpretation,

or reporting of environmental data. The NERC Exposure Manager and Analytical Chemistry Manager are responsible for verifying and qualifying data characterizing the NERC exposure atmospheres.

10.2 Expressing and Documenting Limitations on Data

Not applicable, see Section 10.1 above. (Information on analytical limitations is included with exposure characterization data in the NERC database.)

10.3 Providing Independent Review of Data-Containing Project Reports

Not applicable, see Section 10.1 above. (Reports from the NERC program take the form of peer-reviewed publications, which are reviewed independently by technical experts selected by the editors.)

10.4 Management Approval of Reports

Not applicable, see Section 10.1 above. (All publications and abstracts resulting from NERC research are approved for submission by co-authors and the NERC Director.)

11.0 QUALITY SYSTEM IMPROVEMENT

11.1 Quality Improvement Process

It is the responsibility of every employee to engage continuously in quality improvement in all operations.

The Director of Quality is responsible for the structure, staffing, and procedures of the LRRI QAU. Because the Director of Quality reports to the President/CEO, the President/CEO has management responsibility for ensuring continuous improvement of LRRI quality awareness, policies, and practices.

Quality improvement occurs through three fundamental processes. Improvements are identified and implemented at the initiative of the President/CEO and Director of Quality. Improvements are identified and implemented (or suggested, if they involve formalized quality systems) by employees, and especially supervisors and study managers who observe the quality processes in action daily. The need for improvements also is identified by external regulatory agency or sponsor auditors, and improvements are implemented to maintain compliance with evolving external requirements.

11.2 Preventing, Detecting, and Correcting Quality System Problems

Addressed above in Section 11.1

11.3 Response Actions

Changes in LRRI quality systems in response to problems are approved by the Director of Quality and the President/CEO and are documented by the Director of Quality in the form of memoranda, SOPs, and policies that are distributed to all affected employees. Corrective responses to internal quality assurance audit findings and the closure of findings are documented in study-specific records in the QAU and the study file.