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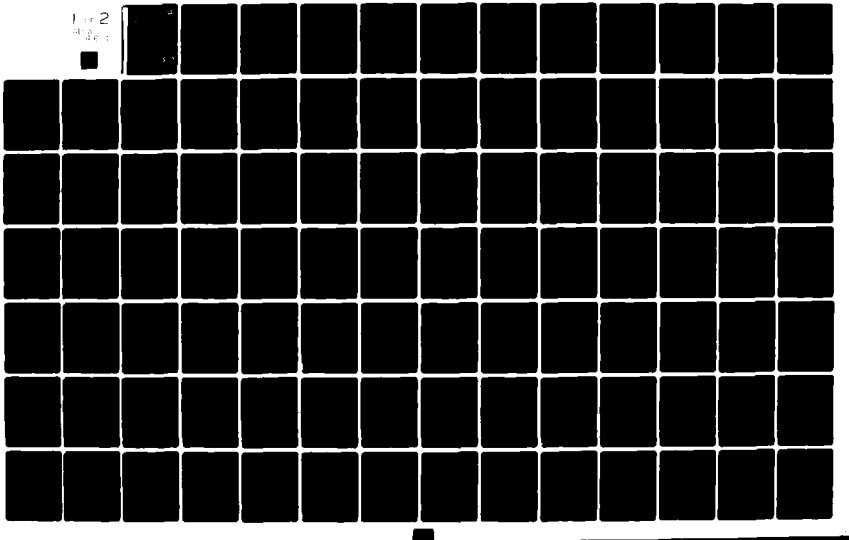

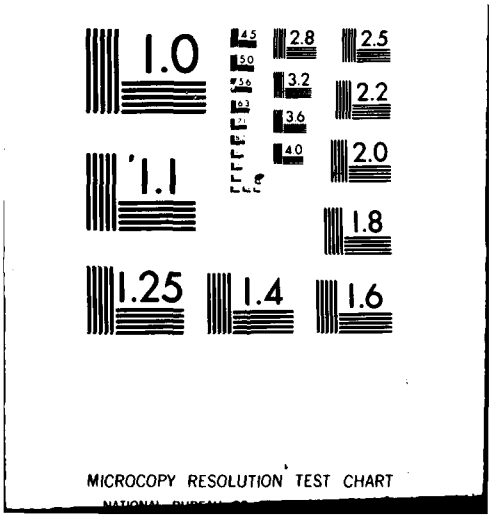
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MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY

FACILITY INSTALLATION REPORT (U)

by

R. A. Wynveen, R. H. Reuter,
R. J. Davenport, J. P. Glennon and G. E. Schiefer

March, 1981

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract DAMD17-81-C-1013

Life Systems, Inc.
Cleveland, OH 44122

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continued-

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This report summarizes plans for technical aspects, facility design, equipment and personnel requirements, and quality assurance for a full service mammalian toxicology testing facility are summarized in this report.

The Technical Plan identifies the business organization, testing requirements, and a generalized scheme for implementing the testing capability.

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Toxicology Personnel Recruitment, Quality Assurance, Toxicology Personnel Requirements, Army Unique Exposures, Toxicology Support Services, Mammalian Toxicology Equipment, LAIR Equipment Availability, Toxicology Testing Costs

20. continued-

The Facility Plan covers the facility's design and construction details. A modular approach was used to allow design flexibility and to establish capability options. Equipment requirements are addressed in the Equipment Plan. These requirements were established for each of the facility's modules. Cost, size, capacity, and special requirements were specified for each item. ~~In the Personnel~~ Plan, specific personnel requirements, recruitment and personnel development are examined. The Quality Assurance ~~The~~ Plan covers protocol and procedure development and outlines responsibilities of the personnel.

A Resources Plan ~~is included which~~ integrates inputs from each of the above plans to determine full utilization testing costs and equipment and facility costs. Options for facility locations are examined and advantages and disadvantages of building a new facility versus renovating an existing facility are compared. Specific conclusions and recommendations are also included.

Reports for the subject contract include three major final reports and twelve supporting documents.

EXECUTIVE SUMMARY

The purpose of the facility installation portion of the Problem Definition Study was to develop plans for the major resources (facilities, equipment, personnel and funding) needed to provide additional toxicology capability and capacity. Since decisions regarding these issues will be made by the US Army Medical Research and Development Command/Department of the Army, the Study Team's efforts focused on generating as much as possible of the information and data upon which the decisions will ultimately be based. Within the Study's scope, these efforts were successful. Nevertheless, there remain unanswered questions and missing information. Recommendations are included for filling these remaining gaps.

To permit the widest possible latitude to the US Army Medical Research and Development Command/Department of the Army or Department of Defense in studying alternatives, Life Systems, Inc., provides in this report design and planning information which is site-independent and which is also compatible with any of the potential business relationships which might eventually be used (i.e., Government-Owned, Government-Operated; Government-Owned, Contractor-Operated; etc.).

Reasonably accurate cost estimates for facilities of various capacities and capabilities were developed. Two model facilities--Letterman Army Institute of Research and the Army's vacant Nuclear Biology Defense Laboratory at Hunter's Point are treated in some detail as to their potential suitability and costs.

Organizational Plan

An organizational plan was developed for a facility which would provide full service toxicological functions and which is, at the same time, suitable for operation as a Government-Owned, Government-Operated; Government-Owned, Contractor-Operated; or Contractor-Owned, Government-Operated. A chart of such an organization is presented. It shows the organizational relationships of the major research/testing functions, laboratories, specialty areas and administrative services.

Scientific and Technical Plan

The testing to be done in meeting the Army's unmet toxicological requirements must take into account certain legal and business objectives as well as scientific and technical ones. All three perspectives, therefore, need to be considered before final decisions are made on the type and amount of testing capability to be established within the Army.

The three basic categories of toxicological testing are general, genetic tests and special studies. Nineteen general toxicological tests most likely to be applicable to the Army's needs are identified, representing combinations of duration, animal species and route of exposure. Costs for each of these tests are presented. A total of 19 standard protocols are also identified.

Five major genetic test categories are identified, some or all of which may be incorporated into the Army's capabilities. More than 20 specific genetic tests are identified within these five categories; costs are presented for each of these specific tests.

Eight types of special studies are identified, six of which are recommended by Life Systems, Inc., to be provided for as a minimum in the Army's capabilities:

- Behavioral
- Oncogenic
- Reproduction
- Teratogenic
- Combined general toxicological and oncogenic
- Combined reproduction and teratogenic

The testing capability eventually selected by the US Army Medical Research and Development Command/Department of the Army will depend on factors such as the level of control desired; funding availability; supply and demand for contractors' testing resources; and the volume, urgency, and timing of testing requirements. Among the kinds of test capabilities that Life Systems, Inc., recommends that the US Army Medical Research and Development Command/Department of the Army include are those which involve Army-unique exposures, inhalation testing related to Army-created environments (weapons, smokes, etc.) and those which are not competitively available elsewhere. Among those that should not be included are those that can be economically contracted out (commercially or to another agency) and long lead time tests where assured quick response is not required.

Facility Plan

The demand for certain toxicological testing facilities and certain professional personnel exceeds the supply, a situation which is expected to worsen during the 1980's. For various reasons, the Army is at a disadvantage in competing for available facilities, a factor which argues for providing in some way for many of its own facilities.

The facility plan developed by the Study Team is divided into an initial five-year phase and a five-year growth phase. This approach will permit efficient, incremental growth in each stage. By not finalizing the second phase design until well into the first phase, the Army will retain the flexibility to incorporate newer technology as it is developed. Incremental growth also realistically reflects the way staff buildup of a new facility occurs, and permits an orderly development of operating procedures, policies, guidelines, etc. that every operation requires.

A modular approach was developed to facility design. Under this concept, a full-service toxicological capability can be created with 63 modular areas and laboratories. Assembled in the proper numbers of each type of module and integrated into one or more sites, this will enable the Army to meet whatever portion of its total requirements it elects to have done in the "facility." It will also permit the use of all of the recommended general toxicological tests, genetic tests and special studies.

The modular concept does not connote a defined size with all rooms based on a multiple of that size, nor a complete lab built off-site and delivered pre-assembled to the site. Rather, each module is defined by five factors:

- Floor plan with dimensions and equipment locations
- Construction information
- Special features
- Special assumptions
- Estimated cost

Use of this concept will provide complete flexibility to provide the desired type and amount of capabilities in the particular site or sites selected by the Army. It also reverses the usual situation where an architect says, in effect, "This is the space you have and it's located there." The modular approach should also help avoid errors of leaving out required facilities through sheer oversight, a situation which can easily occur when concentrating on a large, complex overall facility. Finally, it is an approach which avoids having to re-invent what services/functions/area/labs will be required if the Army postpones development of the facility.

All 63 modules were designed in detail; four are shown in the report as examples.

General specifications were developed covering aspects such as door widths, ceiling heights, wall and floor construction, fire protection, electrical power, air supply, air locks, etc. Specific specifications were developed for each type of module. The annual testing capacity of each module was established as was the estimated cost for each module.

Equipment Plan

The equipment to be needed in each of the 63 modules was defined. It was categorized as essential, desirable and ideal as an aid to prioritizing the Army's equipment-purchase decisions. The lists also contain individual equipment cost, as well as maintenance cost, information which enables useful estimates to be made of the total equipment costs for each module. Identifying all equipment required in a module is also an aid in defining the numbers and types of personnel required (e.g., special equipment operators).

The equipment plan was also divided into two five-year phases but for different reasons than the facility plan--some equipment has a useful life of less than ten years and will have to be replaced. The number of items needed for the first five years was determined so that the first five-year equipment costs could be estimated. The second five-year costs reflect, then, only replacement costs for equipment with less than a ten-year useful life, and are, accordingly, considerably lower than the first five-year equipment costs.

Lists were prepared for extra large and extra heavy equipment which may require special installation or support considerations. An inventory was also prepared of major equipment items at Letterman Army Institute of Research which might potentially be available.

In the detailed floor plans prepared for each module careful attention was paid to equipment location with a view to optimize the flow of work within modules and between modules.

Personnel Plan

Nearly 60 personnel titles to be required by a full-service facility were identified. Seven of these--aerosol chemists, immunologists, pharmacodynamicists, pharmacokineticists, pharmacologists, toxicologists, and veterinary pathologists--are likely or certain to be in short supply. Supply and demand data are presented for several of these categories. Among the impli-

cations of the shortage of personnel is that the facility may have to provide for training/retraining as one of its key functions.

The inertia inherent in a recruiting program for a new facility is described. A minimum of five to six months will be needed to provide the facility's initial cadre, based on the standard ratio of 24 leads being required to hire one person.

A survey of Government-Owned, Contractor-Operated operations revealed the ratio of government staff to contractor staff declines with increasing staff size. In smaller Government-Owned, Contractor-Operated operations (e.g., $5 million annual testing volume) the ratio is about one government person to eight contractor staff. In larger Government-Owned, Contractor-Operated operations ($40 million annually) the ratio is about one to twenty. Based on a plausible volume of $22 million to meet the Army's unmet requirements, a Government-Owned, Contractor-Operated operation would require about 34 government personnel and 450 contractor personnel.

Quality Assurance Plan

Many of the facility's key functions will come under the Food and Drug Administration's and Environmental Protection Agency's Good Laboratory Practice regulations. The regulations mandate creation of a Quality Assurance Unit in facilities performing nonclinical toxicological research and testing. Although observance of Good Laboratory Practice will be required, it should be viewed as an advantage because it will help materially to improve the quality and efficiency of the facility's scientific and management procedures.

A detailed Quality Assurance Plan was developed and is described, including organizational relationships, scope, staff qualifications, responsibilities, procedures, facilities and equipment, etc.

Because it is recommended the facility not begin operation until it has passed a Good Laboratory Practice inspection, early and careful attention needs to be paid to the Quality Assurance function. For example, about 200 Quality Assurance standard operating procedures will be required by the facility. All of these must be prepared and approved before initial operations will be permitted.

Resources Required

Based on a facility consisting of one each of the 63 modules which are used to their maximum capacity to perform the general toxicology tests, genetic tests, and special studies for which they are intended, a total annual testing budget of $27,700,000 would result. At an efficiency of 80 percent, this annual figure would be reduced to $22,200,000.

To renovate Hunter's Point as a facility with 63-module capacity would cost about $8.5 million. To renovate Letterman Army Institute of Research would cost less, the exact amount being dependent on what modules and how many of them would be available. To build a new facility would cost about $12,000,000 (an additional $3.5 million for land, site improvement, utilities, and construction of the shell).

First five-year equipment costs at Hunter's Point will be about $11.4 million; the second five-year costs there would be $4.5 million. Comparable figures for Letterman Army Institute of Research are $6.9 million and $4.5 million, respectively.

Personnel recruitment costs to staff the facility are estimated at $675,000.

The cost of developing quality assurance standard operating procedures will be about $100,000.

Conclusions and Recommendations

About 20 conclusions and 15 recommendations are presented in the report. Some have already been discussed in this Executive Summary. Among the most significant of the remainder are the following:

- Before initiating a facility development program, a clear definition of its specifications is needed (capacity, capability, location(s), schedule, users, sources of funds, etc.)
- The facility's capability should involve more than testing alone: before-testing, parallel-with-testing and after-testing activities can be even more important than testing itself.
- To avoid costly test aborts due to power failures and equipment malfunctions the equipment should be of good quality and well maintained and certain redundancy will be needed.
- A concerted effort should be made to have other federal agencies fulfill some of the US Army Medical Research and Development Command/ Department of the Army's needs. The Environmental Protection Agency, for example, might support construction of an experimental toxic and hazardous waste disposal demonstration process.
- Costs can be reduced if environmental effects toxicology and health effects toxicology are combined for those requirements that relate to the same laws (e.g., Toxic Substances Control Act).
- An epidemiology capability should be included, to focus on Army-unique exposures.
- A portion of the facility's efforts should be directed to applied research to help attract and retain good quality personnel.
- The facility's scientific work should be controlled by a Facility Science Director and also involve an all-Army review team, a non-Army review team and a peer group of advisors.

FOREWORD

A Mammalian Toxicology Testing Problem Definition Study was conducted for the US Army Medical Research and Development Command, Ft. Detrick, Frederick, MD, under Contract DAMD17-81-C-1013. The Study's Principal Investigator was Dr. R. A. Wynveen. COL Alfred M. Allen, Toxicology Project Officer, Letterman Army Institute of Research, was the Contracting Officer's Technical Representative. Mr. Michael F. Travis was the Contracting Officer's Representative. Ms. Jean Smith was the Contracting Officer.

Reports for this contract, DAMD17-81-C-1013, consist of three major final reports and twelve supporting documents. The contract title, MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, is the main title for all the reports. Individual reports are subtitled and referenced with Life Systems, Inc., report numbers as detailed below. Please note that the Life Systems' report numbers in text references are shortened. In the Defense Technical Information Center (DTIC) data base the reports are identified by the complete report numbers (i.e., LSI-TR-477-XXX) and complete numbers must be used for retrieval.

Report Subtitle	Life Systems, Inc. Report Number
Final Reports:	
Part 1. Comparative Analysis Report	LSI-TR-477-2
Part 2. Facility Installation Report	LSI-TR-477-3
Part 3. Impact of Future Changes Report	LSI-TR-477-4
Supporting Documents:	
Technology Changes Impact on Testing Requirements	LSI-TR-477-14
Quality Assurance Plan	LSI-TR-477-17A
Capability Modules	LSI-TR-477-19B
Technical Plan	LSI-TR-477-20A
Equipment Plan	LSI-TR-477-21A
Personnel Plan	LSI-TR-477-23A
Inhalation Chambers and Supporting Equipment Survey	LSI-TR-477-26A
Equipment List for Modules	LSI-TR-477-28B
AMTR Protocol/Pricing Report	LSI-TR-477-29A
Global Army Toxicology Requirements	LSI-TR-477-31A
Comparison Toxicology Test Costs	LSI-TR-477-36A
Annual Testing Capacity	LSI-TR-477-38A

This is the Facility Installation Report.

This contract supported technical effort by Life Systems' personnel, various supporting organizations and consultants

Support Life Systems' personnel included Mr. Richard Alban, Dr. Ron Davenport, Dr. Jack Glennon, Ms. Darlene Jones, Mr. Ron Kohler, Dr. Joel Lantz, Mr. Earl Linaburg, Ms. Pat Marcinko, Mr. Jim McFarland, Ms. Cynthia Patrick, Dr. Roy Reuter, Ms. Dorothy Ruschak, Mr. Greg Schiefer, Dr. Dennis Takade and Dr. Rick Wynveen.

The participating supporting organizations included: ICAIR Systems, Inc.; Theodore Jonas/Associates LTD.; Midwest Research Institute; Relocation Consultants; Stanford Research International; Segner and Dalton; Towers, Perrin, Forster & Crosby; University of California, Davis; and Young & Bertke, Co.

Participating consultants were Donald Culver, Dr. Robert Drew, Dr. Dennis Hsieh, Dr. Wendell Kilgore, Dr. Keith Killam, Dr. Sheldon Murphy and Dr. Ron Shiotsuka.

TABLE OF CONTENTS

continued-

Table of Contents - continued

continued-

Table of Contents - continued

continued-

Table of Contents - continued

continued-

Table of Contents - continued

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Life Systems, Inc. (LSI), its Subcontractors and Consultants, completed a program entitled "Mammalian Toxicology Testing: Problem Definition Study" (Study). The program was divided into four major efforts:

1. A definition of global Army's mammalian toxicology requirements.

2. A comparative analysis of approaches for meeting a portion of the unmet requirements that would be the responsibility of the US Army Medical Research and Development Command (USAMRDC).

3. Preparation of plans for a model toxicology facility to implement a portion of the USAMRDC's unmet requirements.

4. A determination of the impact of changes in toxicology regulations and technology over the next ten years on the Army's toxicology requirements.

This document summarizes that portion of the Study associated with planning a toxicology facility. Several sites were used as models to aid in formalizing the facility installation plans. Efforts one, two and four above are discussed elsewhere (Life Systems, Inc. 1981a,[1] Life Systems, Inc. 1981b), respectively. The material contained in these reports will not be duplicated in the current report.

Study Objectives

The objectives of the Study were:

1. To assist the Army in identifying mammalian toxicology requirements and, if possible, establish a methodology that could continue to be used after the Study.

2. To assist the Army in identifying advantages and disadvantages of various options for carrying out mammalian toxicology, with particular emphasis on production testing.

3. To assist the Army in projecting the impact on Army requirements and planning of changes in toxicology related regulations and technology.

4. To assist the Army in defining the resources needed to add extra toxicology capability and capacity to that available through USAMRDC.

The program was done extramurally because the USAMRDC staff was assigned to other priority efforts, the results were needed quickly and the level of effort was extensive.

(1) References are cited at the end of the report.

Background

The initial thrust of the Study focused on the Army's needs for routine, production toxicology testing. During the early part of the program, however, the definition of toxicology testing was expanded to include applied mammalian toxicology research. The difference is discussed below.

Prior Efforts

Prior to the Study an effort was completed entitled "Report of Mammalian Toxicology Testing Requirements and Concepts for Solution" by Dr. R. H. Reuter dated 1979, USAMBRDL that evaluated the USAMRDC's toxicology requirements. It reflected a growing toxicology testing need. It further identified a major increase in the demand by others for a limited, albeit growing, toxicology testing capability. Following this Study, an evaluation was made concerning the Study's conclusions. One of these was that a new capability should be added for carrying out toxicology testing at an USAMRDC controlled facility (e.g., the Letterman Army Institute of Research (LAIR)) and operated by a contractor.

A team of USAMRDC personnel evaluated the conclusions of the report and visited various national toxicology laboratories and laboratories owned by the Government and operated by contractors. This survey demonstrated that:

1. The requirements included in the initial Study did not encompass the global Army.

2. The LAIR represented only one of several possibilities for one additional toxicology testing facility.

3. Although many government agencies are utilizing the Government-Owned, Contractor-Operated (GOCO) route for overcoming personnel ceilings, a direct comparison between alternatives was needed to select between alternatives.

For these and other reasons the current Study was initiated to be completed within three months. Subsequently, additional effort was added which increased the duration.

Why Mammalian Toxicology Needed?

There are many reasons why the Army has toxicology requirements. Some are in the form of tests mandated by law. Besides complying or demonstrating conformance to laws and regulations, other reasons include generating data to obtain permits and licenses, obtaining approval to manufacture or continue to manufacture Army chemicals, as part of carrying out effective drug and vaccine development processes, developing testing methodologies for Army-unique environments and materiel and establishing standards and criteria for occupational health in Army laboratories, in Army production plants, in field training and for combat. Other toxicology research or testing must be done because they are part of good business practices or for ethical and moral reasons.

The regulatory and nonregulatory requirements for Army toxicology activities are contained in another Study report (Life Systems, Inc. 1981a).

Scope

This report reviews and summarizes some of the Study's more important activities that focused on designing a Facility to carry out a portion of the USAMRDC's unmet toxicology requirements.

Report Objective

The report has as its objective the reviewing of plans for the major resources (facilities, equipment, people and money) needed to provide added toxicology capability and capacity. The Study did not include definition or planning of expendables but did include planning for quality assurance. The latter is a very critical consideration in all toxicology research and testing, especially the latter.

Definitions and Acronyms

Appendix 1 contains the definition of terms and acronyms used in this report or during the program.

Assumptions

Many of the assumptions used in preparing the individual plans that make up this Facility Installation Report are cited at the beginning of each section. The remaining assumptions are contained in supporting documentation that has become part of the Study's data base.

The conceptual design and plans for the new or added Facility were done in a way to be compatible with Government-Owned, Government-Operated (GOGO), GOCO or Contractor-Owned, Government-Operated (COGO).

Clarifiers

Various issues must be reviewed to clarify the information discussed in the remainder of the report.

Toxicology Versus Health Hazard Assessment

Toxicology is one aspect of Health Hazard Assessment (HHA). It is a program recommendation that the Army's toxicology requirements that fall under HHA should be integrated with those cited in the program rather than be incorporated as an added toxicology effort.

Full Service Capability

As noted in the Comparative Analysis Report (Life Systems, Inc. 1981a) toxicology involves more than production testing or applied research. Efforts focused on the Facility did not include, for example, basic toxicology research or personnel training in toxicology. Although these are important portions of toxicology, they were not included in the Study's scope.

A full-service mammalian toxicology facility would include services provided:

1. Before the testing was initiated.
2. The testing itself.
3. Activities carried out in parallel with testing.
4. After the testing was completed.

The Comparative Analysis Report provides a detailed description of the broad range of toxicology tasks associated with each of these four areas of toxicology.

Incorporated Capability

The added Army toxicology capability reflected in this Facility Installation Report will provide a capability to meet a portion of the Army's requirements typically expected to be provided by the USAMRDC.

Deleted Requirements

Of the global Army requirements, several were deleted from being incorporated into this, the facility installation planning, portion of the program. The deleted requirements included:

1. Toxicology requirements associated with drug and vaccine developments.

2. Toxicology associated with offensive chemical warfare (an area of technology in which the USAMRDC has no involvement).

3. Toxicology associated with defensive biological warfare.

4. Toxicology associated with nuclear warfare.

5. Basic toxicology research.

6. Training of Army-required toxicology personnel.

Epidemiology

Although there is growing advocacy for employing epidemiological techniques in human health effects investigations and we will probably see increasing focus on the use of epidemiology in the future, it is not included as part of the Army's toxicology requirements.

Facility Models: LAIR, Hunter's Point, Others

The Study used two models and the possibility of various others as sites where the new capability/Facility could be located. Although the prior effort (report entitled "Report of Mammalian Toxicology Testing Requirements and concepts for Solution" by Dr. R. H. Reuter dated 1979, USAMBRDL) and a review of USAMRDC laboratories, indicated the LAIR was a preferred site, the current Study expanded the analysis to include the Navy's vacant Nuclear Biology Defense Laboratory at Hunter's Point.

A benefit of the Study approach selected is that the results are equally applicable to almost any site selected by USAMRDC and, in most cases, whether the installation is initiated immediately or at some time in the future.

Types of Tests

There are three major areas that must be considered when evaluating toxicology testing. These tests are needed to determine:

1. Physical/chemical properties of the chemical, the chemical and its use, the environment created by use of the chemical, etc.

2. Health effects.

3. Environmental effects.

Health effects toxicology was included in the Study, not environmental effects. As the recommendations indicate, however, merit exists in grouping all of the USAMRDC's/Department of Army's (DA's) toxicology requirements together.

The measurement of the physical/chemical properties of a toxic or potentially toxic chemical or mixture can be included as an activity done before testing or as part of testing. For the present Study, it was included as part of the testing activities.

Capability and Capacity of Selected Facility

The actual capability and capacity included in the new facility (new meaning newly built or a renovated site) remains to be determined and is a USAMRDC/DA decision. The term Facility almost universally refers to the facility resulting from the selected capability and capacity. The Facility can be full service or limited service. The services can be applied to a number of specific toxicology research/testing capabilities.

TECHNICAL PLAN

This section reviews some of the results of the technical planning activities completed.

Objectives

The objectives of the technical planning effort included:

1. Define a full service capability scope.
2. Establish the facility's business and technical organization.
3. Forecast the types of tests needed.
4. Recommend tests to be done at the Facility.
5. Evaluate how to implement the selected capability.

The section ends with a listing of special projects carried out under the technical planning efforts.

Assumptions

The assumptions used on the technical planning included:

1. All science must be good quality for the research and tests purposes.

2. All regulations relating to conformance to Good Laboratory Practice (GLP) will be met.

3. All nonregulatory research and testing will conform to the GLP and protocols established (selected or developed). Some research/testing should not incorporate, however, all the formal activities inherent in GLP regulations. An experiment carried out, for example, under The Surgeon General's nonregulatory responsibility should not necessarily require extensive specimen or recordkeeping procedures nor establish a precise level of training or experience for the person carrying out the experiment. The work, however, should always be good science.

4. There will be both initial Army and external reviews of operating policies and performance.

5. There will be good Standard Operating Procedures (SOPs) developed by the scientists in coordination with the Quality Assurance (QA) function. (See Quality Assurance Section below.)

6. The technical operation will be headed by a Science Director who will control technical performance.

7. Data and recordkeeping will be given prominent attention.

8. The Facility and personnel will conform to the requirements for certification and accreditations for facilities and personnel.

9. Personnel will be allowed the maximum freedom for innovative methodology development consistent with the needs of the Army.

A purpose of technical planning is to ensure that the policies and guidelines are such that the data and scientific output generated by the Facility are scientifically acceptable. Further, that technical personnel will be attracted to the Facility because of its reputation and qualifications of the scientific personnel working at the Facility.

Facility Business Organization

The toxicology Facility has been organized as shown in Figure 1. It includes six major business functions:

1. Administration.
2. Financial.
3. Legal/Contract Administration.
4. Product/Quality Assurance (of which GLP is a subset).
5. Support Services.
6. Toxicology Research/Testing.

Note the organizational chart is depicted as a GOCO facility. The same organizational configuration is recommended for a GOGO or COGO facility.

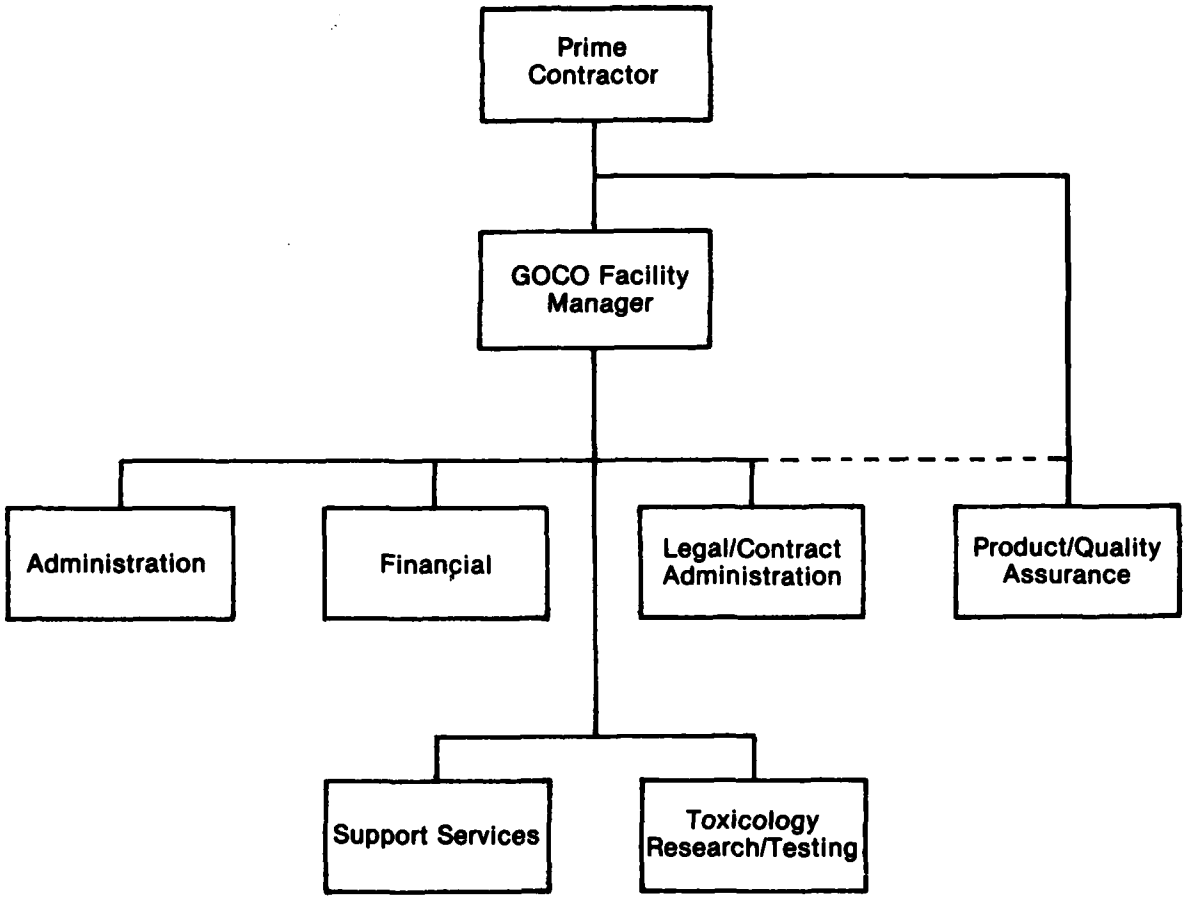


FIGURE 1 TOXICOLOGY TESTING FACILITY ORGANIZATION

The product/quality assurance function reports directly to the parent organization and only indirectly reports to the Manager of the Toxicology Facility. This is to ensure monitoring and enforcement of Product/Quality Assurance are soundly implemented.

If the Facility was implemented as a GOCO, the organizational arrangement should be consistent with the organization of the controlling government agency so like parts of each organization can handle like responsibilities.

Organizational Location of Facility Capabilities

Figure 2 presents a separation of the types of toxicology science and organizational services of the full-service capability conceptually designed into the Facility. It reflects, for example, the difference between those services included in administration, product assurance, supporting services and the toxicology research/testing directorate.

Scientific and Technical Aspects of Testing

Before examining the individual tests the Army should include in the Facility, it is well to state the basic objectives involved:

1. To determine the specific effects of specific substances either predictably or retrospectively.

2. To establish dose response relationships, to predict safe levels (if there are any) and the attendant risk associated with the compound in the environment over ranges of exposure.

3. To screen substances to determine if more extensive and definitive testing is required.

4. To confirm or refute suspicions or concerns from whatever source --structural activity relationships, preliminary laboratory findings, clinical observation, epidemiology.

5. To determine mechanism of action to better understand toxicological and biological processes and phenomena.

6. To determine compound properties.

To these central technical and scientific objectives must be added, in many cases, certain legal ones:

1. To aid in the determination of unreasonable risk.
2. To comply with statutory and regulatory requirements

In addition, there are also certain business objectives involved:

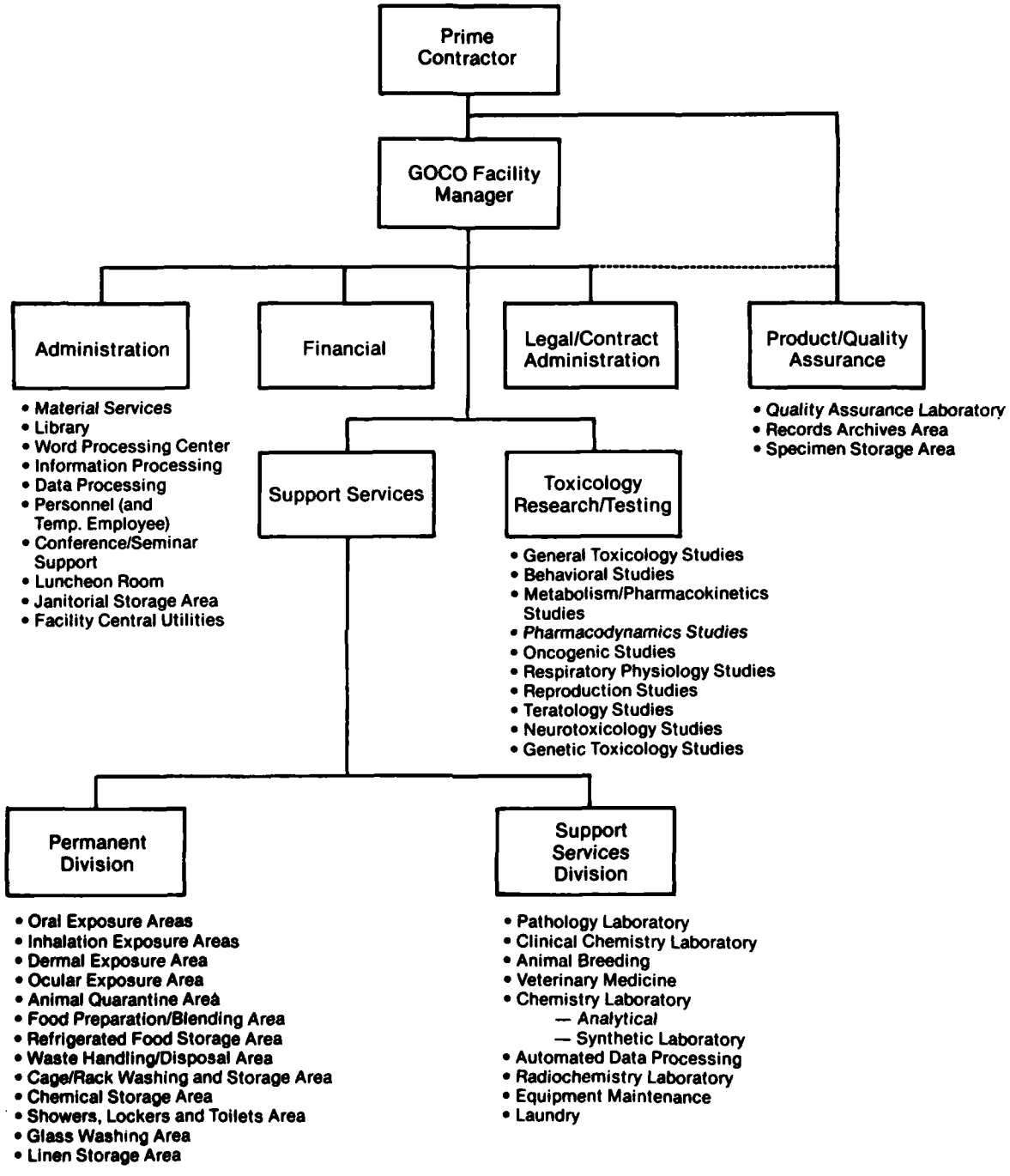


FIGURE 2 ORGANIZATIONAL LOCATION OF FACILITY LABS AND AREAS

1. To make decisions on materiel to development and field.

2. To defend existing Army materiel--based on suspicion or allegations from any source (so-called defensive toxicology).

3. To respond to specific regulatory requirements.

4. To provide data the Army deems essential for conformance to specific laws, e.g., Toxic Substance Control Act (TSCA).

5. To provide information necessary to protect the safety and health of Army soldiers, Army employed civilians and civilians living on or near Army installations.

Testing, therefore, involves many differing objectives based on differing perspectives. All must be integrated within the USAMRDC's approach to the unmet toxicology requirements so logical and cohesive programs are implemented balancing all of the needs and concerns (Dominguez 1979, p. 100).

Types of Tests Needed

Meeting the USAMRDC's unmet toxicology requirements resulted in the identification of three categories of tests. The tests include those required to be compatible with global Army requirements. The three categories of tests include:

1. General Toxicology Tests.
2. Genetic Toxicology Tests.
3. Special Scientific Toxicology Tests (Studies).[(a)]

General Toxicology Tests

Table 1 presents a list of 19 types of Army mammalian toxicology tests. Information on each test includes duration, type of animal, route of exposure and outcome, usually "general toxicology". The latter includes lethality, metabolism/pharmacokinetics and portions of selected scientific toxicology disciplines such as pharmacodynamics. Only portions of the latter are included, however, so as not to be confused with the full scale, special scientific toxicology studies. Also, general toxicology when used in the text, includes dermal irritation and sensitization, ocular irritation and neurotoxicity outcomes.

The list of 19 tests resulted from a survey of all known types of mammalian toxicology test descriptors and which then was reduced to a list of those most likely to be applicable to the Army's requirements. This was followed by an identification of specific protocols for each of the group of 19 tests (Life Systems, Inc. 1981e).

(a) For the remainder of the report the special scientific toxicology tests will be referred to as studies. This is done to reflect the research orientation of these activities.

TABLE 1 SPECIFIC TYPES OF ARMY MAMMALIAN TOXICOLOGY TESTS

No.	Duration		Type of Animal	Route of Exposure	No. of Species	Outcome[a,b]
	General	Specific				
1.	Acute	Short	Rodent	Oral	1	General Toxicology
2.	Subchronic	90-Day	Rodent	Oral	1	General Toxicology
3.	Chronic	Life-Time	Rodent	Oral	1	General Toxicology
4.	Acute	Short	Rodent	Inhalation	1	General Toxicology
5.	Subchronic	X-Day	Rodent	Inhalation	1	General Toxicology
6.	Chronic	Life-Time	Rodent	Inhalation	1	General Toxicology
7.	Acute	Short	Primate	Inhalation	1	General Toxicology
8.	Subchronic	90-Day	Primate	Inhalation	1	General Toxicology
9.	Chronic	Life-Time	Primate	Inhalation	1	General Toxicology
10.	Subchronic	90-Day	Dog	Oral	1	General Toxicology
11.	Acute	Short	Rabbit	Dermal	1	General Toxicology
12.	Subchronic	Z-Day	Rabbit	Dermal	1	General Toxicology
13.	Acute	Short	Rabbit	Ocular	1	General Toxicology
14.	Acute	≥21 day	Chicken	Oral	1	Neurotoxicity
15.	Subchronic	90-day	Chicken	Oral	1	Neurotoxicity
16.	Acute	Short	Rabbit	Dermal	1	Irritation
17.	Subchronic	90-day	Rabbit	Dermal	1	Irritation
18.	Acute	Z-Day	Rabbit	Ocular	1	Irritation
19.	Acute	Short	Rodent[c]	Dermal	1	Sensitization

(a) Efficacy would be included for drugs and vaccines.
(b) General toxicology includes lethality and metabolism/pharmacokinetics plus minor investigations of the several other toxicology disciplines (*e.g., pharmacodynamics*).
(c) Guinea Pig

Genetic Toxicology Tests

Considerable advances in technology are being made to reduce the cost of toxicology testing. A portion of these efforts involve genetic toxicology. The Study identified five major genetic toxicology test categories.

1. Detecting gene mutations.
2. Detecting heritable chromosomal mutations.
3. Detecting DNA repair or recombination as genetic damage indicator.
4. Detecting chromosomal damage.
5. Detecting DNA alkylation.

These five test categories are further defined in Table 2.

It ultimately is the Army's decision as to which of the genetic toxicology tests are incorporated into the Facility's capability, but it is recommended that many of the in vitro tests be included.

Special Scientific Toxicology Studies

The toxicology research/testing capability envisioned as able to be incorporated into the Facility include the following:

1. Behavioral Studies.
2. Metabolism/Pharmocokinetic Studies.
3. Pharmocodynamic Studies.
4. Oncogenic Studies.
5. Respiratory Physiology Studies.
6. Reproduction Studies.
7. Teratology Studies.
8. Neurotoxicity Studies.

The Facility has been designed so each of these eight toxicology studies has separate testing facilities. This enables more detailed investigations than would be included under general toxicology testing.

Of the eight scientific toxicology areas, it is recommended the Facility provide or provide for, as a minimum, those noted in Table 3 to be best prepared for the majority of estimated testing. The majority are chronic studies with rodents utilizing the oral route of exposure. They also include the combined protocols of (a) general toxicology and oncogenic studies and (b) reproduction and teratology studies. The two recommended neurotoxicology studies were included as numbers 14 and 15 within the general toxicology tests.

Tier Tests

In Tables 1 and 3 the toxicology tests were identified as acute, subchronic and chronic. They were cited as a discrete entity. Each test, for example, correlates to a specific protocol (Life Systems, Inc. 19811). In reality, however, the assessment of a product or process, new or old, will include examination of several and, in extreme cases, most of the tabulated tests. This means that, in practice, most toxicological testing will be performed by a battery of tests (Dominguez 1979 p. 116).

TABLE 2 GENETIC TOXICOLOGY TESTS

A. Standards for Detecting Gene Mutations

1. Detection of Gene Mutations in Bacteria
   - The *Salmonella*/Microsomal Assay
   - The *Escherichia coli* WP2 and WP2 *uvrA* Reverse Mutation Assay
2. Detection of Gene Mutations in Eukaryotic Microorganisms
   - *Aspergillus nidulans*
   - *Neurospora crassa*
3. Detection of Gene Mutations in Insects
   - *Drosophila melanogaster* Sex-Linked Recessive Lethal Test
4. Detection of Gene Mutations in Somatic Cells in Culture
   - Mammalian Cell Culture — L5178Y Mouse Lymphoma Cells
   - Mammalian Cell Culture — V79 Chinese Hamster Cells
   - Mammalian Cell Culture — Chinese Hamster Ovarian (CHO) Cells
5. Detection of Gene Mutations in Mammals
   - The Mouse Specific Locus Test

B. Standards for Detecting Heritable Chromosomal Mutations

1. *In Vivo* Cytogenetics Test in Mammals
2. Detection of Heritable Chromosomal Damage in Insects
   - Chromosomal Damage in *Drosophila melanogaster*
3. The Dominant Lethal Test in Mammals
4. The Heritable Translocation Assay

C. Standards for Detecting DNA Repair or Recombination as an Indicator of Genetic Damage

1. Detection of Genetic Damage using DNA Repair-Deficient Bacteria
2. Unscheduled DNA Synthesis in Mammalian Cells in Culture
3. Detection of Mitotic Crossing Over and/or Gene Conversion in Yeast
4. Sister Chromatid Exchange in Mammalian Cells in Culture

D. Standards for Detecting Chromosomal Damage

1. *In Vitro* Cytogenetics Assay
2. Micronucleus Assay

E. Standards for Detecting DNA Alkylation

1. DNA Alkylation in *Drosophila melanogaster* Sperm Cells
2. DNA Alkylation in Rodent Sperm Cells
3. DNA Alkylation in Mammalian Cells in Culture

TABLE 3 SPECIAL SCIENTIFIC TOXICOLOGY STUDIES RECOMMENDED

Special Scientific Toxicology Study	Test No.	Duration	Type of Animal	Route of Exposure
Behavioral	5	Subchronic	Rodent	Inhalation
	8	Subchronic	Primate	Inhalation
Oncogenic	3	Chronic	Rodent	Oral
	6	Chronic	Rodent	Inhalation
	9	Chronic	Primate	Inhalation
Reproduction	3	Chronic	Rodent	Oral
Teratogenic	3	Chronic	Rodent	Oral
Gen. Tox. & Oncogenic	3	Chronic	Rodent	Oral
	6	Chronic	Rodent	Inhalation
	9	Chronic	Primate	Inhalation
Reprod. & Teratogenic	3	Chronic	Rodent	Oral

This battery of tests may be based on the type of effect or duration or may involve one designed to determine one particular effect, such as oncogenic. The latter case may take the form of a progression from the least expensive and most expedient screening procedure to the more expensive and time-consuming, lifetime study. This can be exemplified from the Ames test to chronic two-year animal feeding in two species.

At other times, it is the test's reliability that may be the problem. This type of problem might be solved using mutagenicity testing by in vitro techniques where the use of multiple procedures increases the reliability of results and their extrapolatability. Whichever is the case, a series of tests must be developed relating to the Army's testing objective.

Testing Program Design

The situation, however, is further complicated in that the testing program design must also take into consideration several additional factors if it is to be realistic and cost-effective. The basic parameters usually employed in designing testing systems are:

1. The opportunity for exposure, and the frequency, duration, concentration and route of exposure.

2. The volume of the material or materiel to be produced. In general, the larger the volume produced the greater potential for human (or environmental) exposure, and thus the greater the need for extensive testing and the higher the priority for testing. (This, obviously, is not always the case since considerations of points mentioned in items 1 above and 5 below may mitigate.)

3. The physical and chemical properties of the substance. (Appendix 2 discusses this aspect in more detail.)

4. The structural/activity relationships of the substances under consideration to other tested substances and their known effects. Certain preliminary inferences can be drawn based on such analogies. In the future it will be possible to use this approach more definitively.

5. The known or anticipated uses of the substances. This plays a large part in the intelligent design of a testing system. It is unnecessary, for example, to conduct extensive, if any, tests on a substance formed and totally consumed in the reaction of another substance (e.g., a transient reaction product). At the other end of the spectrum, however, is a product for wide-spread use within the Army which would warrant extensive evaluation.

These five factors ignore statutory or regulatory requirements but view testing from the logical and scientific viewpoints. The implications raised by laws or regulations (TSCA, Federal Insecticide, Fungicide, Rodenticide Act (FIFRA), Resourse Conservations and Recovery Act (RCRA), Occupational, Safety and Health Act (OSHA), etc.), although beyond the scope of this report, are, obviously, instrumental in final test system design.

Table 4 presents a summary of three levels of Tier Testing guidelines (Dominguez 1979, p. 120) modified for this Study. A level called tier zero covers such items as physical/chemical properties, elementary mass balance analysis and preliminary analytical methods determination. The trend is toward increased complexity and resources (cost, facilities, equipment and personnel) as one goes from tier zero to tier three tests.

Testing Protocols and Pricing

A project was completed to assemble the protocols and pricing data for the recommended mammalian toxicology research/testing and studies cited in Tables 1 and 3. The results were provided to the Army under a separate cover (Life Systems, Inc. 19811). The document permits recalculations of price as a function of changes in a protocol or selection of a different protocol.

Protocols. The protocols were those published in the Federal Register and sent out as the test standards for toxic substances and pesticides. They are also representative of the protocols used if the same type tests were done on other materials. A total of 19 standard protocols were identified.

Pricing. A data base was assembled on toxicology testing costs. Two very recent and very thorough sources were included and used extensively (Enviro Control 1980, ICF, Inc. 1980). Appendix 3 provides a summary of the pricing data for each of the toxicology tests projected to meet the requirements included in the Facility.

Criteria for Test Selection

The specific selection of which capabilities (research/testing) should be done within the Facility depends upon decisions made concerning:

1. The control the Army desires over the implementation of each test;
2. The level of funding it desires to invest in establishing the Facility, its capability and capacity;
3. The availability and demand for contractor testing resources; and
4. The success experienced in identifying the level of test volume, urgency and timing for providing the capability.

Major drivers will be the number of times the particular test is ultimately determined to be required, the funding provided by the Facility users and, possibly, the sharing of the Facility capabilities with other organizations. The latter includes the Air Force and Navy, and other Federal Agencies such as those participating in the National Toxicology Program (NTP). In some cases the latter organization might do some of the Army's needed tests.

Implementing Selected Capability at the Facility

It is recommended the Army selected capability should be implemented in two stages. Further, each stage should be built up incrementally.

TABLE 4 PROGRAM TIER TESTING GUIDELINES[a]

TIER 0

- Physical/Chemical Properties
- Elementary Mass Balance Analysis
- Preliminary Analytical Methods

TIER I

- Acute General[b] Toxicity Tests
- Genetic Toxicity Tests for Chronic Health Effects
- Refinement and Application of Analytical Procedures

TIER II

- Subchronic General Toxicity Tests
- Reproduction and Teratogenicity Tests
- Neurotoxicity and Behavioral Toxicity
- Further Refinement and Application of Analytical Methods

TIER III

- Chronic General Toxicity Tests
- Oncogenicity Tests
- Further Refinement and Application of Analytical Methods

(a) Based on approaches for developing testing guidelines under the Toxic Substances Control Act—June, 1978. This approach is a modification of that developed by panelists under the auspices of The Conservation Foundation.

(b) General toxicity tests may include metabolism, pharmacokinetics/ pharmacodynamics and respiratory physiology studies.

Initial Capability

The initial capability should be a balance between priority requirements and the available resources (dollars and personnel and to a lesser extent facilities and equipment). The time frame should be the first five years of the Facility's existence. These five years provide for:

1. Final definition of the Facility Specification.

2. Approved detailed Facility drawings, subsequent construction and transfer to operator.

3. Initial startup of toxicology testing, easier ones first.

4. Fully operational initial capability.

As was noted elsewhere (Life Systems, Inc. 1981a), the time needed to fully debug and be ready for "for the record testing," can vary from four to six years if the Office of Management and Budget (OMB) cost comparison procedures (Executive Office of the President 1979) must be followed or three to five years without them. If, in the unlikely case a brand new Facility is constructed, approximately one year must be added to the schedule. (See also Management Plan Section.)

Growth Capability

The growth capability should be selected and conceptually designed at the time the initial capability is formalized. Details of its configuration should not be formalized, however, until after the third year of the initial capability's existence when more is known about toxicology needs and test requirements.

The purpose of conceptually defining the growth capability while finalizing the initial capability is to ensure that the capability, floor plans, equipment and personnel are compatible. This alerts potential users and the Facility staff to future capabilities and aids in explaining why it is not incorporated initially.

Incremental Buildup in Each Stage

For many reasons, including effective management of resources and the acquisition of personnel, the Facility should have its capability incorporated in a step-wise fashion. This avoids having too many "new" things going on simultaneously. It allows management, both scientific and business, more time to develop, implement, and teach and/or acquire the operating procedures, guidelines, policies, personnel, etc. that make up the Facility.

Preferred Tests at the Facility

Above, it was noted the Facility was conceptually designed to provide full service. Further, it was noted not all of the scientific capability should be incorporated in the Facility either initially or in the growth version. Many ways can be envisioned by which the Army can select the capability to be included. The following two illustrate tests that should be given preference.

Army-Unique Exposure Environments

No major toxicology research/testing capability exists which is able to handle the special exposure conditions that reflect the Army's requirements. These include:

1. Troop exposures associated with weapon systems.

2. Industrial workers in Government-owned plants and Army depots where Army-unique chemicals or materiel are made or processed.

3. Environmental health exposures the general public experiences when living on or near Army activities. These include exposure to Army "generated" air, water and land pollutants.

Testing Not Available Extramurally on Competitive Basis

A second major category of tests that should be given high priority for incorporation into the Facility include those that cannot be obtained extramurally on a competitive basis. The caution, however, is that the volume of these tests should be adequate to justify their incorporation into the Facility's capability.

The incorporation of a behavioral toxicology capability represents the type of tests that cannot be obtained extramurally through a broad base of competition. (It is available on a broader scale through universities but at the basic research level which was outside of the Study's scope.) The trend in toxicology is toward evaluating the effect on behavior of concomitant exposure conditions (temperature, noise, etc.). This aspect of technology directly parallels the Army's need for evaluating the soldier's exposure to toxic chemicals and hazards and/or military-unique environments.

Behavioral toxicology should be given a high priority for the second stage capability. Its high priority for the initial capability must be delayed because of the higher demand for the more traditional, unmet toxicology research/testing requirements.

Tests Not to be Incorporated Into the Facility

Many toxicology research/testing activities can be done within a USAMRDC laboratory, under contract or through another Federal agency. These include:

1. Tests routinely completed within the USAMRDC's laboratories.

2. Tests routinely performed by such organizations as the NTP, Environmental Protection Agency (EPA) and National Institute for Occupational Safety and Health (NIOSH). This is limited for Army requirements in general but still a viable option.

3. Tests characterized by using very routine, standard protocols readily available on a competitive contract basis (e.g., the oral, dermal and ocular tests).

4. Tests of a nonroutine nature but where competitively meaningful numbers of for-hire, GLP qualified laboratories are available.

5. Tests with a long lead time to obtain the results and the quick response, characteristic of a Government-owned and Government-controlled operation, through its own staff or that of a contractor, is not required.

Special Projects

During the technical planning effort, various special projects were completed:

1. A definition of Army-unique exposures.
2. A definition of concomitant exposures.
3. A projection of shortages in mammalian toxicology.
4. A definition of techniques for meeting changing requirements.

The results of these projects are reviewed below.

Army-Unique Exposures

By nature of its mission, the Army exposes its military and civilian personnel and people living on and around military installations to unique toxic exposures. The most unique are those associated with the soldier in combat or combat training environments. They are characterized as shown in Table 5. The exposure is short-term (less than one minute to one hour), repeated one to sixty times per ten-hour day, etc.

The characteristic called "intense concentration" deserves special mention. It reflects the high concentration of chemicals, chemical mixtures, exhaust gases, etc. in the combat or simulated combat environments. Such environments could result from rapid firing of small arms to periodic missile launches, the generation of smokes to obscure the activities associated with troop and equipment movement and the exposure to chemical and biological warfare agents, etc.

Concomitant Exposure

As the impact of toxicity on performance becomes better known, there will be increasing Army emphasis on performance degradation associated with exposure to toxic chemicals and environments and concomitant exposures such as hot and cold temperatures, loud and intermittent noise, pressures, vibration, etc. These exposures are summarized in Table 6. It is projected this will occur in the late 1980's.

Projected Shortages

The national capability for applied mammalian toxicology research/testing will be limited (ICF, Inc. 1980, Development Planning and Research Associates, Inc. and ICF, Inc 1980). Further, the ability of the Army to compete effectively for extramural toxicology has certain restrictions placed on it. These are summarized in Table 7.

TABLE 5 ARMY-UNIQUE EXPOSURE SCENARIO

Characteristic	Level
Short Term Exposure	<1 min to 1 hr
Repeated Exposure	1 to 60 times/10 hr day
Intermittent Exposure Frequencies	1 day/week to >90 days continuous
Intense Concentration	Above existing ceilings
Unique Environmental Conditions	
Temperature	– 40 to 140 F
Relative Humidity	>10 to 100%
Ambient Pressure	Sea Level to that at 8,000 ft
Associated Stress Conditions	
Noise	Loud, Sporadic
Vibration	Constant, but Varying
Shock	Periodic, Intense
Overpressures	Blasts, Shock Waves
Psychological	Stress, Threats

TABLE 6 CONCOMITANT EXPOSURES THAT WILL MODIFY STANDARD TOXICOLOGY TESTS

Temperature	Hot / Cold
Noise	Loud / Nonauditory, Intermittent and Continuous
Vibration	Continuous, Peaks
Shock	Periodic, Intense
G-Forces	None / ??
Overpressures	Blasts, Shock Waves
Relative Humidity	Dry / Wet
Visibility	Light / Dark; Fog / Rain / Snow
Ambient Pressures	*Mountain*
Psychological State	Stressful (Threatening, Uncertain), Neuropsychiatric
Radiation	Ionizing / Nonionizing

QUESTION: For which tests should these be included in protocol?

TABLE 7 CATEGORIES USED TO PROJECT SHORTAGE OF AMTR CAPABILITIES

	Drivers		
Category	Supply	Demand	Army's Restriction
• Personnel	Low	High	Needs special training, program's not basic (more interesting) research, war versus peaceful
• Facilities	Low		Must meet highly hazardous safety criteria
• Equipment	Low		Must provide unique durations and high concentrations of hard to reproduce environments
• Animals	Low on Primate		Against doing testing on dogs
• Business (Profit)	Small	High	Low fees on contracts (10 vs. 25%), unique material, environments, scheduling, "red tape", etc.

Personnel involved with mammalian toxicology are in short supply. The demand for their services is high because of recent increases in regulatory actions and public/business awareness of the hazards associated with chemicals. Although many testing organizations state they can handle considerably more testing, other issues are involved which are not noted but relate to quality of their work, type of work they would agree to do, etc.

A Contractor-Owned, Contractor-Operated (COCO) testing service must (1) express an interest in bidding on Army toxicology programs, (2) actually bid when the Army's need is presented, (3) be able to do the type of tests being required, e.g., inhalation, and (4) be found technically qualified (adequate balance between toxicology equipment, personnel capability and supporting services capabilities). The USAMBRDL has experienced considerable difficulty in implementing toxicology research/testing as reflected by the number of cancelled toxicology efforts and delays in starting toxicology programs.

The Army's ability to attract toxicology personnel is restricted because of the special training needed for Army exposures, the war versus peace image of the Army's work, the Army's greater requirement for production-type testing as opposed to the more interesting (to the toxicology scientist) basic or applied research, etc.

Adapting to Changing Requirements

Some of the recommendations identified were: plan in advance, obtain firm commitments from those purchasing the services, avoid going too rapidly without firm, funded user requests for service and maintain a constant awareness of pending changes in toxicology technology (e.g., Life Systems, Inc. 1981e). Of course, outside contracting firms are available as topping sources for overloads on equipment and facilities and service contracts for overloads on personnel. Sometimes these alternatives could be at the expense of quality and would be at the expense of program continuity.

Analysis of Toxicology Results

The analysis and evaluation of toxicology results leads to problems of extrapolating this information to humans. In addition, questions arise on procedures employed, the definitiveness of the tests themselves and the relevancy of interrelated yet possibly separate tests. It is often necessary to use several tests, not a single test. Each test may be designed to determine the same end point where a combination of tests may measure different end points that relate to a specific health effect. One example would be a battery of mutagenic screening tests as determinants of either mutagenicity or oncogenicity.

When dealing with tests which are less validated (e.g., behavioral effects testing), even more sophisticated judgments are involved, since the meaning of the tests themselves, no matter how well conducted, come into play.

Another of the more important concepts is that of a concentration below which there is no observable effect--a threshold. Although clearly recognized for acute effects, it is surrounded by controversy when it comes to chronic effects, particularly oncogenicity. The subject is of such complexity we can only call

attention to it and its importance. It also contributes to toxicology cost and testing time.

There are many other factors that must be considered in analyzing a toxicity study to determine its validity, usefulness and application (Dominguez 1979, p. 115). Some of the more significant factors are cited in Table 8.

In the final analysis, obtaining conclusions from toxicology testing calls for a full-scale evaluation of not only the tests themselves and their results but also a combination of personnel experience and their assessments of interrelated evaluations. This assessment, however, is still not the final answer. It does not consider the probability of the event occurring in people or the environment, only whether the test is or is not scientifically valid. This other dimension involves risk/benefit evaluation which was outside of the Study's scope.

FACILITY PLAN

This section reviews some of the results of the Facility planning activities completed.

Objectives

The objectives of the Facility planning efforts included:

1. Provide conceptual and detailed plans for a Facility to accommodate the types of tests required by the Army.

2. Select an approach that would make the results applicable to a range of Facility sites and time frames. The time frames might vary from immediate to ten years or more in the future.

3. Provide a basis for pricing the selected Facility: construction, heating, ventilation and air conditioning (HVAC), electrical and sanitary services.

4. Provide a basis for calculating capacities of testing as a function of floor plan/area.

Assumptions

The assumptions used on the Facility's planning included:

1. The Facility was not to be designed for a specific capability, capacity or site.

2. Characteristics of the Facility should include scientific, supporting and business administration areas.

3. No set amount of Facility area, construction budget or time to startup was to be specified.

4. An airlock/anteroom was used in preference to a pressure zone or clean dirty corridor concept because:

TABLE 8 IMPORTANT FACTORS IN ANALYZING HEALTH OR ENVIRONMENTAL EFFECTS TESTS[a]

Protocols employed, e.g., number of animals, dosage, route of administration, environmental media
Experimental conditions, e.g., housing, feeding, handling, laboratory condition, records, audits
Sample employed, e.g., purity, form, availability
Opportunity for other causation, e.g., contamination, intercurrent infection
Statistical validity of results
Pathological examination (gross and histopathology)
Relationship of test result to other known evaluations (by the same laboratory or others, or by the same procedure or others)
Relationship to anticipated results based on SAR or other criteria
Species selection
Pre-experimental work, e.g., range finding studies, animal isolation
Researchers' or institutions' experience and reputation

(a) This list is not meant to be exhaustive. It is intended to provide some insight into the complexities of analyzing and evaluating test results before they can be reliably used in later risk or risk/benefit assessments and in final decision-making whether by government, industry or public interest sectors.

a. Most times the contaminant in the room is worse than in the corridors, but sometimes it is reversed. With a fixed pressure differential system, no flexibility exists to handle such an occurence.

b. It has been found that initially established pressure differential relationships change with time as a function of a broad range of very hard to control factors. Thus, the high-to-low pressure protection assumed during the design phase often disappears or even reverses itself at certain times or permanently after certain events in the operational phase.

Modular Concept

A modular concept was used as the approach to design flexibility and to establish capability options available in finalizing the Facility's ultimate capability. This final capability will be determined by the Army's decision makers.

Why Modular Concept Selected

The modular design is a means to an end. It was pursued during the Study because:

1. The research/testing requirements were not available at the Study's beginning to allow a specific design to be developed based upon one set of requirements. The timing did not allow a sequential approach of: first, determining requirements; second, selecting those to be met within the Army's own facility; and third, designing a specific facility to satisfy those requirements.

2. Results of the comparative analysis were not available before the Facility's design had to be initiated. The subsequent analysis results demonstrated certain testing should be done within the Facility and others done by organizations external to the Facility. The latter included other Army sites, other Federal agencies and "for hire" laboratories.

3. The USAMRDC desired to consider multiple sites for locating the Facility. This was subsequently expanded to include the concept of one "facility" with capabilities located at various Army locations.

4. It provided more flexibility and lower costs.

5. Development work could be done simultaneously on the three major program end-item deliverables:

   a. Comparative Analysis Report (including the requirements definition).

   b. Facility Installation Plan (including equipment, facilities, personnel, quality assurance and resources plan).

   c. Future Research Report (including the impact of changes in technology and regulations).

6. Greater focus could be put on the details of each module. Without the modular approach this would normally have been excessively complex.

7. It allows voicing the individual "functional" capabilities as entities in themselves before finalizing an overall facility architectural layout. The standard approach leaves little flexibility for users of the space to modify the areas and laboratories they will use to suit their needs, because architectural decisions made on floor areas, ceiling heights, location of elevators, location of stairways, duct work, etc. all are made without adequate Facility user inputs.

What The Modular Concept Is Not

The modular concept is different than modular construction. It is not, for example:

1. A defined modular size with all rooms based on being a multiple of this size, as is often architecturally done.

2. A module built off-site and delivered pre-assembled to the facility.

Approach

The modular approach divided the Army's projected Mammalian Toxicology Research/ Testing Facility into a series of 63 areas/laboratories. When assembled in an integrated manner, these areas/laboratories and the correct number of each, will provide the capability and capacity to carry out that portion of the Army's requirements it elects to have done in the Facility. Further, it will allow testing of the 19 specific types cited in Table 1, the genetic toxicology testing cited in Table 2 and the eight types of Special Scientific Toxicology Studies (listed on page 12, this report).

The approach was to develop a set of assumptions, features or benefits and specifications for each area or laboratory. Then a cost was determined. It was based on the various elements of construction costs and the equipment to be incorporated in the module.

Benefits

Had one design been developed, it would have been site specific. The use of the modular concept enables the capability reflected by the module, or multiples of the modules, to be arranged and rearranged to best fit the particular site or sites being considered by the Army.

Another major benefit is that the architect can sit with each expert or group of personnel to utilize the given module or provide a given service, to evaluate and arrive at what is needed in the module prior to being told, "This is the space you have available and it's located over there.".

The modular approach also enables the Facility to be designed to meet different testing combinations and qualities.

Finally, the modular concept avoids the errors of leaving out facilities because of failing to look at all the pieces. This often occurs when concentrating on a large, complex overall facility. Further, it is a method that will prevent re-inventing what services/functions/areas/laboratories should be considered in a Mammalian Research/Testing Facility if the Army desides not to build now, but to delay and re-evaluate in the future.

Modules

Sixty-three toxicology Facility modules were identified and arbitrarily divided into four areas based on relative importance in a toxicology facility:

1.	Areas of Most Importance	(23 modules)
2.	Areas of Intermediate Importance	(12 modules)
3.	Areas of Minor Importance	(15 modules)
4.	Facility Central Utilities Areas	(13 modules)
	Total	63 modules

They are described elsewhere (Life Systems, Inc., 1981d). With time, several additional modules will be found and some of the selected ones found not appropriate. The group, however, is one of the most representative existing.

For each of the 63 modules a description was prepared (Form F-650). This form provides information on the following five major categories:

1. Floor plan with dimensions and equipment locations (scale 1 inch equals 15 feet).
2. Construction information.
3. Special features or benefits.
4. Special assumptions (general assumptions are described below).
5. Cost estimate.

The construction information contained with each module's description varied from identification of air flow needed to type of fire-suppressing sprinkler system. The complete range of information is cited on the forms contained in Appendix 4. The general specifications and assumptions are discussed below.

The cost estimate was divided into:

1. General Construction.
2. Heating, Ventilation and Air Conditioning.
3. Electrical.
4. Sanitary.
5. Equipment.

The total dollar cost as well as the dollars per square foot cost are presented.

Areas of Most Importance

The areas considered most important were:

1. Acute Oral Exposure Area, Rodent
2. Subchronic Oral Exposure Area, Rodent
3. Chronic Oral Exposure Area, Rodent

4. Subchronic Oral Exposure Area, Dog
5. Acute Inhalation Exposure Area, Rodent
6. Subchronic Inhalation Exposure Area, Rodent
7. Chronic Inhalation Exposure Area, Rodent
8. Acute Inhalation Exposure Area, Primate
9. Subchronic Inhalation Exposure Area, Primate
10. Chronic Inhalation Exposure Area, Primate
11. Dermal Testing Area, Rabbit
12. Ocular Testing Area, Rabbit
58. Dermal Testing Area, Rodent(a)
13. Behavioral Studies Area
14. Metabolism/Pharmacokinetics Studies Area
15. Pharmacodynamics Studies Area
16. Oncogenic Studies Area
17. Respiratory Physiology Studies Area
18. Reproduction Studies Area
19. Teratology Studies Area
61. Neurotoxicology Studies Area, Chicken
62. In Vitro Genetic Toxicology Studies Area
63. In Vivo Genetic Toxicology Studies Area

Areas of Intermediate Importance

The areas considered of intermediate importance were:

20. Food Preparation/Blending Area
21. Non-radioactive Waste Handling/Disposal Area
22. Refrigerated Food Storage Area
23. Quality Assurance Laboratory
24. Animal Quarantine Area
25. Pathology Laboratory
26. Clinical Chemistry Laboratory
27. Animal Breeding Area
28. Veterinary Medicine Area
29. Analytical/Synthetic Chemistry Laboratory
30. Automated Data Processing Area
31. Radiochemistry Laboratory

Areas of Minor Importance

The areas considered of minor importance were:

32. Cage/Rack Washing and Storage Area
33. Chemical Storage Area
34. Showers, Lockers and Toilets Area
35. Glassware Washing Area
36. Library Area
37. Technical Offices Area
60. Administrative Offices Area

(a) Some modules are numbered out of sequence since they were added after the module numbering system was established.

38. Shipping and Receiving Area
39. Luncheon Room Area
40. Record Archives Area
41. Specimen Storage Area
42. Linen Storage Area
43. Janitorial Storage Area
45. Equipment Maintenance Area
46. Laundry Area

Facility Central Utilities Areas

The Facility central utilities were:

44. Central Cylinder Gas Storage Area
47. Central Power Area
48. Central Standby (Emergency) Power Area
49. Central Water Supply Conditioning Area
50. Central Wastewater Conditioning Area
51. Central Air Handling Area
52. Central Heating Area
53. Central Compressed Air/Vacuum Area
54. Central Communications Area
55. Central Refrigeration Area
56. Central Toilet Area
57. Central Vacuum Cleaning Area
59. Central Automated Facility Systems Control Area

Module Examples

Appendix 4 provides examples of four Facility modules: rodent acute oral exposure area, rodent acute inhalation exposure area, pathology laboratory and Quality Assurance Laboratory.

General Specifications and Assumptions

Prior to and during the design of the 63 modules, certain general specifications and general assumptions were used and made, respectively. These are cited below.

General Specifications

The general specifications for the module designs included:

1. All doors subject to cage rack passage shall be 4-ft. wide. All others shall be 3-ft. wide except for those that employ double doors which would then be 6- or 8-ft. wide.

2. Doors to laboratories and test areas will have view panels.

3. In general the wall construction is 6 in. block partitions or 2 x 4 in. studs (or equivalent).

4. The floors will be chemically resistant, antislip, monolithic, epoxy floors (e.g., Selba-Clad) with floor-to-wall junctions covered for cleaning and sanitation. To protect the walls from damage when moving the rack and cages, the floor-to-wall junction will be offset into the corridor forming a tapered interface.

5. No floor drains are located in the corridors.

6. In all wet areas and those subject to washdown, weatherproofed electrical outlets will be used.

7. Sprinklers will be installed throughout the animal rooms and laboratories, except where inappropriate such as the computer areas, incinerator room and boiler room. In the latter cases, a Halon 1301 fire extinguishing system will be used.

8. A smoke detection system shall be used throughout.

9. The electrical power to outlets shall be 120 V, single phase in general. In certain locations 208 V, single phase will be available at special equipment outlets. With certain equipment 208 V, three phase direct wiring will be used.

10. The air supply to all animal areas will be prefiltered and High Efficiency, Particulate Air (HEPA) filtered.

11. The exhaust air from hoods, animal rooms, treatment rooms, blending areas and other contaiminated spaces will be prefiltered, HEPA filtered and carbon filtered.

12. The normal ceiling heights will be either 8 or 9 ft. except where noted. The corridor ceiling will be moisture-resistant, epoxy painted drywall. The ceiling-to-wall junctions will be sealed with epoxy caulk.

13. The telephone system will provide for intercoms in all laboratories, offices, animal areas and high volume use areas. In wet areas and those subject to washdown they will be provided with suitable weatherproof covers.

14. Certain floors associated with animal movements shall be color coded to reflect level of cleanliness.

15. Utilize air locks and anteroom concept instead of pressure zones or clean-dirty corridor concept. This provides ready access to all storage rooms, electrical breaker switches, non-animal holding rooms, laboratories, elevators and the rest of the building.

Animal Rooms - The following characteristics are incorporated into the animal room specifications:

1. All cracks are to be sealed with epoxy caulk (floor-to-wall, ceiling-to-wall, exhaust ducts, electrical fixtures. etc.)

2. Each room will have timed lighting with a recessed light timer just outside the access door to control the light cycles in the room.

3. A two-stage lighting system will be used. When only the animals are in the room, a light level of 50 ft. candles will be used. When personnel are working or observing within the room, a light level of 100 ft. candles can be made operable by activating a switch next to the light timer control at the door. An automatic timer will switch from the high level to the energy conservation level if personnel forget to turn off the second stage lights. In the complete off position, both first and second stage lights will be turned off.

4. An automatic animal watering system will be used throughout all animal treatment and holding areas.

5. Only one permanent piece of equipment will be included. It will consist of a wall mounted, hooded treatment table with sink. It will be without a storage area underneath to prevent accumulation of unneeded supplies and avoid areas for infestation.

6. The fluorescent-light fixtures will be sealed and moisture-proof.

7. The doors leading into the animal rooms will contain a viewing window. A drop seal at the bottom of each door will be used to prevent any escaped animal from entering various rooms.

8. All doors opening into a room will be self-closing and have recessed hardware and locks.

9. The wall construction will be masonry block sealed with block filler and painted with epoxy paint 8 mils thick minimum.

Module Specific Specifications - The module specific specifications illustrated for a few modules are:

1. Each Cold Storage Room will have a high- and low-temperature alarm. The room volume will be in submodule units of 12 x 18 x 7 ft.

2. The ceiling height of the Cage/Rack Washing (sanitation) Area shall be 13 ft. to allow more space for dispersion of the steam generated by the washing equipment. All cold air ducts in this area will be insulated to eliminate condensation and moisture dripping on employees and equipment.

   The only passage from the "dirty" side of the cage wash subarea to the "clean" side will be through the rack or tunnel washers. The washer doors are to have electronic interlocks so only one door can be opened at a time.

3. The Record Archive and Specimen Storage Areas will have their rooms separated by fire-rated walls with fire-rated, self-closing doors. The ceilings will be constructed of fire-rated materials. Floors are to be concrete. The areas are to be equipped with a Halon 1301

fire extinguishing system. A central security system is provided to prevent unauthorized system. A central security system is provided to prevent unauthorized entry. A temperature control system will maintain storage rooms at 50-80° F. A routine test and/or vermin control service will be employed. Fireproof metal shelving will be employed.

4. Because of the use of volatile chemicals (organic) and their potential danger due to flammability and explosive properties, the floors of the Necropsy Laboratory will be made of conductive material. This minimizes the risk of electrical-charge build-up. All electrical outlets will be explosion-proof. All tables will have hooded exhaust systems above them.

5. For animal watering, city water will be softened and passed through charcoal filters to absorb traces of chlorine, taste and odor. It will then pass through a reverse osmosis membrane barrier where 90% of the dissolved solid and 98% of the bacteria, colloidals and organic materials will be removed. From the reverse-osmosis unit it will go to a reservoir tank. Water exits this tank with a centrifugal pump. It will pass through an ultraviolet light source to kill microorganisms and sterilize the water. It will then pass through three charcoal filters to remove ozone and hydrogen peroxide generated by the ultraviolet light.

   An important aspect of the automated animal watering system is that the water will be constantly flowing and is not stagnant in the room distribution piping system.

General Assumptions

The following general assumptions were made regarding the Facility Module Description, four completed examples of which are contained in Appendix 4:

1. The overall dimensions are approximate, allowing for wall thicknesses and rounded to the nearest ft.

2. No burglar alarm system was included.

3. Corridor air lock doors are generally not shown but implied. Direction of opening is to be subject to exit code requirements.

4. No breeding or quarantine areas were assumed for primates or dogs.

5. No provisions were made for housing chickens. These will be added when the Neurotoxicity Studies get more clearly defined.

6. The quarantine area has been modularized so that one, two, three ..., can be added in parallel to meet the total Facility's requirements capacity.

7. Direction of air flow, i.e., higher to lower pressure, is shown only where critical. If it is not shown it assumes equal pressure acceptable or to be determined.

8. Budget estimates for individual modules would not include costs for: building shell, floor slabs, structural elements (columns, beams, footings), stairways, elevators, main corridors, land, site improvement, site utilities, renovation work, special phrasing costs, design costs, contingencies, permits, fees or legal work.

9. Individual module layouts are conceptual, intended to account for all necessary space in a logical arrangement. When applied to a specific site, they must be adjusted to suit all physical constraints, provide an orderly corridor system and eliminate redundant features.

Toxicology Testing Capacity Per Module

A special project was completed to establish the annual testing capacity based upon incorporating one of each of the 63 modules. Table 9 correlates the number of tests per year per module as a function of test number. To illustrate, the rodent acute oral exposure area (Module 1) can have 773 general toxicology tests done within it in one year assuming 100% efficient use of testing time.

It should be noted the capacity per Module could be varied over a range. Different people would select different design capacities. The approach used was to get experts to design a module and other experts to define the capacity of the module designed. In the majority of cases this proved effective. In some cases, for example, module No. 58, Guinea Pig Acute Dermal Sensitization, the number of tests per year turns out to be high (1,685). The three months of the program did not allow time to redesign module No. 58 for a lower, and possibly more realistic, capacity. Different capacities would result in needing different levels of resources to fabricate and staff.

Supporting Services Capability

As reflected in Figure 2, the support services business area was subdivided into two divisions: Permanent Division and Support Services Division. The former are considered services that are not readily accomplished external to the Facility. Those considered to be able to be purchased on the outside were grouped in the Support Services Division. One additional source of services is through the host Government facility itself.

Permanent Support Services

Figure 2 cites 13 permanent support services varying from oral exposure areas to linen storage. These are services which are difficult, very inconvenient or impossible to have done under contract outside the Facility.

Externally Purchased Services

Figure 2 cites nine services considered obtainable external to the Facility. The chemistry laboratory services, however, can be further subdivided into analytical and synthetic. Table 10 summarizes an analysis completed of Support Services. It evaluates the impact of various factors on deciding whether to incorporate the capability or purchase it.

TABLE 9 TESTING CAPACITY SUMMARY

Test No.	Relates to Test No.	Title	Test Duration D[a]	Module No.	Module Test Capacity	Module Capacity Tests/Yr[b]
		General Toxicology Tests				
1		Acute Oral, Rodent	17	1	36	773
2		Subchronic Oral, Rodent	92	2	4	16
3		Chronic Oral, Rodent	817	3	2	1
4		Acute Inhalation, Rodent	25	5	6	142
5		Subchronic Inhalation, Rodent	100	6	3	11
6		Chronic Inhalation, Rodent	825	7	1	0.4
7		Acute Inhalation, Primate	25	8	1	24
8		Subchronic Inhalation, Primate	100	9	2	7
9		Chronic Inhalation, Primate	825	10	1	0.4
10		Subchronic Oral, Dog	182	4	2	4
11		Acute Dermal, Rabbit	16	11	7	56
12		Subchronic Dermal, Rabbit	105	11	8	56
13		Acute Ocular, Rabbit	14	12	14	311
14		Acute Oral, Neurotoxicology, Chicken	24	61	6	91
15		Subchronic Oral, Neurotoxicology, Chicken	92	61	6	24
16		Acute Dermal Irritation, Rabbit	5	11	58	58
17		Subchronic Dermal Irritation, Rabbit	22	11	8	64
18		Acute Ocular Irritation, Rabbit	14	12	78	311
19		Acute Dermal Sensitization, Guinea Pig	39	58	180	1,685
		Genetic Toxicology Tests				
S20		*In Vitro* Genetic Toxicity	31	62	3	35
S21		*In Vivo* Genetic Toxicity	100	63	1	4
		Special Scientific Toxicology Studies				
SBSa	5	Subchronic Inhalation, Behavioral, Rodent	100	13[c]	1	4
SBSb	8	Subchronic Inhalation, Behavioral, Primate	90	13[c]	2	7
SOSa	3	Chronic Oral, Oncogenic, Rodent	902	16	4	2
SOSb	6	Chronic Inhalation, Oncogenic, Rodent	902	16	1	0.4
SOSc	9	Chronic Inhalation, Oncogenic, Primate	902	16	1	0.4
SRS	3	Chronic Oral, Reproduction, Rodent	412	18	1	1
STS	3	Chronic Oral, Teratology, Rodent	37	19	3	30
SG/OSa	3	Chronic Oral, Gen./Oncog., Rodent	902	16	2	1
SG/OSb	6	Chronic Inhalation, Gen./Oncog., Rodent	902	16	1	0.4
SG/OSc	9	Chronic Inhalation, Gen./Oncog., Primate	902	16	1	0.4
SR/TS	3	Chronic Oral, Repro./Terato., Rodent	412	18	1	1

(a) Includes preparation and cleanup time.
(b) Rounded to nearest whole number if greater than or nearly equal to one. Assumes operation of seven days per week.
(c) Module contains two testing areas, one for rodents and one for primates. Capacity based on testing in specific portion of module.

TABLE 10 EVALUATION OF SUPPORT SERVICES

	Equipment			Service				Personnel		Facility	
				Outside availability							
Service	High cost items req'd	Maintenance cost high	Infrequent utilization expected	Local	National	Schedule demands critical	Required routinely	Specialized training	Labor intensive activities	Space req't. large[a]	Special Considerations
Pathology Laboratory	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	Most applicable to reading slides.
Clinical Chemistry Laboratory	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	Sample preservation and changeable workloads need to be considered.
Animal Breeding	NO	NO	YES	NO	YES	NO	NO	NO	YES	YES	Special strains and special handling may preclude external support.
Veterinary Medicine	NO	NO	YES	YES	YES	NO	NO	YES	NO	YES	Primarily a personnel service, with veterinarian coming into facility.
Analytical/Synthetic Chemistry Laboratory	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	Can be used for QA support, special studies or a capability to handle overload.
Automated Data Processing	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	Safeguarding of classified information may be required.
Radiochemistry	YES	YES	YES	NO	YES	NO	NO	YES	NO	NO	Radiolabeling of compounds available at limited number of locations.
Equipment Maintenance	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	Selecting external support will involve "house-calls" for some maintenance.
Laundry	NO	NO	NO	YES	YES	NO	YES	NO	YES	NO	Storage areas will be required if an outside service is selected.

(a) Module area greater than 2000 ft²

Host-Government Facility Services

A total of 246 business services were identified that could be provided from the host Government Facility especially if the Facility were co-located with other activities within the same building (Life Systems, Inc. 1981e, p. 27). They were coded to include those which should be given serious consideration for being provided by the host Government organization (e.g., LAIR, if LAIR was the site of the added Facility), and those which could be considered good candidates for consideration (total of 40). Final selection depends upon USAMRDC's/DA's priorities, resources, requirements addressed and capability and capacity incorporated.

Special Projects

During the Facility planning effort various special projects were completed:

1. The preparation of a preliminary Facility Specification.
2. A recommendation on locating major equipment items within each of the Facility's modules.
3. Definition of an approach to ensuring compatibility with local pollution laws.
4. A definition of methods for storage and disposal of Army-unique chemicals.

The results of these projects were assembled in the data base. The recommended location of major equipment items, for example, are contained directly in each of the modules and illustrated in Appendix 4.

EQUIPMENT PLAN

This section reviews some of the results of the equipment planning activities completed.

Objectives

The objectives of the equipment planning effort included:

1. Define the equipment needed as a function of each Facility module.

2. Divide the identified equipment into essential, desirable or ideal items so priority decisions can be made and visibility given to type of equipment included.

3. Assemble a data base on equipment costs so that once the final Facility capability and capacity is selected, the data needed to make economic judgments will be available.

Assumptions

The assumptions used in the equipment planning included:

1. No specific budget existed.

2. No supporting services would be obtained externally.

3. Technology and regulatory changes were not considered in determining the types of equipment required for the Facility.

4. Medium quality equipment was selected for establishing the price of the equipment.

5. None of the existing major or minor items available at the Government-owned site were to be considered available for shared use or to be provided to the Facility.

6. When cost for minor equipment items were to be summarized, if appropriate, to be done as a total cost for miscellaneous items for each module.

7. Moveable equipment could be selected in preference to built-in equipment to provide flexibility and reduce installation costs.

8. It was acceptable for nonscientific equipment to be priced as a lump sum figure for each module.

9. Equipment items will be procured only two times during the ten year period: prior to start of operations and at the end of five years of testing.

10. Unless specified, all items will be available within two and one-half months of their requisition date.

11. Built-in equipment will be installed during the Facility construction phase.

12. Equipment utility needs will be provided by the Facility during construction.

13. Although a module's equipment can be considered moveable within the module, for planning purposes it was not considered to be moveable from one module to another.

14. It was acceptable to have the preparer of each list equip the module to provide a first-rate testing facility.

Equipment Types

The program identified three different types of equipment:

1. Moveable scientific equipment.
2. Built-in equipment.
3. Office furniture and other nonscientific equipment.

Moveable Scientific Equipment

Many equipment items can be used at several different locations within a module. A preference was given, therefore, to moveable over built-in equipment.

Built-in Equipment

Two types of built-in equipment existed: scientific (e.g., the inhalation chamber) and nonscientific (e.g., the Facility heating plant). All built-in equipment required for the full ten years of operation was incorporated during the installation phase of each stage in the buildup of the Facility's capability.

Office Furniture and Other Nonscientific Equipment

These items were itemized on the equipment lists or included as a lump sum cost per module if the total cost did not exceed $1,000.

Two Five-Year Phases

As noted above, the Facility was planned to be implemented in two phases. The equipment needed was also identified in two phases. In this case, however, the phases reflect which items of equipment might not have a lifetime of ten years and, therefore, require replacement.

Each item of equipment was evaluated to determine its projected lifetime. The number of items needed for five years of operation were determined and included in the cost for the first five years. The same was true of equipment items whose life exceeded five years but was less than ten years. No replacement cost was included for equipment with a life over ten years.

Equipment Lists

Equipment lists were prepared for each of the 63 modules. This enabled an accurate picture of the equipment costs for each module to be obtained, and allowed equipment cost per square foot per module and cost for the total Facility to be calculated. The lists were also an aid in defining the Facility personnel requirements (e.g., special equipment operators).

Information

The information contained on the lists is shown in Appendix 4 where copies of four examples are provided. The information contained on the lists includes:

1. Date it was prepared.
2. Name of the individual who prepared it.
3. Module number (area/laboratory).
4. Module title.
5. Equipment title, its function and estimated cost.
6. Title of any special operator--important in determining personnel needs.
7. Capacity of the equipment (where appropriate and in terms of samples per unit time).

8. Expected life (greater than five to ten years or greater than ten years).

9. Weight and dimensions as this relates to ensuring Facility compatibility (providing for movement of the equipment through halls, doors, elevators, and stairs and for acceptable structural capability).

10. Voltage requirements as this relates to special power needs.

11. Special requirements, such as scrubbers or filters for exhaust air.

The equipment lists for all 63 modules were submitted previously (Life Systems, Inc. 1981k).

Experts with first-hand experience in operating and/or managing similar modules were selected to prepare the equipment lists. Personnel from five organizations participated. Each list was then reviewed by a Life Systems' team to ensure all information was complete, the data consistent, equipment compatible with the Facility's module design and the built-in equipment designated on the module's floor plan.

Essential, Desirable or Ideal Categories

Equipment on the lists were coded into essential, desirable or ideal categories.

Essential equipment included all items a module must have to satisfy QA and GLP requirements as well as to carry out the module's function.

Desirable equipment included items felt not absolutely critical to meeting the testing requirements. Often, however, the deletion of the desirable equipment would result in higher operating costs once the Facility was operational.

Ideal equipment included those items that would have low utilization rates. These items were considered to have the lowest priority and not vital to satisfying QA and GLP requirements.

Special Projects

During the equipment planning effort various special projects were completed. They included:

1. Identification of high cost equipment items.

2. Compatibility of equipment with the dimensions of the Facility's corridors, doors, etc.

3. Equipment cost savings because of equipment available at the LAIR.

4. Analytical chemistry capability that is available external to the Facility in the San Francisco Bay area.

5. A study of inhalation chamber sources of supply, availability and characteristics.

6. Techniques for acquiring Government-Furnished Equipment to lower equipment costs.

The results of these projects were presented elsewhere (Life Systems, Inc. 1981f).

High Cost Items

These items are defined as those having a cost of $20,000 or greater. As Table 11 indicates, the total cost for a complete set of these items would be $3.9 million.

Compatibility with Facility

Table 12 lists the large equipment items for the Facility. They also represent the heavier equipment items that, during the final design phases should be screened to ensure the structural capability of the selected site is adequate. None was found or considered to be greater than the structural capability of LAIR or Hunter's Point.

Equipment Available at LAIR

Table 13 contains a list of major equipment items potentially available if the LAIR was selected as the Facility's site. The availability of this equipment would represent a $4.5 million savings in equipment cost. No equipment is available at Hunter's Point. Even the central utilities will need replacing there.

External Analytical Chemistry Support

Analytical chemistry support is available at a number of laboratories within the San Francisco Bay area. A study of this support was made and, as expected, as the level of testing sophistication increases, the number of laboratories with the equipment and personnel to perform the analyses decreases.

Inhalation Chamber and Supporting Equipment

A survey was performed to provide a comprehensive and detailed collection of information and data needed for designing the inhalation toxicology systems. It involved the surveying of 16 different research/toxicology sites for their chamber characteristics and six chamber manufacturers for the identification of inhalation chamber characteristics and operating procedures. Appendix 5 presents the summary tables (Life Systems, Inc. 1981i).

Government-Furnished Equipment

Use of Government-Furnished Equipment can decrease the cost of the equipment needed by the Facility. The availability of excess DA and DOD equipment can be obtained from a computer-based equipment reutilization program. Federal stock numbers for each equipment item must be identified. The Defense Property Disposal Office initiates computer searches for equipment items on either a national or regional basis. Requisitioning procedures can be initiated when the acceptable equipment item is found.

TABLE 11 HIGH COST[a] EQUIPMENT ITEMS FOR AMTR FACILITY

Items	No. Required in a Facility Containing One of Each Module	Cost, $(000)	
		Estimated Each	Total
Pyrolyser	1	300	300
GC (Electron Capture/FID)	2	30	60
GC-MS with Data Processing	1	150	150
HPLC	3	40	120
Electrophoresis Integrator and Recorder	1	30	30
Infrared Spectrophotometer	1	20	20
Atomic Absorption Spectrophotometer	2	20	40
Autoclave	1	50	50
Microscope	1	22	22
Electron Microscope	1	100	100
Liquid Scintillation Counter	4	20	80
Recording Chambers	4	20	80
Walk-in Freezer	2	20	40
Tunnel Type Cage Washer and Dryer	1	75	75
Centrifugal Analyzer with Pipettor and Computer	1	75	75
Storage Building	1	30	30
Microfiche System	1	22	22
Special Inhalation Chamber for Primate Behavioral Studies	2	25	50
Transformer	6	20	120
Diesel Generator	2	140	280
Parallel Switch Gear	2	20	40
Water Softener	2	25	50
Deionizer	1	100	100
Wastewater Treatment System	1	800	800
Centrifugal Chiller	4	20	800
Air Supply System	1	100	100
Air Exhaust System	1	100	100
Boiler, Primary	1	60	60
Boiler, Secondary	2	40	80
Telphone Communication System	1	35	35
			3,909

(a) Equipment cost of $20,000 or more.

TABLE 12 LARGE EQUIPMENT ITEMS FOR AMTR FACILITY

Equipment Item[a]	Dimensions[b]
Safety hood system	72 x 30 x 84
Cage rack[c]	72 x 30 x 72
Inhalation exposure chamber for acute studies with rodents[d]	30 x 30 x 84
Inhalation exposure chamber for subchronic studies with rodents[d]	36 x 36 x 84
Special purpose inhalation exposure chamber[d]	72 x 36 x 84
Inhalation exposure chamber for chronic studies with rodents and for primate exposures[d]	72 x 72 x 132
Walk-in freezer	180 x 120 x 96
Walk-in refrigerator	108 x 144 x 84
Hood inclosure	120 x 120 x 96
Feed pallet[c]	96 x 24 x 24
Cold box	96 x 96 x 84
Primate housing unit	30 x 30 x 80
Dog pens	48 x 96 x 72
Refrigerator[c]	72 x 96 x 84
Rack washer	84 x 90 x 96
Tunnel type cage washer and dryer	30 x 360 x 72
Autoclave	36 x 72 x 96
Freezer[c]	84 x 33 x 84
Magazine rack[d]	36 x 12 x 82
Bookcase[d]	36 x 12 x 82
Mirror	36 x 0.5 x 72
Electric pallet cart[c]	33 x 26 x 92
Shelves[d]	36 x 24 x 85
Table[d]	30 x 72 x 29
Hobart mixer (50 kg)	48 x 60 x 60
Pyrolyzer	Various
Walk-in hood	90 x 42 x 108
Worktable w/sink	84 x 29 x 37
Transformer	80 x 96
Diesel generator	48 x 1400 x 72
Parallel switch gear	36 x 54
Fuel storage tank	240 x 96 x 60
Muffler	120 x 36
Water softener	120 x 300 x 180
Deionizer	180 x 360 x 300
Wastewater treatment system	Variable
Centrifugal chiller	156 x 216 x 96
Air supply system	Various
Air exhaust system	Various
Boiler, primary	348 x 120
Boiler, secondary	120 x 96
Steam condensation tank	91 x 42
Expansion tank	91 x 42

(a) Items with at least one dimension 72 in. or items with all dimensions 48 in. All are built-in unless indicated.
(b) Width x depth x height in inches.
(c) Movable equipment items.
(d) Movable or built-in depending on design chosen.

TABLE 13 MAJOR EQUIPMENT ITEMS POTENTIALLY AVAILABLE AT LAIR

- Racks
- Cages
- Non-scientific Equipment, Administrative Furniture (e.g., Files)
- Laboratory Benches
- Laboratory Balances
- Installed Hoods
- Necropsy Room Equipment
- TOXSYSTEM (Hardware and Software)[a]
- Data General Eclipse C330 Computer[a,b]
- Electron Microscope
- Cage Washer[a]
- Animal Feed and Storage Items[a]
- Pathology Laboratory Items[a]
- Radioisotope Counting Items[a]
- Transformer
- Diesel Generator
- Fuel Storage Tank
- Parallel Switch Gear
- Deionizer
- Centrifugal Chiller

(a) Trained operator currently available within LAIR.
(b) Available for on-site scientific computation efforts.

A second source of excess DOD equipment is through the Defense Logistics Service Center. Both this and the Defense Property Disposal Office, however, should have access to the same list of excess equipment items.

Excess equipment from non-DOD Government agencies can be found by using the General Services Administration's (GSA's) Property Disposal Offices. It maintains a separate listing of high value items (those in excess of $100,000). Again, the federal stock numbers are needed for identification.

PERSONNEL PLAN

This section reviews some of the results of the personnel planning activities completed.

Objectives

The objectives of the personnel planning effort included:

1. Identify the types of personnel required.
2. Determine supply and demand for these personnel and project lead times for their hiring.
3. Determine the level of Government staffing if the Facility is operated as a GOCO.
4. Identify the key portions of the recruitment portion of the personnel plan.

Assumptions

The assumptions used on the personnel planning effort included:

1. The Facility might be located in San Francisco (LAIR or Hunter's Point).
2. The Facility will be contractor-operated.
3. Government staffing will be minimized, but will be consistent with fulfilling responsibilities set out in regulations.
4. The personnel will be for the full service capability: research and testing, special scientific toxicology studies and all supporting services (both permanent and those that might be acquired outside). The personnel will include operators of special pieces of equipment (e.g., GC/MS operator).

Person Power Plan

An outstanding team of people can overcome many Facility shortcomings. Personnel and the policies and guidelines established for the Facility are the most important keys to a quality operation.

The approach used was to address people power from an organizational viewpoint. This allowed meeting the personnel requirements for a modular conceived Facility ablt to perform all the various tests and research projected to be needed to meet the Army's and USAMRDC's requirements.

Personnel Organization

Figure 2 presented the business organization for the Facility.

Personnel Descriptions

Table 14 provides a list of titles for required personnel. It shows the labor category: professional, technician, management or administration and it also identifies which personnel are expected to have one or more special certifications. A description of the titles is presented elsewhere (Life Systems, Inc. 1981g), including a statement of the education and experience level required for each of the personnel cited.

Personnel Requirements

First, the types of personnel required for each of the modules were identified (Table 15). Then the data were tabulated according to personnel type and the modules in which they are expected to function. From the results in Table 14 and 15 it can be seen that animal caretakers, animal technicians, laboratory technicians, maintenance personnel, pharmacologists, general toxicologists, immunologists, instrument operators, necropsy supervisors and necropsy technicians are each required for nine or more modules.

Recruitment Plan

Many factors go into assembling a recruitment plan. Some of those identfied during the Study are reviewed below.

Lead Time

Five steps are typically involved between identifying a potential candidate for hire and actual hiring. These include: identification of leads, invitation for interview, actual interview, offers, acceptance of offers and actual hiring. Typically it is found that 24 leads are required to hire one person (Hawk 1967).

Figure 3 predicts the time versus number of personnel for each step in the recruitment process. A minimum of five months is needed to hire 100 employees. Regardless of exact size of the Facility, it is expected that a minimum of five to six months will be needed to staff the Facility. Conservatively, a minimum of one-person year of effort is needed for each 50 people hired.

Forecast of Supply and Demand of Key Facility Personnel

The Study identified the following key personnel likely to be in short supply:

1. Aerosol chemists.
2. Immunologists.
3. Pharmacodynamicists.

TABLE 14 AMTR PERSONNEL TITLES

Title	Category: Technical — Professional	Technical — Technician	Management & Administration	Special Certification(s)
Administrative Clerk			X	
*Aerosol Chemist	X			
Analytical Chemist	X			
Animal Caretaker		X		
Animal Technician		X		X
Biochemist	X			
Biologist	X			
Bookkeeper			X	
Cage Washer		X		
Clinical Chemist	X			
Compound Preparation Technician		X		
Computer Coder			X	
Computer Programmer			X	
Electron Microscope Operator	X			
Facility General Manager			X	
Histology Supervisor	X			
Histology Technician		X		
HVAC Engineer	X			
*Immunologist	X			X
Industrial Hygienist	X			X
Information Specialist	X			
Instrument Operator		X		
Keypunch Operator			X	
Laboratory Technician		X		
Literature Review Specialist		X		
Maintenance Personnel		X		
Necropsy Supervisor	X			
Necropsy Technician		X		
Occupational Physician	X			X
Organic Chemist	X			
Personnel Officer			X	
*Pharmacodynamicist	X			X
*Pharmacokineticist	X			X
*Pharmacologist	X			X
Pharmacology Chemist	X			X
Physiologist	X			X
Purchasing Agent			X	
Quality Assurance Officer	X			
Radiological Health Officer	X			X
Secretary			X	
Statistician	X			
Supply Clerk			X	
Technical Editor			X	
Test Manager	X			
*Toxicologist	X			X
a. Behavioral	X			X
b. General	X			X
c. Metabolist	X			X
d. Mutagenesist	X			X
e. Neurotoxicologist	X			X
f. Oncologist	X			X
g. Pulmonary	X			X
h. Teratologist	X			X
Toxicology Program Manager			X	
Training Officer			X	
Typist			X	
Veterinarian	X			
a. Lab Animal Officer	X			X
*b. Ophthalmologist	X			
*c. Pathologist	X			X

TABLE 15 PERSONNEL BY AMTR FACILITY/AREA LABORATORY

Personnel Titles	No. of Modules	AMTR Facility Areas/Laboratories[a,b]
Administrative Clerk	1	60
Aerosol Chemist	6	5, 6, 7, 8, 9, 10, 13, 16
Analytical Chemist	2	29, 31
Animal Caretaker	24	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 16, 17, 18, 19, 24, 27, 28, 58, 61, 63
Animal Technician	24	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 27, 28, 58, 61, 63
Biochemist	3	14, 15, 26
Biologist	1	62
Bookkeeper	1	60
Cage Washer	1	32
Clinical Chemist	1	26
Compound Prep. Tech.	1	20
Computer Coder	1	30, 59
Computer Programmer	1	30, 59
Electron Microscope Operator	1	25
Facility General Manager	1	60
Histology Technician	1	26
Histology Supervisor	1	26
HVAC Engineer	6	5, 6, 7, 8, 9, 10, 13, 16
Immunologist	9	1, 2, 3, 4, 5, 6, 7, 8, 9, 16
Industrial Hygienist	1	37
Information Specialist	1	36
Instrument Operator	9	5, 6, 7, 8, 9, 10, 13, 14, 15, 23, 27, 29, 31
Keypunch Operator	1	30, 59
Lab. Technician	15	13, 14, 15, 16, 17, 18, 19, 23, 25, 26, 29, 31, 61, 62, 63
Literature Review Specialist	1	36
Maintenance Personnel	13	21, 32, 35, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 59
Necropsy Supervisor	9	1, 2, 5, 6, 8, 9, 11, 12, 16, 25
Necropsy Technician	9	1, 2, 5, 6, 8, 9, 11, 12, 16, 25
Occupational Physician	1	37
Organic Chemist	4	14, 15, 29, 31
Personnel Office	1	60
Pharmacodynamicist	1	15
Pharmacokineticist	1	14
Pharmacologist	23	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 16, 17, 18, 19, 58, 61, 62, 63
Pharmaceutical Chemist	2	14, 15
Physiologist	2	13, 17
Purchasing Agent	1	60
QA Officer	1	23
Rad. Health Officer	2	31, 37
Secretary	2	37, 60
Statistician	1	37
Supply Clerk	1	38
Technical Editor	1	37
Test Manager	1	37
Toxicologists		
Behavioral	1	12
General	12	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Metabolic	1	14
Mutagenic	2	62, 63
Neurotoxicology	1	61
Oncogenic	3	3, 7, 10
Respiratory	1	17
Teratology	1	19
Toxicology Prog. Manager	1	37
Training Officer		37, 60
Veterinarians		
Lab. Animal Officer	3	24, 27, 28
Ophthamologist	1	12
Pathologist	1	25

(a) Principal areas where personnel would be expected to perform their work.
(b) Refer to attached AMTR Facility Areas/Laboratories List for definition of area codes.

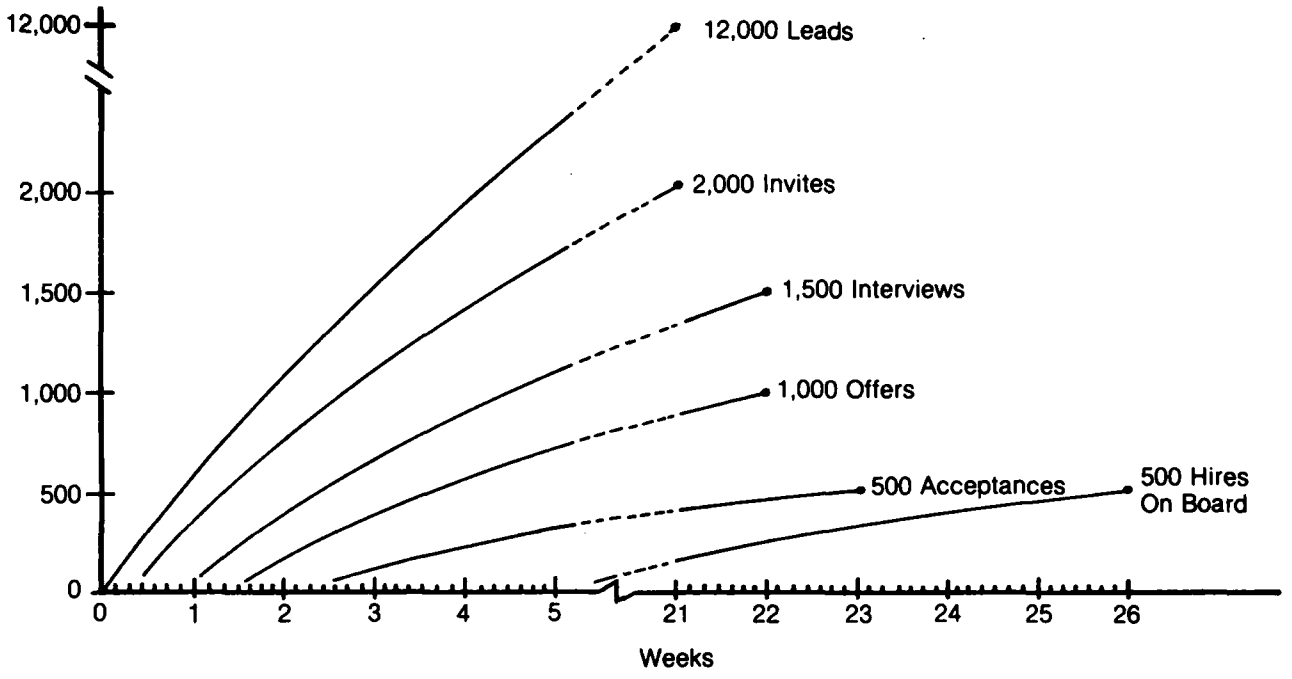


FIGURE 3 RECRUITMENT SCHEDULE

4. Pharmacokineticists.
5. Pharmacologists.
6. Toxicologists.
7. Veterinary Pathologists.

More details concerning the forecasted short supply of these personnel are presented elsewhere (Life Systems, Inc. 1981g).

Competition for Scarce Personnel Resources

Competition for scarce personnel must be met by effective recruitment and retention of personnel once hired. Also, efforts to reduce or eliminate the need for scarce resources should always be followed. Note, however, personnel that are scarce for the Facility are also scarce nationally.

Aerosol Chemist. An aerosol chemist is critical to many inhalation toxicology studies. No supporting data was obtained, however, on the number of trained aerosol chemists available or the demand for their services.

Toxicologist/Pharmacologist. A recent report (The Conservation Foundation 1978) estimated there are approximately 2,700 senior toxicologists and a total of 5,000 toxicologists in the United States. The report projects an immediate need for an additional 900 and 300, respectively, toxicologists based upon projected industrial and Government requirements to meet just the TSCA and RCRA regulations. In addition, the report notes 200 more such individuals are needed per year to offset attrition through retirement, career changes, etc. By comparison, the estimated number of toxicologists entering the field annually from university programs is between 135 and 150.

The Federal Government traineeship programs (through the National Institute of Environmental Health Science (NIEHS)) are expected to increase the annual output of toxicologists from university training to about 200. This program is currently undergoing budget review and its continuation and level of support are uncertain. The NIEHS also has a program that retrains scientists from ancillary fields for up to three years to enable them to perform as toxicologists. As currently funded, it can provide an additional 25 toxicologists annually.

Two additional supply and demand studies (Developmental Planning and Research Associates, Inc. and ICF, Inc. 1980, ICF, Inc. 1980) have concluded the availability of experienced toxicologists and pathologists is a limiting factor in designing, conducting and interpreting applied mammalian toxicology research and testing.

Veterinary Pathologists. Veterinary pathologists are the most critically-in-short-supply of all toxicology personnel. Only 512 practicing members existed in the United States as of March, 1980. Of these, less than 140 are employed in contract or sponsor laboratories. The majority are in teaching, in research, in the military or with drug firms.

Competition for Personnel

The Study determined competition for personnel can be enhanced by using a combination of compensation, location, professional environment, training and

ownership. A combination of techniques will be needed to properly staff the Facility with quality personnel.

The Study went into the detail on each of these factors. Adequate compensation, (salary, job enjoyment, location of the Facility in the vicinity of universities, etc.) contribute significantly to attracting personnel.

Personnel Development

As part of the personnel planning activity, an outline for a personnel development program was completed. It included eight areas:

1. Compensation policy - to attract, retain, provide incentives and maintain competitiveness with competitors for the personnel.

2. Salary structures - needed for staffing the Facility.

3. Job evaluation - to systematically define the duties and responsibilities of each position and to determine its relative value to the Facility.

4. Performance appraisal - as a process to foster growth and evaluate performance (considered secondary to furnishing a sound and consistent basis for salary administration).

5. Job objectives and performance standards - to ensure objective performance appraisals and that actual performance can be measured against the standards for the position.

6. Various bases for salary adjustments.

7. Communication with employees - essential to ensure each is systematically and fairly reviewed.

8. Personnel training - both short and long-term, informal and formal included in-house, at a local university, etc. Training is a key to career development.

Special Projects

During the personnel planning effort various special projects were completed:

1. Identification of special skills needed by personnel.

2. Identification of the most applicable Federal and California State laws.

3. Establish techniques to avoid potential conflicts between Government and non-Government employees.

4. Establish techniques to maximize the utilization of pathologists.

All were evaluated during the Study but not found to be major issues.

Government Staffing

If the Facility is operated as a GOCO, Government personnel are required to provide technical and contract administration. Government regulations establish minimum requirements to be satisfied by the USAMRDC to fulfill it's obligations relative to contract administration. A survey of various GOCO operations indicated that the ratio of Government staff to contractor staff varies as a function of GOCO size from approximately one to eight for a smaller GOCO to 1 to 20 for a larger GOCO. These results are summarized in Table 16 but compiled from actual data presented later (Figure 5).

QUALITY ASSURANCE PLAN

This section reviews some of the results of the Quality Assurance (QA) planning activities completed.

The Facility has been designed as a full service capability mammalian toxicology research/testing facility. As such, much of its key functions will come under the GLP regulations. The purpose of these regulations is to assure that tests to prove the safety of materials to human health are performed in accordance with accredited procedures, and that the study data are of suitable quality and integrity.

The GLP regulations of the Food and Drug Administration (FDA) and EPA require the creation of a Quality Assurance Unit (QAU) within facilities performing nonclinical toxicology research and testing. However, the GLP's also form the basis of effective Quality Assurance programs for use in other research as well.

Objectives

The objectives of the QA planning effort included:

1. To provide a plan for organizing and implementing a QA Department for the Facility. The primary function of this department will be to ensure all toxicology research and testing complies with the Facility's QA requirements and GLP regulations.

2. To facilitate preparation of the necessary QA Manuals (i.e., separate QA Manuals will be required for different technical areas):

    a. To provide a systematic plan for their preparation.
    b. To provide needed guidelines.
    c. To minimize the time, effort and cost for their preparation.

3. To budget resources required by the QA activities, including compliance with GLP:

    a. Personnel requirements.
    b. Facility and equipment requirements.

Assumptions

The assumptions used on the QA planning efforts included:

TABLE 16 PERSONNEL REQUIREMENT ESTIMATES FOR GOCO AMTR FACILITIES[a]

Annual Amount of Testing, $(Millions)	Government Staff[b]	Contractor Staff[c]
5	10	83
10	17	166
20	30	400
40	40	800

(a) Assumes all services required for testing are provided in-house.
(b) Calculated from analysis of data collected from survey of GOCO AMTR facilities.
(c) Figures calculated from analysis of AMTR facility staffing and person power requirements/tests. Assumes contractor provides all professional and technician level personnel required to perform all toxicology testing.

1. The Facility will have a full service capability.

2. The QA Manager will be on-board at startup.

3. The Facility will conform to the FDA's GLP regulations and the EPA's proposed GLP regulations. It will undergo and pass FDA GLP inspections.

4. The Facility will be divided into the six business functions cited in Figure 1.

5. The Toxicology Research/Testing Directorate will include a division/department/section for each of the ten scientific toxicology disciplines indicated in Figure 2 (e.g., behavioral toxicology).

Facility and Organization

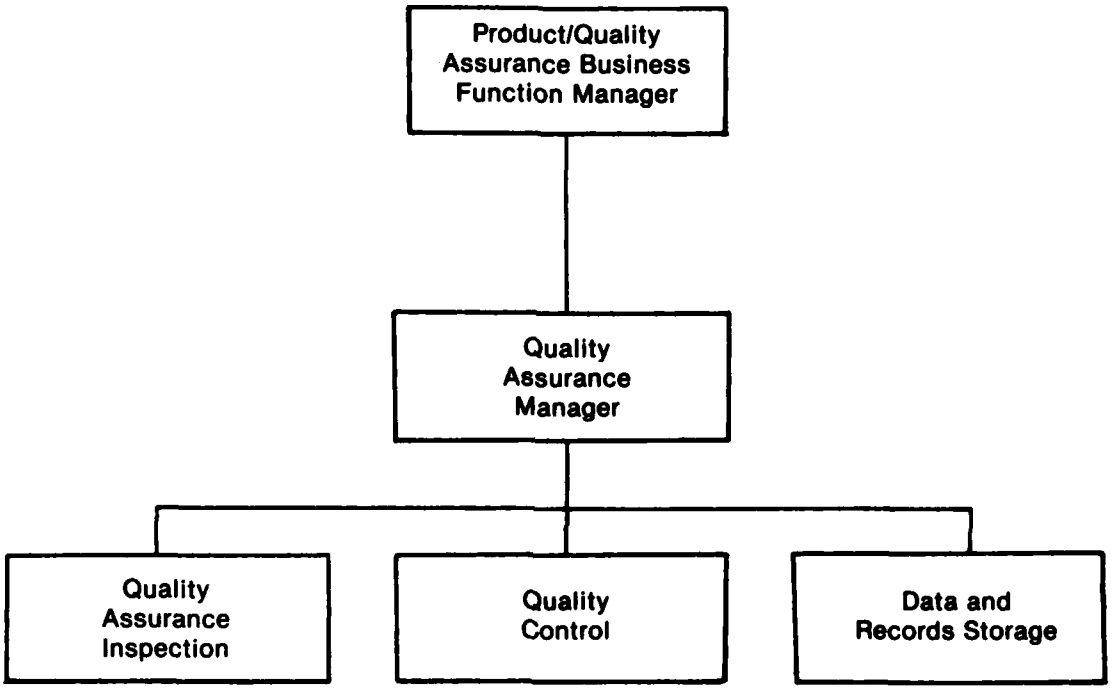
By its very nature, the QA function in a laboratory such as the mammalian toxicology research and testing Facility permeates the entire operation. The Facility's management should view this as an advantage and capitalize on it by encouraging QAU participation in protocol development, research problem solving, interdepartmental liaison, overall QA and even sponsor (user) contact. In essence, QAU will be management's and the sponsor's assurance that GLP's are being met. The QAU will scrutinize laboratory procedures from a management as well as from a scientific perspective.

The QAU will help in such areas as staff training and research and testing efficiency. Standardization, systematization and documentation will produce a method--independent of financial and scientific management--of managing projects and data. Standardization and documentation will be, in fact, the major manifestations of GLP influence on the Facility's operations. This will cause management to review procedures, such as the use of computers for direct access to test animal weights, observations and pathology data. This will not only reduce recording time and errors, but will also make final report preparation more efficient.

In light of the foregoing and with information provided elsewhere (Life Systems, Inc. 1981c), the Facility will develop an entire QA Program that includes GLP compliance as one of its basic parts. It will take into account the interactions between components of the Facility. It will reflect that FDA inspectors and study sponsors will be concerned with more than one of the Facility's components and, because of this, the QA system must be standardized and uniform throughout the Facility.

Description

The functions of the QA Department (which serves the functions of the QAU mandated by GLP regulations) shall be organized as illustrated in Figure 4. The QA business function is organized around the GLP regulations and guidelines, but also covers the internal QA requirements of the Facility. The QA Manager is directly responsible to the Product/Quality Assurance Business Function Manager of the Prime Contractor. The QA Manager is only indirectly responsible to the Facility Manager. This preserves the requirement of QA not reporting to personnel associated with or involved in a nonclinical or hazard evaluation study.



- Facilities Inspection
- Equipment Inspection
- Audit Inspection

FIGURE 4 QUALITY ASSURANCE DEPARTMENT ORGANIZATION CHART

There are three functions reporting to the QA Manager to ensure unbiased and independent judgments concerning the conduct and evaluation of these studies: (1) QA Inspection, (2) Quality Control (QC) and (3) Data and Records Storage.

Scope of Operation

The scope of operation of the QA Department is as follows:

1. Define, identify, prepare and implement procedures.

2. Assure GLP compliance and compliance with all other QA requirements by monitoring, inspecting and auditing all study phases.

3. Assure inspection, calibration and maintenance of all instruments and scientific equipment.

4. Establish and maintain a QC and proficiency testing program in all areas utilizing quantitative analytical instrumentation.

5. Maintain the Record Archives Area in which all data generated as a result of a study will be stored.

6. Maintain a storage area for all test and control articles.

7. Receive, log and control all test and control articles.

8. Maintain primary certified weights and measures and ensure an ongoing certification program.

9. Maintain a QC Acceptance Program for all incoming consumables.

10. Maintain a complete file of all original SOP's and revisions as a historical file.

11. Establish and implement SOP's for the conduct of QA internal inspections and inspections by the FDA, EPA and/or individual study sponsors.

Responsibilities

The QA Department is responsible for ensuring the facilities, equipment, personnel, methods, practices, records and all other pertinent elements of a study are in conformance with the QA requirements, GLP regulations and guidelines including:

1. Maintaining a copy of the master schedule sheet of all studies, including descriptive titles, nature of the study, start and projected completion dates, sponsor status, study director's name and final report status.

2. Maintaining copies of all study protocols, including changes.

3. Periodically inspecting each phase of a study.

4. Maintaining written and signed records of each inspection, giving inspection date, study identity, phase, name of inspector, findings and problems, and any other recommendations or actions and reinspection dates.

5. Periodically submitting written status reports to management and the Study Director of each study inspection, noting any problems and recommended actions.

6. Determining if deviations from protocols or SOP's were made, and ensuring that proper authorization and documentation exists.

7. Reviewing the final report to ensure the report accurately documents the efforts performed, the SOP's used and the raw data.

8. Preparing and signing the statement to be included with the final report which specifies inspection dates and dates of reports to management.

9. Ensuring that any required corrective actions are taken in a timely manner.

Personnel Responsibilities

The following sections are descriptions of the titles and responsibilities of personnel required to function in the QA Department. More detail is presented elsewhere (Life Systems, Inc. 1981c).

Quality Assurance Manager

The QA Manager is responsible for direction, coordination and execution of the QA Scope of Operation (see above); defines QA/GLP requirements; ensures all aspects of GLP regulations and guidelines are met; assigns QA specific tasks to be conducted; prepares detailed implementation plans for QA activities; sets guidelines for technical training and documentation; identifies, defines and prepares specific QA SOP's and acts as focal point for coordination and distribution.

Quality Assurance Inspector

The QA Inspector is responsible for carrying out the plans and programs initiated by the QA Manager with regard to facilities, equipment and audit inspection for QA/GOP compliance. The QA Inspector coordinates and supervises the activities of the QA Facilities Inspector, QA Equipment Inspector and QA Audit Inspector.

The functions reporting to the QA Inspector are defined in greater detail below.

Facilities Inspector. The function of QA Facilities Inspection is to determine and assure that facilities associated with inhalation exposure, oral exposure, dermal/ocular exposure, animal quarantine, food preparation/blending and waste handling/disposal in all laboratory areas conform to Federal regulations (GSA 1980a, GSA 1980b, GSA 1979). The Facilities Inspection function secondarily serves other areas such as equipment, records, reports and studies efforts.

Quality Assurance Equipment Inspector. The primary duty of the QA Equipment Inspection function is to assure the proper inspection, maintenance, calibration of all technical equipment used in the conduct of a toxicology study. Secondarily, an Equipment Inspector may carry out the functions of inspecting facilities, records, reports and studies.

Quality Assurance Audit Inspector. The primary duty of the QA Audit Inspection function is to validate toxicology studies by data trail audit to include corrective action and traceability of instruments, control articles, test articles and test systems. Secondarily, an Audit Inspector may act as an inspector of facilities and equipment.

Quality Control Chemist

The QC Chemist function is responsible for administering the chemistry proficiency testing program in the facility; maintaining the control article repository; preparing and assigning control article blind samples; receiving and reviewing the analytical data (this includes notebook information, chromatograms and other raw data) and determining if they are within performance specifications. The QC chemist function maintains control charts, informs management of problem areas, and conducts a testing program to determine the acceptability of consumables.

Data and Records Storage Supervisor

The Data and Records Storage function is responsible for organizing and maintaining the data storage repository in a systematic fashion. This function checks out and maintains records of laboratory books, including their return, and files, distributes and assists in updating SOP's.

Protocols and Procedures

The GLP regulations require that each study has an approved written protocol which clearly indicates the objectives of the study and all the procedures planned for conducting it. There are 16 specific protocol requirements contained in the regulations. Regulations also require that SOP's be written which detail all operations employed by the Facility in conducting studies.

The combined impact of protocol and procedural documentation can be enormous. Thousands of pages will be involved. Multiplying that number by the many copies needed to provide the documentation to all who require it can result in hundreds of thousands of pages. It is clearly imperative, therefore, that an effective system be developed which will constrain and control the entire procedure so that it does not become a burden.

Protocols

Three factors are important (in addition to responding to the 16 specific protocol requirements) in developing study protocols:

1. Protocol format.
2. Procedure reference.
3. Protocol approval.

Protocol Format. A standardized format for study protocols will be developed. Its purpose is to place certain technical details into predetermined sections of the protocol. These sections will always be maintained in the same order relative to each other. Users, therefore, can quickly find specific information in a lengthy protocol.

Procedure Reference. The protocol procedure will require specific SOP's be listed in the text by their identification number. These numbers will identify the exact technical activities used in the study without having to write lengthy technical procedures into each study protocol.

Protocol Approval. Although GLP regulations state that approval by only the study sponsor and the Study Director are sufficient for new or amended protocols, Life Systems recommends that approval by the QA Department and at least one member of management also be required. This will help to ensure that each key member of the Facility's management team is aware of the requirements placed on the Facility and its personnel before any study starts.

SOP Development

Several types of SOP's will be required to describe such Facility functions as policy, administration, technical operations, equipment operation and analytical methods. Written standards will be established for each of these. In effect, this will provide specific written instructions on how to prepare procedures for each of the Facility's discrete operations.

The need for preparing written procedures for SOP's is apparent when one considers there will be hundreds of procedures required for the Facility. The result would be chaotic if each had a style and format different from every other.

The SOP system will not only satisfy the requirements of GLP regulations but also will be a valuable management tool. The SOP's will minimize training efforts for new employees and will greatly reduce errors and misunderstandings concerning the proper procedural conduct of studies.

Once procedures covering preparation of SOP's are written and approved, the authorship of individual SOP's will be the responsibility of suitably qualified personnel who are designated to write them. All SOP's will be reviewed and edited by the QA Department which will also maintain the master file or manual of the SOP's protocols and amendments.

Appendix 6 contains a listing of titles of QA SOP's that will be required by the Facility. Brief discussions which summarize the salient points of each of the categories of SOP's contained in Appendix 6 are presented elsewhere (Life Systems, Inc. 1981c).

Other Documents

In addition to protocols and SOP's, other documents needed include position descriptions for personnel. Such descriptions will be prepared by Personnel.

Position Descriptions. These will contain information on the following topics:

1. Preparation date.
2. Position title.
3. Department.
4. Individual's supervisor.
5. Personnel reporting to the individual.
6. Duties and responsibilities.
7. Position requirements:.

    a. Education.
    b. Experience.
    c. Certification.

Curriculum Vitae (CV) must be prepared for the personnel. All CV's should include additional and/or on-the-job training acquired by staff members. Particularly important is verification of training in performance of specific SOP's, health and safety requirements, etc.

Quality Assurance Manual. The QA Manual is the document that contains the QA SOP's and personnel documents described above. The Master QA Manual will be used primarily only within the QA Department. Other departments within the Facility will be provided with smaller QA Manuals that include only the information they need to perform their functions.

Facilities

The facilities for the QA Department consist of the Quality Assurance Laboratory (given designation of Module 23), the Record Archives Area (Module 40) and the Specimen Storage Area (Module 41). Dimensions, planned arrangement of the major pieces of equipment, significant construction details and cost information are shown for these modules in Appendix 4.

Equipment

Appendix 4 also contains a list of equipment required by the Quality Assurance Laboratory, Record Archives Area and Specimen Storage Area.

Standard Reference Equipment

The QA Laboratory will require various pieces of standard reference equipment, such as weights (Class S), volumetric flasks (Class A), thermometers, a wide variety of calibration standards for selected analytical methods and instruments, and National Bureau of Standard standards reference samples.

Management Information System

The Management Information System (MIS) is a comprehensive, computer-based information system which includes:

1. A recordkeeping system.
2. A comprehensive data base.
3. An integrated data processing system.

The MIS must be comprehensive and operate in real time. Some characteristics of a typical MIS are:

1. Immediate recording of any transaction or changes.

2. Complete data base (historic and current) with decision-making rules.

3. Continuous monitoring of the impact of internal and external events which are called to the immediate attention of concerned parties.

4. A hierarchy of record output, including periodic and special reports (on request).

5. Decision models and files structured so that significant relationships can be discovered by people-machine interaction.

The MIS capability should be facility-wide and the QA Department should only be a user of this capability. This type of system will greatly reduce the cost of trail audits and other QA duties.

RESOURCES PLAN

This section reviews some of the results of the resources planning activities completed.

Objectives

The objectives of the resources planning effort included:

1. Quantify the cost of the Facility in a manner that allows the resulting data base to be useful even if the full service/capability is not implemented.

2. Establish a basis for justifying the resources needed.

It must be remembered that different capabilities and capacities selected for the Facility modules would result in different amounts of resources whether at the design, fabrication or operation phases. To quantitatively illustrate the resources required, a facility was arbitrarily defined as consisting of one each of the 63 modules and then expanded by an additional 22 modules to provide office areas for personnel needed in the facility when it was operating at 80% capacity. A scaled-down or scaled-up version can be developed by using the data provided here and expanded elsewhere (Life Systems, Inc. 1981d).

Assumptions

The assumptions used on the resources planning effort included:

1. The Facility will utilize one of each module except in the case of technical and administrative office areas.

2. The Facility will use as its baseline a renovation approach as opposed to a newly constructed facility.

3. The Facility's capacity will be 80% of the maximum testing capacity resulting from one each of the testing modules. This accommodates loss of capability because of scheduling, etc.

4. The cost analysis includes testing activities only and will not include before, parallel or after toxicology activities other than testing.

5. The corridors, halls, stairs, etc. will be 9% of the Facility's total area as reflected by a summation of the areas of the 63 modules.

6. Twenty percent of the personnel staffed will have Ph.D. degrees or equivalent.

7. A professional internal recruiter can hire 50 people per work year having 1,920 hours at a rate of $40 per hour including cost and fee.

8. Ten percent of the required personnel will be available initially (from the contractor assuming a GOCO Facility).

9. The cost for recruitment for the QA personnel will be included in the personnel costs as opposed to being included in the cost of QA.

10. The preparation of a SOP will take 14 people-hours at a rate of $35 per hour (i.e., $490 per SOP).

11. No startup costs for the preparation of several hundred scientific SOP's will be needed since assumed to be available within the Army's SOP's.

12. If a new, as opposed to renovated, Facility is to be built, the cost of the land will be $50,000 per acre. The cost of improving the site will be 5% of the land cost. The cost of bringing utilities to the site and to the building shell will be 2% of the land cost. The cost of the building's shell will be $15 per square foot.

13. Thirty-five percent of the area of the land will be available for the Facility, the remaining 65% will be needed for parking, landscaping, etc.

14. Any new Facility would be assumed to be a single story as opposed to multiple stories.

15. No requirement exists to recalculate any of the resource analysis results to improve or modify the data obtained initially.

16. The cost of the Facility's testing is based on the prices presented in Appendix 3, i.e., assumming they were obtained competitively from a COCO.

Resources Required

The actual resources required will be a function of the capability and capacity selected. More resources are needed as the number of types of tests, the number

of scientific technology disciplines, the number of tests of a specific type, etc., increases. The combinations of capabilities and capacities that can be developed for a given amount of resources makes the selection of any particular combination arbitrary unless guidelines are provided specifying the needs. This information did not exist at this time, therefore, a data base was developed which can be used to define actual resources needed when capability and capacity are selected. Establishing resource requirements is an interactive process between level of funding available and capability/capacity required. The program's short, three-month time frame did not allow generating a series of tables and figures that could be used as universal costing sheets.

Full Utilization Testing

As indicated in Table 9, one each of the testing modules can provide a variety of tests per year depending upon the particular test and module needed for it. The data from Table 9 are further expanded in Table 17 to provide the cost of carrying out testing in a module when operating at 100% capacity. It summarizes the total testing costs based on the cost data for each type of test contained in Appendix 3 and indicates the nineteen General Toxicology Tests would require $21,120,000 per year, the two types of Genetic Toxicology Tests would require $3,087,000 per year and the seven selected special scientific toxicology studies would require $3,502,000. The latter does not include the $1,445,000 for combined tests. The combined tests are not included in the total since this would be accounting for a module's testing capacity twice, since they require using more than one module. Thus, the total testing budget, assuming 100% utilization of the Facility's testing modules, would be about $27,700,000. It is estimated, however, the testing "efficiency" would be 80% of the maximum capacity. This lowers the testing volume cost for a hypothetical Facility operating with one of each module to $22,200,000.

Note, it is unlikely the selected hypothetical facility would be one containing one each of the 63 modules. Many reasons can be cited why this would be true. For example, more than one module of some types might be preferred (e.g., module No. 7, Rodent Chronic Inhalation); less than one module of some types might be preferred (e.g., module No. 58, Guinea Pig Acute Dermal Sensitization) or more office area is needed than one each of module numbers 37 and 60, etc. The approach of using one each of the modules was considered the best because it gave visibility to the capacity and cost for a given area of laboratory devoted to a specific function and could be utilized, based upon specific needs, in multiples (including fractional increments) of the standard size selected. As seen later, such an adjustment was made in the case of office areas.

Cost of Facility

The cost to renovate the Facility amounted to $8,519,000 assuming one each of the 63 modules. This total cost is a composite of four cost areas:

1.	General construction	$3,111,000
2.	HVAC	$2,012,000
3.	Electrical	$2,422,000
4.	Sanitary	$ 974,000
	Total	$8,519,000

TABLE 17 ANNUAL TESTING COSTS OF THE FACILITY OPERATING AT FULL CAPACITY

Test No.	Title	Test Cost[a] $ (000)	Module No.	Module Capacity Tests/Yr	Total Cost/Yr, $ (000)
	General Toxicology Tests				
1	Acute Oral, Rodent	2	1	773	1,546
2	Subchronic Oral, Rodent	56	2	16	896
3	Chronic Oral, Rodent	495	3	1	495
4	Acute Inhalation, Rodent	5	5	142	710
5	Subchronic Inhalation, Rodent	64	6	11	704
6	Chronic Inhalation, Rodent	613	7	0.4	245
7	Acute Inhalation, Primate	39	8	24	936
8	Subchronic Inhalation, Primate	196	9	7	1,372
9	Chronic Inhalation, Primate	518	10	0.4	207
10	Subchronic Oral, Dog	104	4	4	416
11	Acute Dermal, Rabbit	4	11	56	224
12	Subchronic Dermal, Rabbit	75	11	56	4,200
13	Acute Ocular, Rabbit	3	12	311	933
14	Acute Oral, Neurotoxicology, Chicken	5	61	91	455
15	Subchronic Oral, Neurotoxicology, Chicken	20	61	24	480
16	Acute Dermal Irritation, Rabbit	1	11	58	58
17	Subchronic Dermal Irritation, Rabbit	3	11	64	192
18	Acute Ocular Irritation, Rabbit	1	12	311	311
19	Acute Dermal Sensitization, Guinea Pig	4	58	1,685	6,740
				Subtotal	**21,120**
	Genetic Toxicology Tests				
S20	*In Vitro* Genetic Toxicity	77	62	35	2,695
S21	*In Vivo* Genetic Toxicity	98	63	4	392
				Subtotal	**3,087**
	Special Scientific Toxicology Studies				
SBSa	Subchronic Inhalation, Behavioral, Rodent	100	13	4	400
SBSb	Subchronic Inhalation, Behavioral, Primate	150	13	7	1,050
SOSa	Chronic Oral, Oncogenic, Rodent	377	16	2	754
SOSb	Chronic Inhalation, Oncogenic, Rodent	515	16	0.4	206
SOSc	Chronic Inhalation, Oncogenic, Primate	420	16	0.4	168
SRS	Chronic Oral, Reproduction, Rodent	114	18	1	114
STS	Chronic Oral, Teratology, Rodent	27	19	30	810
				Subtotal	**3,502**
	Combined Studies				
SG/OSa	Chronic Oral, Gen./Oncog., Rodent	600	16	1	600
SG/OSb	Chronic Inhalation, Gen./Oncog., Rodent	1,000	16	0.4	400
SG/OSc	Chronic Inhalation, Gen./Oncog., Primate	800	16	0.4	320
SR/TS	Chronic Oral, Repro./Terato., Rodent	125	18	1	125
				Subtotal	**1,445**

(a) Rounded to nearest one thousand.

but does not include costs of adequate office area, initial staff recruiting, equipment, corridors or initial QA SOP's preparation. These are defined below.

Number of Personnel

To carry out $22 million of testing requires a large staff and more than one each of the Technical Office Area (No. 37) and Administrative Office Area (No. 60) modules.

The personnel required by the Facility can be divided into those provided by the contractor and those provided by the Government. Figure 5 contains a plot of the staff required as a function of annual testing volume for both contractor and Government assuming a GOCO Facility.

A total of 570 contractor personnel and 34 Government staff would be needed to handle the annual mammalian toxicology testing volume when operated at 100% capacity ($27,700,000) in the Facility as a GOCO or 450 and 31, respectively, when operating at 80% capacity ($22,200,000).

Cost of Added Office Space

The 480 people needed by the 80% testing capacity Facility requires more than one each of Technical and Administrative Office Area modules. An analysis indicated 21 additional Technical Office Area modules and one additional Administrative Office Area modules are needed. This increases the cost of the Facility another $950,000.

Cost of Recruitment

The cost of recruiting the contractor's personnel will be $664,000 based on the recruiting cost assumption (No. 7 above and on 10% of the required personnel being available initially (Assumption No. 8 above).

Cost of Equipment

The cost of the equipment was divided into two increments, that needed for the first five years and that needed for the second five years. Each of these increments were further subdivided into equipment considered essential, desirable or ideal. The equipment costs are summarized below:

First Five Years		$11,380,000
Essential	$10,257,000	
Desirable	$ 1,061,000	
Ideal	$ 62,000	
Second Five Years		$ 4,490,000
Essential	$ 3,523,000	
Desirable	$ 949,000	
Ideal	$ 18,000	

The cost of the equipment in the 24 added Technical and Administrative Office Areas adds another $192,000 to the first five year equipment cost figure. These equipment costs assume none of the existing equipment at LAIR is used.

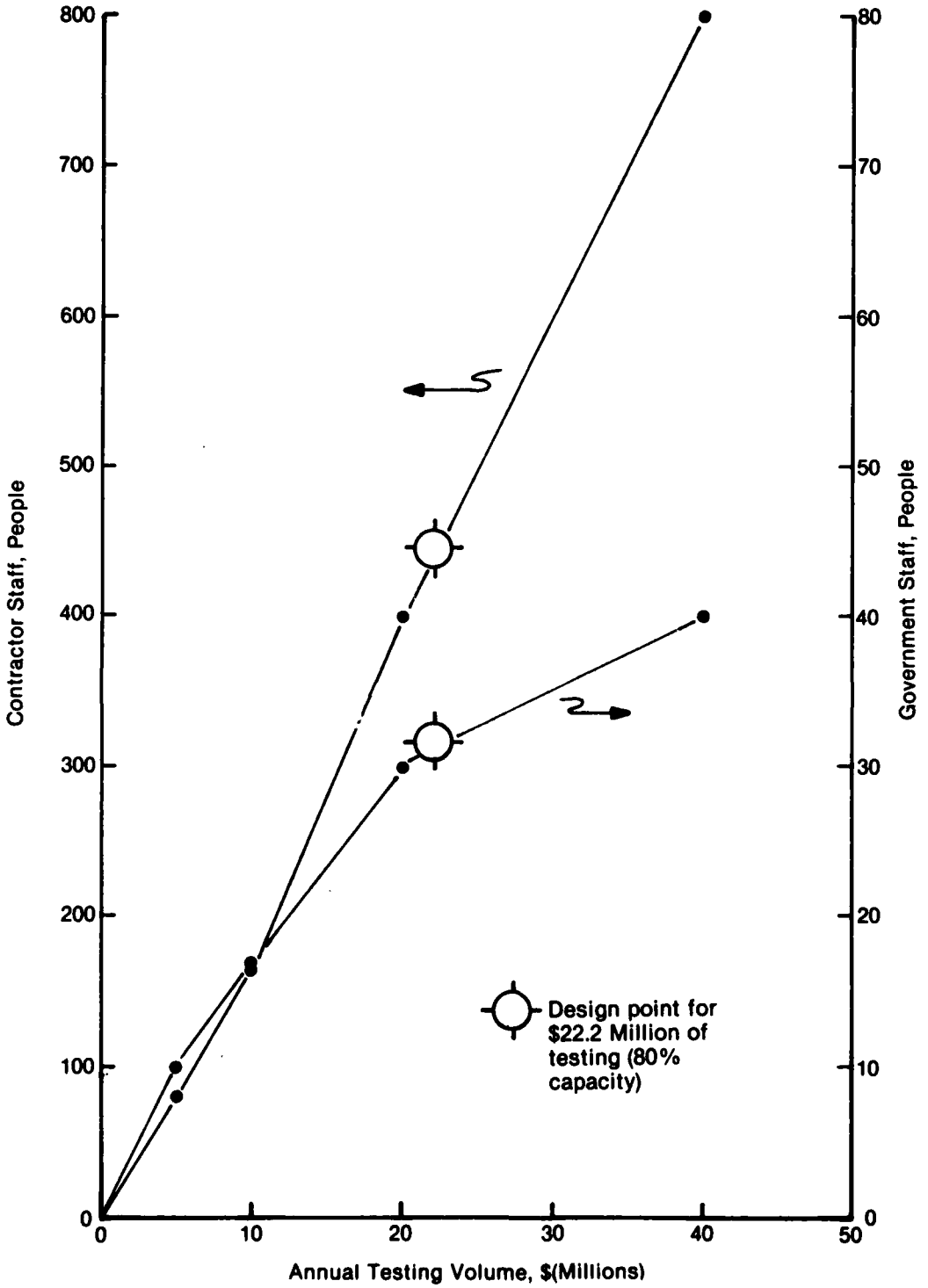


FIGURE 5 PERSONNEL NEEDED AS A FUNCTION OF TESTING VOLUME

Cost for Corridors

Approximately 14,400 square feet (about 9%) of corridor area exists for the hypothetical Facility containing one each of the 63 modules. The added corridor area associated with the 22 additional office modules amounts to 2,900 square feet. The cost of the corridors is approximately $499,000 and $97,000 for the corridors associated with one of each module and for the additional office areas, respectively.

Cost of Quality Assurance

The cost of the QA effort is basically a function of the number of SOPs to be prepared. The total is estimated to be 210 SOP's (only 207 were cited in Appendix 6).

Based on the cost to prepare QA SOP's, (assumption No. 10), the startup cost of QA would be $103,000. The QA costs associated with modules, equipment and personnel are included in the numbers previously cited for these three cost categories.

Total Cost

The total cost is summarized in Table 18 for the start-up of a hypothetical Facility consisting of 85 modules (one each of 63 modules plus 22 additional office areas). The numbers have been rounded off to the nearest $10,000. The total of $23 million consists mainly of equipment ($12 million) and modules ($9 million). Remember, this is for a capability and capacity arbitrarily selected. When the latter are accurately specified, the costs can be more accurately defined.

Special Projects

During the resources planning effort various special projects were completed:

1. Comparison of two model sites for locating a GOCO.

2. Study of the impact on cost because of equipment potentially available at LAIR.

3. Study of the resulting impact on cost because of the modules potentially available at LAIR.

4. Study of the added cost associated with a new Facility versus a renovated Facility.

5. Study of the impact of obtaining the analytical and synthetic chemistry services externally.

Facility Location

The Study specified several models as sites for adding to the Army's applied mammalian toxicology research/testing capability:

TABLE 18 ADJUSTMENTS FOR ADDED OFFICE AREA TO HANDLE 480 PEOPLE[(a)]

	One of Each Module	Sufficient Offices	Total
Total Area, ft²	158,900	31,500	190,400
Corridors Area, ft²	14,400	2,900	17,300
Modules Area, ft²	144,500	28,600	173,100
Total Cost, $(000)	20,580	2,110	22,690
Modules	8,520	950	9,470
Recruitment	80	870	950
Equipment	11,380	190	11,570
Corridors	500	100	600
QA SOPs	100	0	100

(a) Number of people estimated to handle $22.2 million (80% capacity) of testing. Approximately 600 people would be needed to handle the 100% capacity level.

TABLE 19 COMPARISON SUMMARY OF FACILITY MODELS

Characteristic	Model Facility Sites		
	LAIR	Hunter's Point	Other (?)
Total Square Feet	160,000	300,000	?
Government Building	Yes	Yes	?
Army Building	Yes	No	?
USAMRDC Building	Yes	No	?
Location	San Francisco	San Francisco	?
Designed Purpose	Med. Research & Animal Studies	Radiobiology Research & Animal Studies	?
Status	Partially Occupied	Unoccupied since 1968	?
Age	< 10 yr.	> 25 yr.	?
Condition	Excellent	Poor	?
Existing Equipment Available	Some	None	?
Growth Capability			
Internal	Good	Excellent	?
External	Poor	Excellent	?
Central Utilities Needs	More Capacity	Total Replacement	?
Access to Local			
Universities	Good	Good	?
Analytical Chem. Labs	Good	Good	?
Pathology Labs	Good	Good	?
Attractiveness to Personnel			Very Important
City/State	Excellent	Excellent	?
City Location	Excellent	Poor	?
Ability to be Renovated	Good	Better	?
Needs to Renovate While Occupied	Yes	No	?
Available External Haz. Chem. Storage	Limited	Extensive	?
Independence	Tied to LAMC	Complete	?

1. LAIR.
2. Hunter's Point.
3. Unspecified Others.

To a degree, the two specified models represent extremes in potential sites for locating the toxicology Facility. The LAIR represents a modern (four to eight years old), functioning facility. Hunter's Point represents an absolete (J25 years old), dormant facility. Table 19 summarizes the comparisons made of the two sites.

LAIR Restrictions. The Study determined the deficiencies of the LAIR facility. Major among them were the need for renovation work while the existing activities continue; inadequate capacity of many building utilities for a modern, GLP qualifiable Facility and several minor structural arrangements which made module layout difficult.

None of the restrictions found with LAIR, however, inhibit it from becoming an effective structure/facility to incorporate the mammalian toxicology capability.

Hunter's Point Restrictions. The Study determined the deficiencies of the Hunter's Point facility. Among them were the poor state of the property, the considerable repair needed (e.g., most of the facility's central utilities will have to be replaced) and the lack of any host Government organization services. The structural arrangement, however, is better than LAIR's.

None of the restrictions found with Hunter's Point, however, inhibit it from becoming an effective structure/facility to incorporate the mammalian toxicology capability.

LAIR Facility Services. As a USAMRDC program guideline, the Study was to assume the LAIR would provide no facilities. It is known, however, the LAIR can provide animal, laboratory, administrative and storage space on an as available/as needed basis. In addition, certain amounts of heating and air conditioning, electricity, tap water, sewage treatment, telephone system, compressed air and laboratory gases, general building maintenance and janitorial services could be available.

Hunter's Point Services. Hunter's Point has virtually no services available. The building has been "in mothballs". No current people-provided services exist. Also, most of the central facilities are in a state of disrepair.

Savings From Equipment Potentially Available at LAIR

Table 13 cited the types of equipment potentially available through the LAIR. The availability of this equipment would decrease the first five year cost of equipment $4.5 million, from $11.4 to $6.9 million.

First Five-year Savings		$4,504,000
Essential	$4,388,000	
Desirable	$ 79,000	
Ideal	$ 37,000	

Modules Potentially Available at LAIR

Appendix 7 codes which modules were considered potentially available through the LAIR. Availability levels were completely available, 75% available, 50% available or 25% available. All the others were considered not available. As a result the cost of renovating the LAIR Facility would be reduced from $8,519,000 to some lower dollar value depending on a confirmation of which modules are available.

New Facility Versus Renovation

If the Facility did not have an existing shell (e.g., LAIR or Hunter's Point), the increased cost would be $3,520,000. This was calculated as follows:

	Cost, $	Assumption Number
Land	$ 624,000	11, 12
Site Improvements	31,200	11
Utilities	12,400	11
Shell	2,856,000	11, 13
Total	$3,524,000	

(This assumes one of each module, the extra office area and corresponding corridors.)

CONCLUSIONS

The following are conclusions resulting from the Facility Installation planning portion of the Study:

1. A toxicology facility able to handle all the projected USAMRDC's unmet requirements does not exist. Additional new capability and capacity is needed.

2. The needed added toxicology capability and capacity is a continuing requirement. This added toxicology would focus on requirements other than those already being handled (such as that associated with drugs and vaccines development, defense against biological warfare, etc.). The unmet requirements driving the need for added capability are the recently enacted toxicology testing related laws such as TSCA. These requirements will continue indefinitely.

3. The toxicology efforts that should not be included in the added Facility's capability are:

    a. Tests already being done at other USAMRDC laboratories,
    b. Tests which the NTP can and should do for the Army, and
    c. Tests characterized as very routine and available competitively priced from industry.

4. Toxicology efforts that should be included in the Facility's capability are:

a. Testing that focuses on Army-unique exposures and
b. Inhalation toxicology testing especially as it relates to environments created as part of Army activities (e.g., firing of weapons, field use of smokes and obscurants, etc.

5. Important information on specific users, time tables and source of funds must be acquired by USAMRDC working with other DA organizations before initiating a Facility development program. Justification for the added Facility exists but a clear definition of its specification (capability, capacity, location, time frame, etc.) does not exist.

6. Implementation of a Facility development program will be expensive to USAMRDC in time (two to five years) money (10- to over 20- million dollars for the Facility, its equipment, personnel acquisition and startup activities) and USAMRDC management time (two to five staff people detailing options, plans, specifications and communicating the need to those that would ultimately commit the resources).

7. A significant data base has been generated upon which to select, price, plan and coordinate the Army's mammalian toxicology requirements that are not being met.

8. The LAIR will be a more cost effective site of a GOGO or GOCO than Hunter's Point. This results from its better physical condition and the availability of equipment and services to support the added capability selected for incorporation into the new Facility.

9. The Facility's capability should focus on more than testing. The before testing, parallel with testing and after testing efforts are, in many cases, more important than testing itself. These activities, are labor as opposed to equipment cost intensive.

10. The ultimate Facility service and capacity selected is a function of USAMRDC/DA decision-making processes.

11. The modular design conceived provides for full-service capability. It permits the decision-makers the option to pick and choose which capabilities and capacities are essential based upon requirements, priorities, budgets, personnel resources, etc.

12. The Facility must produce scientifically sound technical results, able to be scrutinized by peer groups, regulatory agencies and developers of standards and criteria.

13. It will take two to five years for the added toxicology capability to be operationally ready for "for the record" testing. This includes major efforts to finalize the Facility specification, perform the renovation, assemble the staff, develop the procedures and start up testing.

14. Use of an airlock/anteroom approach was found more acceptable than use of pressure differential zones or clean/dirty corridors. The

preferred approach incorporates into each testing module its own air handling and ventilation system for greater safety, flexibility and lower life cycle operating costs.

15. Equipment identification, acquisition, installation, debugging and maintenance represents a complex effort. It requires careful planning and implementation to ensure efficiency, effectiveness and timeliness. These efforts must be coordinated and integrated with the planning and implementation of the other Facility development tasks. Handled properly, all parts needed by the Facility can be integrated into an optimal Facility.

16. All toxicology testing is expensive, however, longer term inhalation toxicology work is the most expensive of all exposure routes. Thus, the need to restart or redo experiments due to power outages, equipment failures, etc. are prohibitively expensive. Equipment redundancy and quality are essential, but costly.

17. Certain toxicology personnel will be in short supply for the next decade including aerosol chemists, immunologists, pharmacodynamicists, pharmacokineticists, pharmacologists, toxicologists and veterinary pathologists.

18. A well-planned Quality Assurance program is essential, possible and can be cost-effective. It requires management support, however, to become a meaningful part of every aspect of the toxicology Facility.

19. Excess capacity will exist during a startup phase. The final plans must minimize this and, in so doing, conserve resources and define additional Army users of such excess capacity.

20. Significant savings of money should result by USAMRDC's making a concerted effort to have other federal agencies (e.g., NCTR) mandated by Congress support toxicology technology to fulfill some of the USAMRDC's needs. The most likely areas for support are the more civilian and environmental health areas. The EPA, for example, should support construction of an experimental toxic and hazardous waste disposal demonstration process at the Facility. The EPA would provide the funds, the Army would provide the Facility and communicate the results.

21. Overall the construction cost is slightly less than $60 per square foot. The ratios of general construction to electrical to HVAC to sanitary costs are 3.2 : 2.4 : 2.1 : 1.0.

22. Overall equipment cost is slightly less than $80 per square foot or about 10% less when corridors are considered.

RECOMMENDATIONS

The following are recommendations resulting from the Facility Installation planning portion of the Study:

1. A project should be completed defining available sources of money and specific user commitments so the final selection of the Facility's capability and capacity can be made. This assumes the Comparative Analysis of alternatives results in a decision to proceed with a Facility.

2. The Facility should focus on Army-unique toxicology testing requirements as a priority area. These are the most difficult to obtain elsewhere and have the greatest need for organizational memory of the technology and program results.

3. Environmental effects toxicology should be combined with health effects toxicology efforts for those requirements that are being unmet and relate to the same laws, e.g., TSCA. This will decrease costs and ensure uniform treatment of both health and environmental toxicology requirements. The effort, for example, could be managed by the Facility's staff but the testing would be done extramurally to the Facility.

4. Genetic toxicology should be included in the Facility's capability.

5. An epidemiology capability should be added to the Facility's capability even if done external to the Facility but coordinated by the same staff. The epidemiology efforts, however, should focus on Army-unique exposures, primarily those of the soldier and, to a limited extent, civilians exposed to environments created only by the Army.

6. A portion of the Facility's effort should be focused on applied research. This is necessary to attract and retain quality personnel and stimulate involvement with the technology.

7. The Army, USAMRDC or the Facility should not devote any portion of its efforts to basic toxicology research. Continued support of university research and participation in the National Toxicology Program are more effective mechanisms.

8. The Facility should devote a portion of its efforts to training personnel. It is needed to provide the Army with personnel for:

    a. Determining toxicology requirements as a function of materiel development cycle.

    b. Inspectors to be utilized to ensure standards and criteria are being met.

    c. Develop personnel to relieve those known to be in limited supply (e.g., veterinarian pathologists) and to train a generation of middle and lower level technical supporting personnel.

9. Toxicology research involving concomitant exposures should be delayed for five years or until the higher priority, unmet conven-

tional requirements have been handled, and technology advances enable development of better data bases on concomitant exposures.

10. The Facility should be divided into two capability stages, an initial and a growth capability stage. Each stage is assumed to be five years.

11. A stepwise increase in capability within each of the two stages should be used to effectively integrate capability and personnel with available resources and ability to stimulate the growth.

12. Because toxicology is very much a science-oriented discipline and the results are dependent upon scientists, the manner in which the work is carried out and the standards followed should be controlled directly by a Facility Science Director in conjunction with an all Army review team, a non-Army review team and a peer group of advisors.

13. The specific tests utilizing standard protocols, the new protocols to be developed, the special scientific experiments to be carried out and the genetic toxicology tests to be included must be defined prior to initiation of a Facility Development Plan.

14. A special study addressing toxicology testing scheduling should be performed. One of several companies noted for their techniques in

    scheduling toxicology testing activities should be contacted to obtain proven procedures for minimizing overloads of facilities and equipment and excessive workloads on personnel in short supply.

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APPENDIX 1

ACRONYMS AND TERM DEFINITIONS

AAALAC - American Association for Accreditation of Laboratory Animal Care.

Acute Effects Tests - Tests employed to determine the immediate or short-term effects following a single chemical exposure.

AMTR - Applied Mammalian Toxicology Research/Testing.

Applied Mammalian Environmental Toxicology Research - Studies performed to predict adverse human health effects associated with environmental exposures to air, water and soil pollutants. These exposures affect the general population via contaminants in ambient air, drinking, bathing and swimming area water and the food chain (eating of meat, fish, seafood and vegetables). These exposures are not associated with the individual's occupational exposure.

Applied Mammalian Toxicology Research - Studies aimed at measuring the effects of chemicals in mammalian systems using established test protocols. Excluded are all human epidemiological studies, non-mammalian testing, such as mutagenic studies tests to determine the adverse effects of ionizing and non-ionizing radiation and physical factors such as pressure, temperature, noise and vibration. Applied toxicology research provides for data base and criteria and standards development.

AR - Army Regulation.

Archives - The area used to store all raw data, notes, specimens, slides and other information generated as the result of a toxicology study.

Basic Toxicology Research - Studies aimed at understanding the effects and fate of chemicals in biological systems including modifying factors. It includes the studies to develop methods for reducing the future cost of toxicology testing and improving extrapolation of test data, including concomitant effects.

Behavioral Dysfunctions - Disturbances in behavior.

BML - Biomedical Laboratory. This facility has been redesignated USAMRICD, United States Army Medical Research Institute of Chemical Defense.

Built-in Equipment - Fixed, nonmovable equipment that is either connected to the floor, walls, or ceiling and/or is connected to a piped water line, fixed power line, fixed wastewater line, or intake or exhaust vents.

Carcinogenicity - The induction of cancer

CARDS - Catalog of Approved Requirements Documents.

CCA - Clean Air Act (1970).

Chronic Effects Tests - Tests employed to determine the long-term effects of multiple chemical exposures.

CITA - Commerical/Industrial-Type Activities.

COCO (Contractor-Owned, Contractor-Operated) - A function performed by contractor personnel in a contractor-owned facility. Material and equipment may be furnished by the Government or by the contractor.

COGO (Contractor-Owned, Government-Operated) - A function performed by Government personnel in a contractor-owned facility. Material and equipment may be furnished by the Government or acquired for the Government by the contractor.

Control Article - Any chemical, substance or mixture of materials that is administered to the test system in the course of a study for the purpose of establishing a basis for comparison (often used synonymously with Referenced Standard).

Cost Comparison - An accurate determination of whether it is more economical to acquire the needed products or services from the private sector or from an existing or proposed Government commercial or industrial activity.

CPSA - Consumer Products Safety Act (1972). A statute defining some of the responsibilities of the Consumer Product Safety Commission (CPSC).

CPSC - Consumer Products Safety Commission.

Criteria - Levels and/or a set of conditions established to serve as guidelines for evaluating the general acceptability and risk of a situation. Criteria are not enforceable in a court of law.

CSL - Chemical Systems Laboratory.

CV - Curriculum Vitae.

CWA - Clean Water Act. Title assigned to the 1977 amendments of the Federal Water Control Act.

DA - Department of the Army.

DARCOM - Materiel Development & Readiness Command.

DCSRDA - Deputy Chief of Staff for Research, Development and Acquisition.

Debug - Efforts to correct initial defects or malfunctions in equipment process or procedure.

DHEW - Department of Health, Education and Welfare; now the Department of Health and Human Services and the Department of Eduction.

DOD - Department of Defense.

DOL - Department of Labor.

DOT - Department of Transportation.

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MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY. PART 2.--ETC(U)
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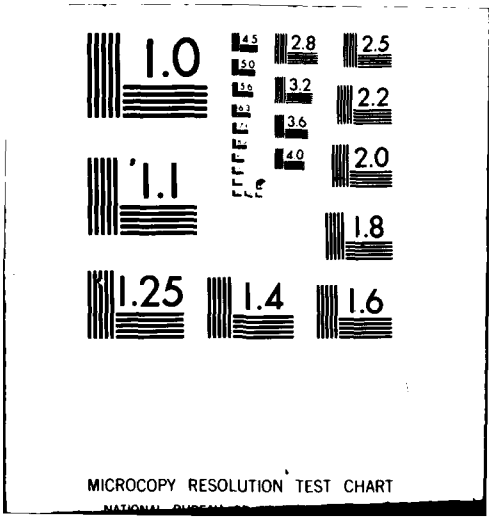
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MICROCOPY RESOLUTION TEST CHART

EPA - Environmental Protection Agency.

Epidemiology - That field of science which deals with the relationships of various factors as determinants in the distribution and frequency of disease or death in the human population. As such it attempts to identify by actual human experience the nexus between chemical and their effects on people.

Equipment Acquisition - All ordering and receiving activities for selected items.

Equipment Categories - Classification of items into built-in (scientific and nonscientific) and movable (scientific and nonscientific).

Equipment Identification - Process of selecting the item, its specifications, manufacturer and model number but not designating the vendor.

Equipment Installation - The placement and connection of items in their designated location such that they are ready for turnover to the operational staff.

Equipment Life - The length of time an item is expected to perform satisfactorily when it receives scheduled maintenance and is operated by a properly trained individual.

Existing Equipment - Items that are on the property books of the host Governmental Facility.

External Support Services - Those functions that can be provided satisfactorily by a performer outside of the Facility.

Extrapolation - The extension of animal or other studies to potential effects on another species - especially man.

FDA - Food and Drug Administration.

FDCA - Food, Drug and Cosmetic Act.

FFA - Flammable Fabric Act.

FFDCA - Federal Food, Drug and Cosmetic Act (1938).

FHSA - Federal Hazardous Substances Act (1966). A statute defining some of the responsibilities of the Consumer Product Safety Commission (CPSC).

FID - Flame Ionization Detector.

FIFRA - Federal Insecticide, Fungicide and Rodenticide Act (1972).

FORSCOM - Forces Command.

FR - Federal Register. The official organ of the U.S. Government; published every working day.

Full Service Toxicology - Includes all 19 specifically identified toxicology tests, special scientific toxicology studies and genetic toxicology tests needed to meet Army's toxicology requirements and the tasks before, in parallel with and after toxicology testing.

FWPCA - Federal Water Pollution Control Act.

FY - Fiscal Year. The fiscal year of the U.S. Government is October 1 to September 30.

General Toxicology - Includes all testing that has lethality as an end point. In addition, it includes dermal irritation and sensitization and ocular irritation and metabolism and organic specific studies. It does not include oncogenic, behavioral, neurotoxicologic, mutagenic, reproductive or teratologic studies.

GLP - Good Laboratory Practices.

GOCO (Government-Owned, Contractor-Operated) - A function performed by contractor personnel in a Government-owned facility. Material and equipment may be furnished by the Government or acquired for the Government by the contractor.

GOGO (Government-Owned, Government-Operated) - A function performed by Government personnel in a Government-owned facility. Equipment may be owned or leased by the Government.

GSA - General Services Administration.

HEPA - High Efficiency, Particulate Air.

HHA - Health Hazard Assessment.

HMTA - Hazardous Materials Control Act (1975).

Hierarchical Testing - A progressive testing system which proceeds in increments of complexity, duration and cost based on several factors.

HSC - Health Services Command.

Hunter's Point - Navy's vacant Nuclear Biology Defense Laboratory.

HVAC - Heating, Ventilation and Air Conditioning.

In-house performance - The performance of CITA by Army military or Federal civilian personnel.

Inhalation Chamber - The enclosure and its connections used to house the laboratory animals during inhalation toxicology studies.

Inhalation Chamber System - The inhalation chamber and all supporting instrumentation, controls, test agent generators, air supply and exhaust air piping, filtration and conditioning equipment, and cages and racks required to expose laboratory animals for inhalation toxicology studies.

IPR - In-Process Review.

ITC - Interagency Testing Committee as established by Section 4 of TSCA.

LAIR - Letterman Army Institute of Research.

Lead Time - Time between start of the acquisition process and delivery of the item at its destination.

LSI - Life Systems, Inc.

MAM - Mission Area Manager.

MAP - Materiel Acquisition Process.

MENS - Mission Element Need Statements.

MIS - Management Information System.

Mutagenic testing - Testing to assess the potential hazard to human beings of a test substance due to interaction with genetic mechanisms with a resultant heritable change (mutation).

Mutagenicity - The induction of gene mutations.

NCI - National Cancer Institute.

NIEHS - National Institute of Environmental Health Sciences.

NIOSH - National Institute for Occupational Safety and Health.

Nonregulatory Requirements. - Self-imposed requirements for toxicology testing, not regulated by law. Results from problems that are preceived or anticipated (carried out under implied requirements or for "moral" issues). These requirements may be reflected in Army regulations or DOD Directives. Meetings those requirements can improve combat effectiveness or reduce compensation and ligation payments.

Nonscientific Equipment - Equipment needed in the Facility but not critical to laboratory experimental studies (such as office furniture and administrative equipment).

NTP - National Toxicology Program.

OMB - Office of Management and Budget.

OSHA - Occupational Safety and Health Act (Administration).

OTSG - Office of the Surgeon General.

P/C Properties - The physical and chemical properties of a chemical substance.

Permanent Service - Functions essential to a Facility that will not be provided externally.

Pharmacokinetics - The science of determining the interrelationships of the chemicals, on body metabolism and body metabolism on chemicals including the effect of time of exposure, dose, metabolism, excretion and related phenomena.

PL - Public Law.

PPPA - Poison Prevention Packaging Act.

Private commercial source - A private business, university, or other non-Federal activity located in the United States, its territories and possessions, or the Common wealth of Puerto Rico. This source is able to provide products or services required by the Government. States or State political subdivisions are considered private commercial sources.

Protocol - A detailed description of the design and technical conduct of a study e.g., procedures by which health effects tests are conducted.

QA - Quality Assurance.

QAU - Quality Assurance Unit.

QC - Quality Control.

Quality Assurance - A comprehensive system of plans, specifications and policies such as audits and inspections that are designed to ensure the collection, processing and reporting of data.

Quality Control - The system of activities designed to achieve and maintain a previously specified level of performance in data collection, processing and reporting.

Raw Data - Any laboratory worksheets, records, memoranda, notes, chromatograms or exact copies thereof, that are the result of original observations of a study.

RCRA - Resource Conservation and Recovery Act (1976).

RDT&E - Research, Development, Test & Engineering.

Redundancy - Backup items necessary to avoid loss of capability.

Regulation Requirements - Legally imposed toxicology testing, needed to conform to regulations. Criteria oriented with stated requirements. The protocols to be utilized are defined.

Reproductive effects - Impairment of reproduction.

San Francisco Bay Area - A 50 mile radius of the LAIR.

SAR - Structural Activity Relationship, the relationship between a chemical and its effects (biological, etc.) which form the basis for predicting effects based on structural relationships.

Scheduled Maintenance - Periodic servicing required to keep equipment functioning efficiently.

Scientific Equipment - Equipment required to perform laboratory experiments.

SDWA - Safe Drinking Water Act (1974).

SOP - Standard Operating Procedure.

Specimen - Any material derived from a test system for examination or analysis.

Standard - Levels established by a regulatory agency and used to determine compliance.

Startup - Time period starting with the acceptance date of the Facility and ending when the Facility achieves Operational Status.

STO - Science and Technology Objectives.

STOG - Science and Technology Objectives Guide.

Subchronic Tests - Tests of intermediate duration following continuous or repeated administration of a test substance over a period (typically 90 days). Used to determine effects or indications thereof without the longer time required for full-scale chronic effects tests.

Support Service - Those functions that can effectively be performed internally or externally to the Facility.

Support Service Contract - A situation wherein contractor personnel are on-site at a Government facility providing some degree of service or operation, but at which Government personnel are still working. A Support Service Contract could be as small as provisions of instrumentation maintenance and calibration or it could be complete research activities within the Government Facility but still under direction or operational control of Government managers.

Teratogenic - Potential of a test substance to produce defects in offspring resulting from prenatal exposure.

Teratogenicity - The induction of birth defects.

Test Article - A specific form of a chemical substance or mixture used to develop data (often used synonumously with Sample).

Test Facility - The establishment or organization actually conducts a non-clinical or toxicology study.

Test Mixture - A combination which results from mixing a test substance with another substance or substances (e.g., water, feed) for the purpose of exposing the test system.

Test System - The animal, microorganism or subpart thereof to which the test or control article is administered.

Tier Testing - See Hierarchical Testing.

Toxicology Method Development - Studies aimed at developing and/or validating new methods, procedures, protocols, etc. for toxicology testing purposes, including concomitant effects.

Toxicology or Toxic Effects or Hazards - For the study these terms are limited to the health effect aspects.

Toxicology Services or Toxicology Requirements - All tasks associated with toxicology from requirements identification thru to completion of the toxicology activities associated with a specific requirement.

Toxicology Testing - Studies aimed at measuring the effects of chemicals in biological systems using established test protocols.[a]

TRADOC - U.S. Army Training and Doctrine Command.

TSCA - The Toxic Substances Control Act (1976).

Unscheduled Maintenance - Service and repairs required because of an equipment failure or malfunction.

USAARL - US Army Aeromedical Research Laboratory.

USAEHA - US Army Environmental Hygiene Agency.

USAIDR - US Army Institute of Dental Research.

USAISR - US Army Institute of Surgical Research.

USAMEDD - US Army Medical Department.

USAMBRDL - US Army Medical Bioengineering Research & Development Laboratory.

USAMRDC - US Army Medical Research and Development Command.

USAMRICD - US Army Medical Research Institute of Chemical Defense.

USAMRIID - US Army Medical Research Institute of Infectious Diseases.

USARIEM - US Army Research Institute of Environmental Medicine.

USDA - United States Department of Agriculture.

WRAIR - Walter Reed Army Institute of Research.

APPENDIX 2

PHYSICAL/CHEMICAL PROPERTIES TESTING

Determination of a product's physical and chemical properties (including reactivity) commonly expressed as P/C properties, is important for several reasons:

1. It enables characterization of the compound - selected specific values or a combination thereof which are peculiar to a particular substance. In those instances where the values are not, they are indicative of certain characteristics, such as pH (acidity or alkalinity) or melting point (purity).

2. It is essential to proper labeling - corrosiveness, explosiveness, volatility, flammability.

3. It can be used to predict activity and reactivity.

4. It is important for proper packaging - protection against corrosiveness.

5. It relates to storage and handling requirements and precautions.

6. Is legally required under some specific rules and regulations - DOT regulations.

7. It relates to certain storage restrictions applied depending upon P/C data - flammability, explosiveness.

8. It is essential to toxicological and environmental effects testing, since the characteristics and properties of the substance must be known to design toxicological and environmental effects tests. In some instances, the appropriateness of individual tests is related to P/C properties. For instance, there is little purpose in performing inhalation toxicity on nonvolatile compounds.

9. It is essential for appropriate chemical processing and engineering purposes, such as design and operation of equipment.

Table A2-1 lists the P/C properties most commonly determined. The methods employed in their assessment are standard (Dominguez 1979).

TABLE A2-1 MOST COMMONLY DETERMINED PHYSICAL CHEMICAL AND REACTIVITY PROPERTIES[a]

Property
Spectra (ultraviolet, visible, infrared)
Density
Solubility in water
Melting point
Boiling point
Sublimation point
Vapor pressure
Dissociation constant
Particle size distribution
pH
Other physical/chemical or fate characteristics tests (specify)
Chemical Reactivity:
Photochemical degradation
Hydrolysis
Chemical oxidation
Chemical incompatibility
Flammability
Explodability
Other
Biodegradation
Adsorption/desorption characteristics
Formation of persistent transformation products

(a) Based on EPA recommendations FR Vol. 44, No. 7, Wed. Jan. 19, 1979 - Toxic Substances Control - Premanufacturing Notification Requirements and Review Procedures.

APPENDIX 3

MAMMALIAN TOXICOLOGY TESTING PRICE LIST (3/8/81)

TABLE A3-1 MAMMALIAN TOXICOLOGY TESTING PRICE LIST (3/8/81)
GENERAL AND SPECIAL TOXICOLOGY STUDIES

Test No.	Duration	Type of Animal	Route of Exposure	Price, $(000) Per Outcome[a]: General Toxicology[c]	Special Scientific Toxicology Studies[b]: Behavioral	Onco-genic	Repro-duction	Terato-genic	Neuro-toxi-cology	Combined Protocols: Gen. Tox. + Oncog.	Combined Protocols: Repro./ Terato.
1	Acute	Rodent[d]	Oral	2.4[e]	—	—	—	—	—	—	—
2	Subchronic	Rodent[d]	Oral	56[e]	—	—	—	—	—	—	—
3	Chronic	Rodent[d]	Oral	495[e]	—	377[e]	114[e]	27[e]	—	600[f]	125[f]
4	Acute	Rodent[d]	Inhalation	5.0[e]	—	—	—	—	—	—	—
5	Subchronic	Rodent[d]	Inhalation	64[e]	100[f]	—	—	—	—	—	—
6	Chronic	Rodent[d]	Inhalation	613[e]	—	515[f]	—	—	—	1000[f]	—
7	Acute	Primate	Inhalation	39[f]	—	—	—	—	—	—	—
8	Subchronic	Primate	Inhalation	196[f]	150[f]	—	—	—	—	—	—
9	Chronic	Primate	Inhalation	518[f]	—	420[f]	—	—	—	800[f]	—
10	Subchronic	Dog	Oral	104[e]	—	—	—	—	—	—	—
11	Acute	Rabbit	Dermal	4.2[e]	—	—	—	—	—	—	—
12	Subchronic	Rabbit	Dermal	75[g]	—	—	—	—	—	—	—
13	Acute	Rabbit	Ocular	2.5[f]	—	—	—	—	—	—	—
14	Acute	Chicken	Oral	—	—	—	—	—	5.4[e]	—	—
15	Subchronic	Chicken	Oral	—	—	—	—	—	20[e]	—	—
				Irritation	Sensitization						
16	Acute	Rabbit	Dermal	0.7[e]	—						
17	Subchronic	Rabbit	Dermal	3.0[g]	—						
18	Acute	Rabbit	Ocular	0.9[e]	—						
19	Acute	Guinea Pig	Dermal	—	3.9[e]						

(a) Rounded off to nearest $1,000 for prices in excess of $5,000. Assumes one species.
(b) Special Scientific Toxicology Studies: Metabolism/Pharmacokinetics, Pharmacodynamics, and Respiratory are deleted since they are not a part of the 19 tests.
(c) General Toxicology includes lethality, metabolism and pharmacokinetics/pharmocodynamics.
(d) Rodent studies price was based on use of the rat.
(e) SOURCE: Enviro Control, Inc. 1980, Cost Analysis Methodology & Protocol Estimates. TSCA Health Standards and FIFRA Guidelines. Rockville, MD. Enviro Control, Inc. U.S. Environmental Protection Agency.
(f) Price estimated by LSI since no quotable source was identified.
(g) SOURCE: ICF, Inc. 1980 Profile of the Chemical Safety Testing Industry: An Assessment of Pesticide Testing Capacity. Final Report. Washington, DC. ICF, Inc. U.S. Environmental Protection Agency.

TABLE A3-2 GENETIC TOXICOLOGY TEST PRICES

	Price, $(000)[a]
A. Standards for Detecting Gene Mutations	
1. Detection of Gene Mutations in Bacteria	
• The *Salmonella*/Microsomal Assay	1.0
• The *Escherichia coli* WP2 and WP2 *uvrA* Reverse Mutation Assay	1.0
2. Detection of Gene Mutations in Eukaryotic Microorganisms	
• *Aspergillus nidulans*	1.0
• *Neurospora crassa*	1.0
3. Detection of Gene Mutations in Insects	
• *Drosophila melanogaster* Sex-Linked Recessive Lethal Test	7.0
4. Detection of Gene Mutations in Somatic Cells in Culture	
• Mammalian Cell Culture — L5178Y Mouse Lymphoma Cells	4.5
• Mammalian Cell Culture — V79 Chinese Hamster Cells	4.5
• Mammalian Cell Culture — Chinese Hamster Ovarian (CHO) Cells	4.5
5. Detection of Gene Mutations in Mammals	
• The Mouse Specific Locus Test	40.0
B. Standards for Detecting Heritable Chromosomal Mutations	
1. *In Vivo* Cytogenetics Test in Mammals	13.0
2. Detection of Heritable Chromosomal Damage in Insects	
• Chromosomal Damage in *Drosophila melanogaster*	14.0
3. The Dominant Lethal Test in Mammals	15.0
4. The Heritable Translocation Assay	30.0
C. Standards for Detecting DNA Repair or Recombination as an Indicator of Genetic Damage	
1. Detection of Genetic Damage using DNA Repair-Deficient Bacteria	0.6
2. Unscheduled DNA Synthesis in Mammalian Cells in Culture	2.5
3. Detection of Mitotic Crossing Over and/or Gene Conversion in Yeast	5.0
4. Sister Chromatid Exchange in Mammalian Cells in Culture	2.5
D. Standards for Detecting Chromosomal Damage	
1. *In Vitro* Cytogenetics Assay	0.7[b]
2. Micronucleus Assay	2.2[b]
E. Standards for Detecting DNA Alkylation	
1. DNA Alkylation in *Drosophila melanogaster* Sperm Cells	10.0[b]
2. DNA Alkylation in Rodent Sperm Cells	10.0[b]
3. DNA Alkylation in Mammalian Cells in Culture	5.0[b]

APPENDIX 4

EXAMPLES OF CAPABILITY DOCUMENTS

The attached documents contain:

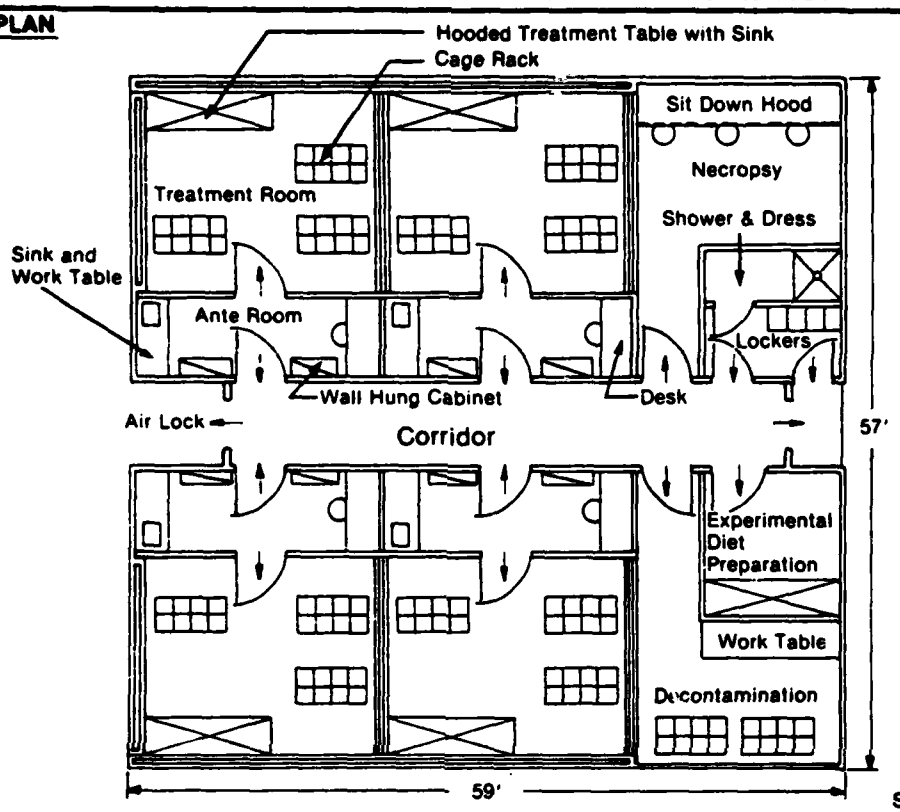
a. Module Description
b. Module Equipment List
c. Test Protocol (where applicable)

Module No.	Module Title	Page Number: Description	Page Number: Equipment List	Page Number: Protocol
1	Acute Oral Exposure Area, Rodent	A4-2	A4-3	A4-5
5	Acute Inhalation Exposure Area, Rodent	A4-6	A4-7	A4-11
23	Quality Assurance Laboratory	A4-13	A4-14	
25	Pathology Laboratory	A4-17	A4-18	
40	Record Archives Area	A4-22	A4-23	
41	Specimen Storage Area	A4-24	A4-25	

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



CONSTRUCTION INFORMATION

Dimensions: 59 x 57 Ft.
Area: 3,363 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐ _____
Air Flow: 7,500 CFM ☐ Variable
Air Changes/Hour: 15
Floor Drains: ☒ Capped ☐ Flushing ☐ Other
Water: ☒ Hot ☒ Cold ☐ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☒ Yes ☐ No
Local Exhaust Filtration: ☒ Yes ☐ No
Epoxy Coated: ☒ Walls ☒ Floors ☒ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☒ Timed Lighting
☐ Compressed Air; ☐ Vacuum; ☐ Other Gases
☐ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

1. Can test four chemicals simultaneously.
2. Double walls for air pressure control in rooms and sound isolation.
3. Compatible with highly hazardous tests:
   - Ante room isolates corridor
   - Local diet preparation
   - Local necropsy
   - Local cage/rack decontamination

SPECIAL ASSUMPTIONS

1. Tests of highly hazardous materials must be performed.
2. Safety considerations require local necropsy and diet preparation.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	84	25
Heat, Vent., Air Cond.	54	16
Electrical	64	19
Sanitary	27	8
Equipment	83	25
Total	312	93

TITLE Acute Oral Exposure Area, Rodent

NO. 1

F-650 (2/15/81)

Equipment List

Date 2/6/81
Complete by Jones, Jorgensen
Area Laboratory No. 1
Title Acute Oral Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen (c) (in.)		
Cage Rack, 30 rat cages or 60 mouse cages 1	Hold cages	2.2	Animal Technician	Hold ≤ 150 rats or 300 mice	12		X	400	72x30x72	NA	Automatic watering system
Cage, rat 1	House rats	0.02	Animal Technician	Hold ≤ 5 rats	360	X		2	22x12.5x8	NA	NA
Cage, mouse 1	House mice	0.01	Animal Technician	Hold ≤ 5 mice	720	X		1	9.25x12.5 x8	NA	NA
Feeder, rat 1	Hold diet: pellet or meal	0.02	Animal Technician	900 gms	360	X		1	4x5x5 4x4x7	NA	NA
Feeder, mouse 1	Hold diet: pellet or meal	0.01	Animal Technician	150 gms	720	X		1 1	3x4x4 3x3x6	NA	NA
Balance, 1200 or 4400 gm cap 1	Weigh rodents, feeders, etc.	0.30	Animal Technician	20 cages (animals & feeder per hour)	1		X	10	3x14x7	110	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/6/81
Complete by Jones, Jorgenson
Area Laboratory No. 1
Title Acute Oral Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Table, utility 1	Hold balance, feeders, etc.	0.30	Animal Technician	NA	1		X	80	60x30x30	NA	Casters
Safety Hood System 1	Personnel protection from toxic chemicals during exposure	7.5	Animal Technician	NA	5		X	800	72x30x108	110	NA
Worktable w/sink 1	Work area	3.5	Animal Technician	NA	4		X	500	84x29x37	NA	NA
Balance 1	Feed weighing	3.7 ±0.10	Animal Technician	100 measure-ments/ hour	1		X	10	8x12x4	110	NA
Additional Equipment 1	Misc. small items to completely equip area	1.5 ±0.5	Staff	NA	Variable			Variable		110 or NA	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

PROTOCOL

Test No. 1: Acute Oral Toxicity Study (772.112-21), Rodent[a]

§ 772.112-21 Acute oral toxicity study.

(a) *Study design.* (1) *Species.* Testing must be performed with the laboratory rat.

(2) *Sex and age.* Young adult male and female animals must be used.

(3) *Number of animals and selection of dose levels.* (i) A trial test is recommended for the purpose of establishing a dosing regimen which must include one dose level higher than the expected LD_{50}. If data based on testing with at least 5 animals per sex are submitted showing that no toxicity is evident at 5g/kg, no further testing at other dose levels is necessary. If mortality is produced, the requirements of paragraph (a)(3)(ii) of this section must apply.

(ii) Enough animals per dose level and sufficient dose levels spaced appropriately must be used to produce test groups with mortality rates between 10 percent and 90 percent and to permit the calculation of the LD_{50} for males and females with a 95 percent confidence interval of 20 percent or less. At least 3 dose levels of the test substance, in addition to controls (if any), must be tested. Though the group sizes may vary for each dose level, each group must contain equal numbers of male and female animals.

(4) *Control animals.* (i) A concurrent vehicle control group is recommended if the vehicle or diluent used in administering the test substance would be expected to elicit any important acute toxicologic response, or if there are insufficient data on the acute effects of the vehicle.

(ii) A concurrent untreated control group is not required.

(5) *Dosing.* All animals must be dosed by gavage. All animals must receive the same concentration of dosing solution. They should also receive about the same volume of dosing solution, which should not exceed 4–5 ml per animal.

(6) *Duration of test.* The animals must be observed for at least 14 days after dosing, or until all signs of reversible toxicity subside, whichever occurs later.

(b) *Study Conduct.* (1) *Fasting.* Food shall be withheld from the animals the night prior to dosing.

(2) *Observation.* The animals must be observed frequently during the day of dosing and checked at least every 12 hours throughout the test period. The following must be recorded: Nature, onset, severity, and duration of all gross or visible toxic or pharmacological effects, e.g., abnormal or unusual cardiovascular, respiratory, excretory, behavioral, or other activity, as well as signs indicating an adverse effect on the central nervous system (paralysis, lack of coordination, staggering); pupillary reaction; and time of death. The weight of each animal must be determined at least semi-weekly (3–4 day intervals) throughout the test period, and at death.

(3) *Sacrifice and necropsy.* All test animals living at the termination of the observation period must be sacrificed. All test animals, whether dying by sacrifice or during the test must be subjected to a complete gross necropsy following their death, in accordance with § 772.100-2(b)(7), Subpart A. All abnormalities must be recorded.

(c) *Data reporting and evaluation.* In addition to the information required by § 772.100-2(b)(8), Subpart A, the test report must include the following information:

(1) Tabulation of response data by sex and dose level (i.e., number of animals dying per number of animals showing signs of toxicity per number of animals exposed);

(2) Time of death after dosing.

(3) LD_{50} for each sex for each test substance calculated at the end of the observation period (with method of calculation specified);

(4) 95 percent confidence interval for the LD_{50}; and

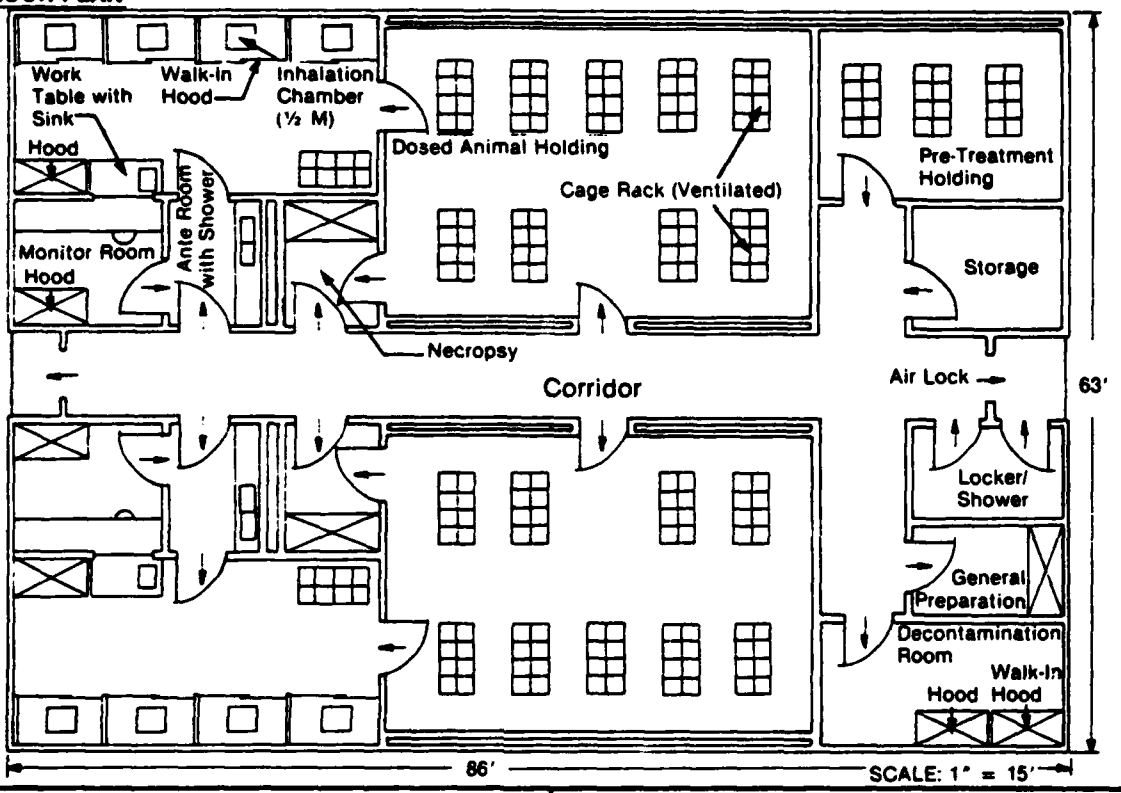
(5) Dose-response curve and slope.

(a) Test No. 1 uses rodent as the animal, price is based on rat.

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



CONSTRUCTION INFORMATION

Dimensions: 86 x 63 Ft.
Area: 5,418 Sq. Ft.
Ceiling Height ☐ 8' ☐ 9' ☒ 13' ☐_____
Air Flow: 17,600 CFM ☐ Variable
Air Changes/Hour: 15
Floor Drains: ☒ Capped ☐ Flushing ☐ Other
Water: ☒ Hot ☒ Cold ☐ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☒ Yes ☐ No
Local Exhaust Filtration: ☒ Yes ☐ No
Epoxy Coated: ☒ Walls ☒ Floors ☒ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☒ Timed Lighting
☐ Compressed Air; ☐ Vacuum; ☐ Other Gases
☐ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

1. Can test two chemicals simultaneously.
2. Separate dosed animal holding areas avoids cross-contamination.
3. Walk-in hoods provide safe maintenance of chambers from all sides.
4. Compatible with highly hazardous tests:
   - Ante room permits personnel decontamination
   - Local necropsy
   - Local decontamination

SPECIAL ASSUMPTIONS

1. Desirable to have local pre-test animal holding area.
2. Desirable to have local necropsy.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	135	25
Heat, Vent., Air Cond.	87	16
Electrical	103	19
Sanitary	43	8
Equipment	270	50
Total	638	118

TITLE Acute Inhalation Exposure Area, Rodent

NO. 5

F-650 (2/15/81)

Equipment List

Date 2/12/81
Complete by Ronald N. Shiotsuka
Area Laboratory No. 5
Title Acute Inhalation Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Exposure chamber, (stainless steel and glass) 1	Acute exposure of rodents	3.0 ± 1.0	Toxicologist	≤40 rats	8		X	300	27x27x84	110	Conditioned HEPA filtered air for chambers and room; scrubbers/filters for exhaust air
Cages, wire (stainless steel) 1	House rodents during exposure	0.03 ± .01	Animal technician	≤5 rats/ cage	32		X	2	8x10x8	NA	NA
Walk-in safety hood 1	Containment of toxic chemicals from exposure chambers	8.0	Toxicologist	NA	8		X	800	90x42x108	110	NA
Safety hood system 1	Personnel protection from toxic chemicals during exposure	7.5	Animal technician	NA	8		X	800	72x30x108	110	NA
Worktable w/sink 1	Work area	3.5	Staff	NA	2		X	500	84x29x37	NA	NA
Additional Equipment 1	Mis. small items to completely equip area	3.0 ± 1.0	Staff	NA	Variable			Variable		110 or NA	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/12/81
Complete by Ronald N. Shiotsuka
Area Laboratory No. 5
Title Acute Inhalation Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Infrared spectrophotometer 1	Dedicated to sampling chamber atmosphere	15.0± 3.0	Toxicologist or HVAC engineer	10 samples/ hour	1	X		50	36x18x19	110	NA
Integrated volume meters 1	For sampling chamber atmosphere (gravimetric, etc.)	0.5± 0.1	Laboratory technician or aerosol chemist	NA	4	X		15	16x8x24	NA	Vacuum pump
Magnehelic gage 1	Measure chamber static pressure, air flow, etc.	0.05± 0.01	Aerosol chemist or toxicologist	NA	80	X		2	4x1x4	NA	NA
Rotameters 1	Flow rate determination eg. test gas input to chambers	0.2± 0.05	Toxicologist	NA	20	X		1	1x1x12	NA	NA
Electronic balance, top loader 1	Weigh animals (computer interactive)	3.0 ± 0.1	Animal Technician	Samples 40/hr	3	X		15	6x10x13	110	NA
Analytical balance (microgram) 1	Gravimetric analysis of aerosols	8.0 ± 2.0	Toxicologist or laboratory technician	Samples 40/hr	1		X	20	12x18x16	110	"Vibration-free" table

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/12/81
Complete by Ronald N. Shiotsuka
Area Laboratory No. 5
Title Acute Inhalation Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.(c) (in.)		
Multi-channel analyzer 1	Record output of particle size analyzer	6.0 ± 1.0	Toxicologist or laboratory technician	Real-time analysis	1	X		25	9x20x10	110	NA
Strip-chart recorder (2-channel) 1	Record output of particle counter during chamber calibration	1.5 ± 0.3	Staff	NA	2	X		5	16x10x4	110	NA
Portable hygrothermograph 1	Rapid monitoring of areas not covered by computer-interactive sensors	0.3 ± 0.1	Instrument operator	NA	1	X		3	12x4x14	NA	NA
Nebulizer 1	Generate liquid aerosols	0.6 ± 0.1	Toxicologist or aerosol chemist	NA	3		X	15	7x9x13	110	NA
Anemometer 1	Calibrate chamber air flow	0.8 ± 0.1	Aerosol chemist or toxicologist	NA	1	X		3	5x7x2	110	NA
Gas chromatograph and control module 1	Dedicated to sampling chamber atmosphere	10.0± 3.0	Laboratory technician	Samples 10/hr	1	X		300	48x18x24	220	Vent for exhaust gases

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/12/81
Complete by Ronald N. Shiotsuka
Area Laboratory No. 5
Title Acute Inhalation Exposure Area, Rodent

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Optical particle counter 1	Measure aerosol concentration	4.0 ± 2.0	Aerosol chemist or toxicologist	Real-time analysis	1	X		7	8x8x8	110	Strip chart recorder
Optical particle size analyzer 1	Determine aerosol particle size distribution	6.5 ± 0.5	Aerosol chemist or toxicologist	Real-time analysis	3	X		30	24x30x10	110	NA
Cascade impactor 1	Collect fractionated samples and determine particle size distribution	3.0 ± 1.0	Aerosol chemist or toxicologist	2 runs/ day	1		X	10	3x3x10	NA	Vacuum pump
Pumps 1	For chamber atmosphere sampling	0.2 ± 0.1	Laboratory technician	NA	10	X		4	5x11x5	110	NA
Fluidized bed generator (small) 1	Generate particulate aerosols for small chambers	5.0 ± 0.5	Laboratory technician, or HVAC engineer	NA	1	X		30	16x10x14	110	Filtered, dried and pressurized (60 psig) air supply
Fluidized bed generator (large) 1	Generate particulate aerosols for medium or large size chambers	7.0 ± 1.0	Laboratory technician, toxicologist, or HVAC engineer	NA	2	X		60	30x16x20	110	Same requirement as for small FBG above

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

PROTOCOL

Test No. 4: Acute Inhalation Toxicity Study (772.112-23), Rodent[a]

§ 772.112-23 Acute inhalation toxicity study.

(a) *Study design.* (1) *Species, sex, and age.* Testing must be performed with the laboratory rat. Young adult male and female animals must be used.

(2) *Number of animals and selection of dose levels.* (i) A trial test is recommended for the purpose of establishing a dosing regimen which must include one dose level higher than the expected LC_{50} and at least one dose level below the expected LC_{50}. If data based on testing with at least 5 animals per sex are submitted showing that no toxicity is evident at 5 mg/1, no further testing at other dose levels is necessary. If mortality is produced, the requirements of paragraph (a)(2)(ii) of this section apply.

(ii) The number of animals per dose level, and the number and the spacing of dose levles must be chosen to produce test groups with mortality rates between 10 percent and 90 percent, and to permit calculation of the LC_{50} with a 95 percent confidence limit of 20 percent or less. At least 4 dose levels of the test substance, in addition to controls, must be tested. Though the group sizes may vary for each dose level, the group must contain an equal number of male and female animals.

(3) *Duration of test.* In selecting the exposure period, allowance must be made for changed concentration equilibration time. Where there is no difficulty in maintaining a steady concentration of the test substance in the chamber(s), the exposure period must be at least 1 hour. Where there is some difficulty in maintaining a study concentration the exposure period must last up to 4 hours. The animals must be observed for 14 days, or until all signs of reversible toxicity subside, whichever occurs later.

(4) *Use of solvent.* A solvent may be added to the test substance, if necessary, to help generate an exposure atmosphere. If a product's labeling instructions specify the use of a particular solvent, that solvent is preferred. If no solvent is specified in the product's labeling instructions, the solvent, if any, which is used to formulate the product should be used.

(5) *Control groups.* (i) A concurrent untreated control group is required.

(ii) If any solvent, other than water, is used in generating the exposure atmosphere, a vehicle control group must be tested. The vehicle control group must be exposed to an atmosphere containing the greatest concentration of solvent present in any test system.

(b) *Study conduct.* (1) *Exposure chamber design and operation.*

(i) Inhalation exposure techniques described in this section are based on the use of whole-body inhalation chambers which allow the experimental animals to receive whole-body dermal exposure and possible large oral exposure, as well as the exposure by inhalation. In some cases, the investigators will want to use other inhalation exposure techniques involving face masks, head-only exposure, intratracheal instillation, or other similar techniques which reduce or preclude added dermal and oral exposures. Some alternative techniques are described by Phalen, 1978. When alternative techniques are used, the procedures and results must be reported in a manner similar to that required with the use of whole-body inhalation chambers.

(ii) Animals must be tested in a dynamic air flow exposure chamber. The chamber design must be chosen to enable production of an evenly distributed exposure atmosphere throughout the chamber. The chamber design also should minimize crowding of the test animals and maximize their exposure to the test substance.

(2) *Operation measurements.* The following measurements must be taken with care to avoid major fluctuations in the air concentrations or major discrepancies in the operation of the chambers.

(i) *Air flow.* The rate of air flow through the chamber must be measured continuously.

(ii) *Chamber concentrations.* (A) Nominal concentrations must be calculated for each run by dividing the amount of the test substance used for the generating system by the air flowing through the chamber during the

(a) Test No. 4 uses rodent as the animal, price is based on rat.

(B) Actual chamber concentrations must be determined by samples of chamber air taken near to the breathing zone of the animals as frequently as necessary to obtain an averaged integrated external exposure which is representative of the entire exposure period. The system used to generate the vapor, gas, or aerosol should be such that the chamber concentrations and particle size distributions are controlled under stable conditions, reflecting the current state-of-the-art, and should not vary in a range greater than 30 percent of the average (range/mean equal to or less than 30 percent).

(iii) *Temperature and Humidity.* The temperature must be maintained at 24 ± 2° C, and the humidity within the chamber at 40–60 percent. Both must be monitored continuously.

(iv) *Oxygen.* The rate of air flow through the chamber must be adjusted to insure that the oxygen content of exposure atmosphere is at least 19 percent.

(v) *Particle Size Measurement.* (A) *General.* In the case of gases and vapors, particulate sampling should be carried out at intervals to insure the animals are not being exposed to unknown and unexpected particulate materials. Aerosol particle size measurements should be made on samples taken at the breathing level of the animals. These analyses should be carried out using techniques and equipment reflective of the state-of-the-art. All of the suspended aerosol (on a gravimetric basis) should be accounted for, even when most of the aerosol is not respirable.

(B) *Sizing Analysis.* The sizing analysis should be in terms of equivalent aerodynamic diameters and should be represented as geometric mean (median) diameters and their geometric standard deviations (see NIOSH syllabus in the Appendix to this section), as calculated from log probability graphs or computer programs. The size analyses should be carried out frequently during the development of the generating system to insure proper stability of aerosol particles, and only as often thereafter during the exposure as is necessary to determine adequately the consistency of particle distributions to which the animals are exposed, maintaining at least 20 percent of the particles at 10 microns or less. At a minimum, these analyses should be carried out once per hour for each level of exposure for gasious test substances, twice per hour for liquid test substances, and 4 times per hour for dusts and powders.

(3) *Observation.* The animals must be observed frequently during the day of dosing and checked at least every 12 hours throughout the test period, for at least 14 days after dosing or until all signs of reversible toxicity subside, whichever occurs later. The following must be recorded: Nature, onset, severity, and duration of all gross or visible toxic or pharmacologic effects, i.e., abnormal or unusual cardiovascular, respiratory, excretory, behavioral, or other activity, as well as signs indicating an adverse effect on the central nervous system (paralysis, lack of coordination, staggering); pupillary reactions; and time of death. The weight of each animal must be determined on the day of dosing, 2, 3, 4, 7, and 14 days after dosing, weekly thereafter, and at death.

(4) *Sacrifice and Necropsy.* All animals living at the termination of the observation period must be sacrificed. All test animals, whether dying by sacrifice or during the test, must be subjected to a complete gross necropsy following their death, in accordance with § 772.100–2(b)(7), Subpart A. Examination must include nasal passages, trachea, bronchi, and lungs, and any other tissues known to be affected by the test substance. All abnormalities must be recorded.

(5) *Preservation of tissues and histopathology examination.* The following are required:

(i) Those tissues designated in paragraph (b)(5)(ii) of this section must be placed in suitable fixative as soon as possible. Tissues and microscopic slides must be prepared according to the standards set forth in § 772.100–2(b)(7)(ii) and (iii), Subpart A. Tissue samples, tissue blocks, and microscopic slides must be preserved and held in accordance with § 772.110–1(j).

(ii) The following tissues must be examined microscopically:

(A) Lungs, liver, and kidneys at all dose levels.

(B) Any tissue or organ that appears abnormal, at any dosage level, as determined in the necropsy examination.

(iii) The histopathology findings must be recorded and reported as required by paragraph (c)(10) of this section.

(c) *Data reporting evaluation.* In addition to information required by § 772.100–2(b)(8), Subpart A, and paragraphs (b)(3) and (b)(4) of this section, the test report must include the following:

(1) Vapor pressure and particulate size (median size with geometric standard deviation).

(2) Description of the chamber design and operation, including type of chamber, its dimensions, the source of makeup air and its conditioning (heating or cooling) for use in the chamber, the treatment of exhausted air, the housing and maintenance of the animals in the chambers, and similar related information. Equipment for measuring temperatures and humidity, the generating system, and the methods of analyzing airborne concentrations and particle sizing must be described;

(3) The following operation data must be tabulated both individually and in summary form, using means and standard deviations (with or without ranges) in tabular form. The data summaries must be grouped according to experimental groups, and nonexpected differences (such as in temperature and airflow) and must be tested for statistical significance.

(i) Airflow rates through the chamber;

(ii) Chamber temperature and humidity;

(iii) Nominal concentrations;

(iv) Actual concentrations; and

(v) Median particle sizes and their geometric standard deviations and percent of particles 10 microns or less.

(4) Tabulation of the response data (number of animals dying per number of animals showing signs of toxicity per number of animals exposed) at each exposure level by sex, and time of death after dosing;

(5) Tabulation of the body weights on the day of dosing, 2, 3, 4, 7, and 14 days after dosing, weekly thereafter, and at death.

(6) The LC_{50} (calculated on an exposure of one hour) for each sex for each test substance;

(7) Specification of the method used for LC_{50} calculation;

(8) The 95 percent confidence interval for the LC_{50};

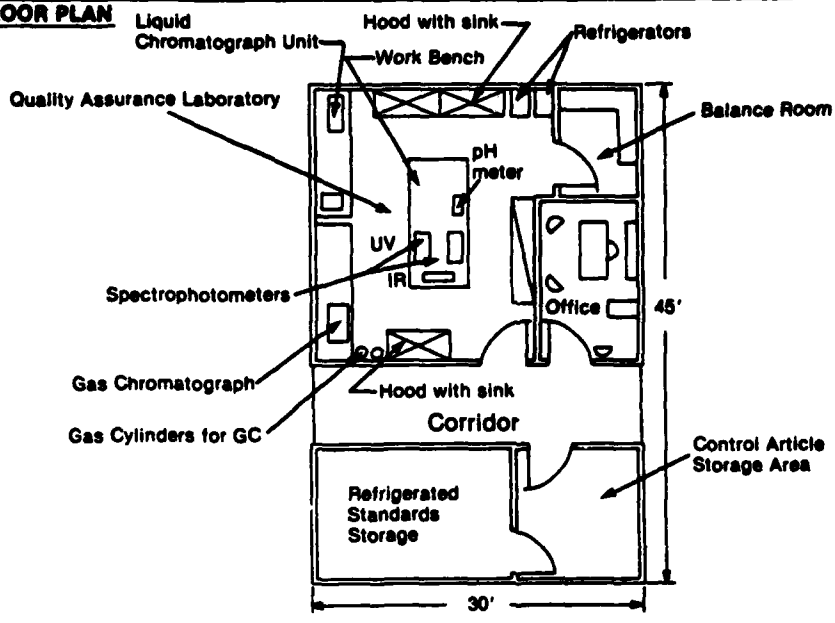
(9) The dose-response curve and slope (with confidence limits); and

(10) The histopathology findings including a complete record of lesions and abnormalities observed, and the histological diagnosis and characterization of each kind of lesion or abnormality observed, naming those which apparently caused death or morbidity.

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 30 x 45 Ft.
Area: 1,350 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐ _____
Air Flow: 1,000 CFM ☐ Variable
Air Changes/Hour: 5
Floor Drains: ☐ Capped ☐ Flushing ☒ Other
Water: ☒ Hot ☒ Cold ☐ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☐ Yes ☒ No
Local Exhaust Filtration: ☒ Yes ☐ No
Epoxy Coated: ☐ Walls ☐ Floors ☐ Ceilings
Sprinklers: ☐ Yes ☐ No ☒ Halon ☐ Optional
☐ Timed Lighting
☒ Compressed Air; ☒ Vacuum; ☐ Other Gases
☒ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

HEPA and charcoal exhaust filter in central article storage area.

SPECIAL ASSUMPTIONS

None.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	18	13
Heat, Vent., Air Cond.	11	8
Electrical	15	11
Sanitary	7	5
Equipment	110	81
Total	161	118

TITLE Quality Assurance Laboratory

NO. 23

F-650 (2/15/81)

Equipment List

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 23
Title Quality Assurance Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Infrared Spectrophotometer 1	Organic analysis	18±2.0	Infrared analytical chemist	25/day	1		X	150-280	Variable	110	NA
Constant Temperature Bath 1	Maintain water at constant temperature	1.0± 0.30	Analytical chemist	Variable	1		X	60	36x16x16	110	Sink
pH Meter 1	Measurement of pH (acid-base)	1.0± 0.20	Analytical chemist	Variable	2		X	10	14x10x10	110	Periodically purchase new electrodes
Balance, analytical (electronic) 1	Accurate gravimetric measurement of materials	6.0±1.0	Analytical chemist	Variable	1		X	30	18x12x10	110	NA
Balance Table 1	Special table, shock resistant for holding balance	0.70± 0.20	Analytical chemist	NA	1		X	60	40x28x18	NA	NA
Constant Temperature Circulating Bath 1	Maintain constant water temperature at remote location	4.0± 0.60	Analytical chemist	Variable	1		X	15	14x12x8	110	Water and sinks

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 23
Title Quality Assurance Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life >5 yrs.	Expected Life >10 yrs.	Size Wt. (lbs)	Size Dimen[c] (in.)	Voltage Reqmt. (V)	Special Requirements
Gas Chromatograph (electron capture FID/F-N-P) 1	Organic analysis	12±3.0	Analytical chemist Gas Chromatograph operator	90/day	1	X		250	30x30x30	220	Venting for exhaust gases, space for carrier & detector gases, licensing for nickle 63 radioactive detector (electron capture).
Liquid Chromatograph (analytical) (variable UV, & fluorescence detector) 1	Organic analysis	14±3.0	High performance liquid chromatography analytical chemist	30/day	1	X		Variable	36x36x36	110	NA
Atomic Absorption Spectrophotometer (flame, flameless & graphite furnace) 1	Inorganic analysis	23±3.0	Atomic absorption analytical chemist	30/day	1	X		300	40x18x20	220	Vented hood for exhaust gases
UV Visible Spectrophotometer 1	Specific wave length or variable wave length detection of organic material; also quantitative determination of primary organics		UV Visible analytical chemist (Any trained analytical chemist should be able to use this)	20/day	1	X		275-350	Variable	110	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/10/81
Complete by G. Podrebarac
Area Laboratory No. 23
Title Quality Assurance Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Hood 1	Handling chemicals	7.0	Technician	NA	1		X	180	36x48x48	110	NA
Additional Equipment 1	Miscellaneous small items to completely equip area	3.9	Technician	NA	Variable			Variable		110 or NA	NA

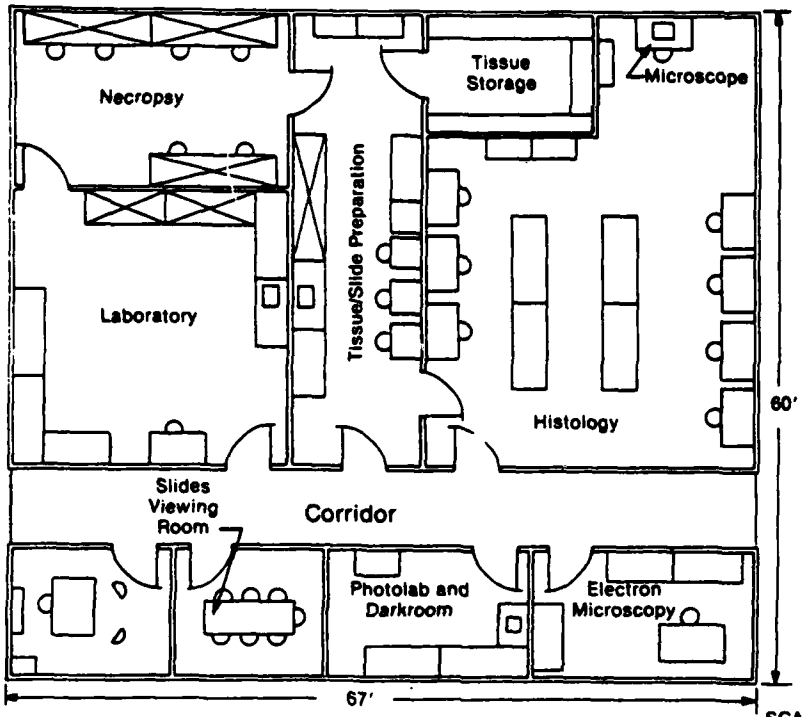
(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 67 x 60 Ft.
Area: 4,020 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐ _____
Air Flow: 9,000 CFM ☐ Variable
Air Changes/Hour: 15
Floor Drains: ☐ Capped ☐ Flushing ☒ Other
Water: ☒ Hot ☒ Cold ☐ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☐ Yes ☒ No
Local Exhaust Filtration: ☐ Yes ☒ No
Epoxy Coated: ☒ Walls ☒ Floors ☒ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☐ Timed Lighting
☒ Compressed Air: ☒ Vacuum; ☒ Other Gases
☒ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

1. Laboratory sized for sacrificing large primates.
2. Capability for histopathology investigations with light or electron microscopy.
3. Capability for group viewing of slides.

SPECIAL ASSUMPTIONS

None.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	101	25
Heat, Vent., Air Cond.	64	16
Electrical	76	19
Sanitary	32	8
Equipment	340	85
Total	613	153

TITLE Pathology Laboratory — **NO.** 25

F-650 (2/15/81)

Equipment List

Date 2/5/81
Complete by B. Kirkhart
Area Laboratory No. 25
Title Pathology Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Balance 1	Weighing reagents	2.5 ± 2.0	Histology technician	Variable	1	X		25	7x13x4	115	NA
pH Meter 1	Compounding stains and buffers, quality	0.45 ± 0.10	Histology technician	Variable	1	X		10	11x6x8	115	Electrodes must be replaced periodically
Cryostat 2	Cutting frozen sections for special procedures	6.0 ± 1.0	Histology technician	50 blocks/ hr	1		X	300	27x25x48	115	NA
Microscope 1	Diagnosing slides	22 ± 17	Pathologist	10 slides/ hr	1		X	5	8x8x20	115	NA
Knife sharpener 1	Sharpening microtome knives	4.0 ± 2.0	Histology technician	2 knife/ hr	2	X		15	30x20x17	110	Periodically must purchase honing compounds and new plates
Automatic stainer 3	H & E Staining	6.5 ± 2.0	Histology technician	80 slides/ hr unattended	1	X		75-400	40x20x12	110	Running water hookup

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/5/81
Complete by B. Kirkhart
Area Laboratory No. 25
Title Pathology Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Oven 1	Drying slides; incubation of special stains	0.30 ± 0.10	Histology technician	NA	1	X		30	18x13x24	115	NA
Slide trays 1	Assembling slides for labelling, cover-slipping, reading	0.004	Pathologist	20 slides/ tray	100		X	<1	7x13x½	NA	NA
Microscope 1	Checking stains, quality control	2.5 ± 0.50	Histology technician	Variable	1		X	5	8x8x20	115	NA
Refrigerator/ freezer 1	Chilling blocks, freezing trays, storage of reagents	1.0 ± 0.20	Histology technician	15 cu. ft.	1		X	250	30x35x60	115	NA
Paraffin dispenser 1	Melting stock paraffin for use in processor and embedding center	0.50 ± 0.10	Histology technician	10 lbs. paraffin per day	1	X		3	8x8x14	115	NA
Microtome knives 1	Sectioning	0.10 ± .02	Histology technician	Variable	6	X		<1	<12x12x12	NA	Require sharpening after each use

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/5/81
Complete by B. Kirkhart
Area Laboratory No. 25
Title Pathology Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Portable fume hood (option: built-in sit-down hoods) 1	Remove formaline and solvent fumes from air during cut-in and covers slipping	1.2 ± 0.60	Histology technician	NA	2	X		5	27x14x12	115	Filter required
Cassette lids 1	Covering cassettes during processing	0.20 ± 0.10	Histology technician	NA	500		X	<1	12x12x12	NA	NA
Tissue processor 2	Automatic dehydration, clearing and infiltration of tissues	15 ± 10	Histology technician	300 blocks/ hr	1	X		500	27x27x30	115	Some less expensive models must be in fume hood; other units are free-standing
Embedding center 1	Embedding processed tissues in paraffin	3.5 ± 2.0	Histology technician	60 blocks/ hr	1	X		90	36x24x15	115	Some models require running water hood-up
Base molds 1	Casting paraffin blocks	0.30 ± 0.10	Histology technician	1 block/ mold; reuseable	120		X	<1	12x12x12	NA	NA
Microtome 1	Sectioning blocks	6.0 ± 4.0	Histology technician	50 blocks/ hr	2		X	100	9x14x9	NA	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/5/81
Complete by B. Kirkhart
Area Laboratory No. 25
Title Pathology Laboratory

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Photomicroscopy apparatus 2	Photographing microscopic observations	0.50 ± 0.10	Pathologist	Variable	1		X	5	Variable	115	NA
Slide storage cabinet 1	Storing completed slides	0.50 ± 0.40	Pathologist	5,000 slides	1		X	10	16x29x5	NA	NA
Electron microscope 1	Histopathology	100	Electron microscope operator	NA	1		X	1500	90x45x110	220	NA
Hood 1	Handling chemicals	7.5	Laboratory technician	NA	2		X	180	36x48x48	110	NA
Additional equipment 1	Misc. small items to completely equip area	1.0 ± 0.5	Staff	NA	Variable			Variable		110 or NA	NA

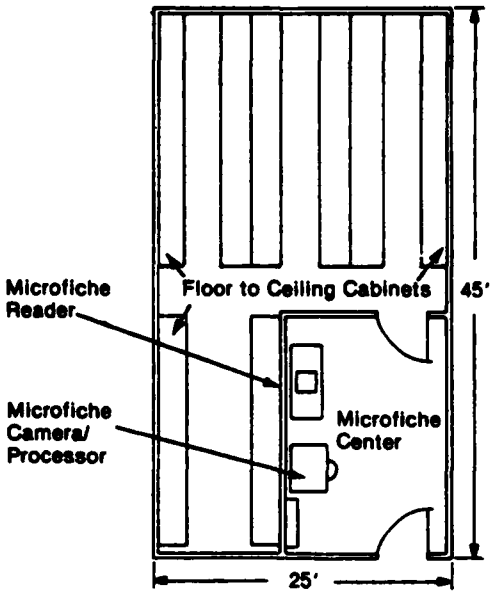
(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 25 x 45 Ft.
Area: 1,125 Sq. Ft.
Ceiling Height ☐ 8' ☒ 9' ☐ 13' ☐_____
Air Flow: 2,530 CFM ☐ Variable
Air Changes/Hour: 5
Floor Drains: ☐ Capped ☐ Flushing ☐ Other
Water: ☐ Hot ☐ Cold ☒ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☒ Yes ☐ No
Local Exhaust Filtration: ☐ Yes ☒ No
Epoxy Coated: ☐ Walls ☐ Floors ☐ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☐ Timed Lighting
☐ Compressed Air; ☐ Vacuum; ☐ Other Gases
☐ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

Microfilm-based storage system maximizes storage capacity, control of records and accessibility of information.

SPECIAL ASSUMPTIONS

Microfilm record storage system will be used.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	12	11
Heat, Vent., Air Cond.	9	8
Electrical	10	9
Sanitary	2	2
Equipment	24	21
Total	57	51

TITLE	NO.
Record Archives Area	40

F-650 (2/15/81)

Equipment List

Date 2/10/81
Complete by E. Podrebarac
Area Laboratory No. 40
Title Record Archives Area

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Microfiche System 2	Filming, duplication, retrieving, and reading records	22	Librarian	NA	1		X	1000	60x36x60	110	NA
Additional Equipment 1	Miscellaneous small items to completely equip area	1.6	Librarian	NA	Variable			Variable		110 or NA	NA

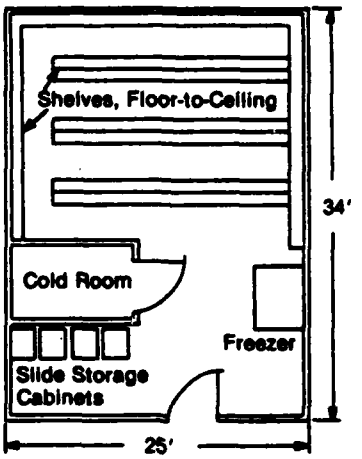
(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

MAMMALIAN TOXICOLOGY FACILITY MODULE DESCRIPTION

Life Systems

FLOOR PLAN



SCALE: 1" = 15'

CONSTRUCTION INFORMATION

Dimensions: 25 x 34 Ft.
Area: 850 Sq. Ft.
Ceiling Height ☐ 8' ☐ 9' ☒ 13' ☐_____
Air Flow: 3,000 CFM ☐ Variable
Air Changes/Hour: 5
Floor Drains: ☐ Capped ☐ Flushing ☐ Other
Water: ☐ Hot ☐ Cold ☒ None ☐ No ☐ Make-up
Central Vacuum Cleaning: ☒ Yes ☐ No
Local Exhaust Filtration: ☐ Yes ☒ No
Epoxy Coated: ☐ Walls ☐ Floors ☐ Ceilings
Sprinklers: ☐ Yes ☒ No ☐ Halon ☐ Optional
☐ Timed Lighting
☐ Compressed Air; ☐ Vacuum; ☐ Other Gases
☐ Emergency Shower/Eye Wash

SPECIAL FEATURES/BENEFITS

1. Freezer provided for storage of cultures.
2. Cold room provided for storage of tissue samples not in preservatives.
3. Shelves provided for preserved tissue samples (7,824 ft³ of storage space).
4. Cabinets provided for storage of slides.

SPECIAL ASSUMPTIONS

Capacity of preserved tissue storage area is 6 years of testing, based on:

- Samples from 100 animals occupies about 1 ft³.
- Storage space required per year for all modules operating at 50% maximum animal testing rate is 1,300 ft³.

COST ESTIMATE

	Total $(000)	Resulting $/Sq. Ft.
General Construction	9	11
Heat, Vent., Air Cond.	7	8
Electrical	8	9
Sanitary	2	2
Equipment	3	4
Total	29	34

TITLE

Specimen Storage Area

NO. 41

F-650 (2/15/81)

Equipment List

Date 2/6/81
Complete by F. I. Metz
Area Laboratory No. 41
Title Specimen Storage Area

Equipment Item	Function	Estimated Cost ($000)(a)	Operator Title	Capacity of Equipment (Throughput per unit of time)(b)	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.(c) (in.)		
Slide Cabinet 6 drawers/ cabinet 1	Store slides (3"xl glass slides)	0.07	Lab Assistant	4,500 slides/ drawer	Number of animals will determine		X	150	16x19x5	NA	Storage space and strong floor space
Base for slide cabinets 1	Support	0.04	Lab Assistant	NA	1 for each drawer		X	60	16x19x1	NA	Storage space
Embedding cassette storage cabinets 6 drawers/unit 1	To store & file finished blocks	0.11	Lab Assistant	1,000 blocks/ drawer	Number of animals will determine		X	150	16x19x5	NA	Storage space
Jar & Lids 1	Specimen storage	0.04/ gross	Histotech Pathology Assistants	4 oz.	Number of animals will determine	X		0.25	Variable	NA	Sufficient storage space
Jars & Lids 1	Specimen storage	0.05/ gross	Histotech Pathology Assistants	9 oz.	Number of animals will determine	X		0.25	Variable	NA	Sufficient storage space
Jars & Lids 1	Specimen storage	0.06/ gross	Histotech Pathology Assistants	16 oz.	Number of animals will determine	X		0.25	Variable	NA	Sufficient storage space

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

Equipment List

Date 2/6/81
Complete by F. I. Metz
Area Laboratory No. 41
Title Specimen Storage Area

Equipment Item	Function	Estimated Cost ($000)[a]	Operator Title	Capacity of Equipment (Throughput per unit of time)[b]	No. Required for the area/lab	Expected Life		Size		Voltage Reqmt. (V)	Special Requirements
						>5 yrs.	>10 yrs.	Wt. (lbs)	Dimen.[c] (in.)		
Jars & Lids 1	Specimen storage	0.08/ gross	Histotech Pathology Assistants	32 oz.	Number of animals will determine		X	0.25	Variable	NA	Sufficient storage space
Additional Equipment 1	Miscellaneous small items to completely equip area	2.4	Histotech Pathology Assistants	NA	Variable			Variable		110 or NA	NA

(1) Essential
(2) Desirable
(3) Ideal

(a) Estimated average cost for item to include a cost range around the average.
(b) Report throughput in samples per hour or 8-hour day if applicable.
(c) Record dimensions in order, width x depth x height

APPENDIX 5

INHALATION CHAMBER PROJECTS SUMMARY

TABLE A5-1 INHALATION CHAMBER CHARACTERISTICS[a]

Manufacturer/ Designer	Approx. Volume (m^3)	Dimensions (L x W x H cm, Diam x H cm)	Shape/Type	Animal Capacity No.	Animal Capacity Species	Major Materials of Construct.	Operational Status	Delivery (mo.[b])	Cost ($000)	Special features (see list)
Charles Spengler and Associates	0.25	46 x 46 x 120	Square/Hinners	24	mice	(m)	(k)	2-5	—	3,8
	0.50	62 x 62 x 130	Square/Hinners	48	mice	(m)	(k)	2-5	—	3,8
	1	92 x 92 x 200	Square/Hinners	96	mice	(m)	(k)	2-5	—	5,8
	1.5	—	Square/Hinners	75	rats	(m)	(k)	6-8	—	8
	3.7	150 x 150 x 350	Square/Hinners	200	rats	(m)	(k)			6,8
	6	180 x 180 x 350	Square/Hinners	250	rats	(m)	(k)	6-8	10-20[c]	6,8
	(d)	62 x 124	Hexagon/Nose Only	12	rodents	(n)	(k)	3	7.9	9
Hazelton Systems, Inc.	0.4	68 x 68 x 210	Square/Hinners	40	rats	(e)	(k)		3[f]	3,5
	0.6	82 x 82 x 210	Square/Hinners	60	rats	(o)	(k)		5[f]	8
	1.0	92 x 92 x 210	Square/Rochestor	80	rats	(m)	(k)		—[f]	8
	1.5	91 x 180 x 210	Rectangle/Hinners	120	rats	(o)	(k)		7[f]	8
	2.2	127 x 132 x 210	Square/Battelle[g]	170	rats	(m)	(h)	1-2	9.4[f]	1,3,4,8
	6.0	180 x 180 x 340	Square/Hinners	240	rats	(o)	(k)		10[f]	2,8
	(d)	—	-/Nose Only	200	rats	(n)	(l)		3-5[f]	
King-Lar Co.	8	180 x 220 x 350	-/Nose Only	—		(n)	(l)	3-6		5,6
	16	250 x 260 x 350	-/Nose Only	400	rats	(n)	(l)	3-6	—	5,6
The Upjohn Co.	0.15	—	Cubical/Leong[i]	—	—	—	(j)	—	—	1,3,7,10,11,12
	0.9	—	Cubical/Leong[i]	—	—	—	(j)	—	—	1,3,7,10,11,12
	6	—	Cubical/Leong[i]	—	—	—	(j)	—	—	1,3,7,10,11,12
Wahmann Mfg. Co.	0.2	—	Square/Hinners	—	—	(m)	(k)	6	—	5
	1	—	Square/Hinners	—	—	(m)	(k)	6	—	5
	2.5	110 x 120 x 250	Square/Hinners	60	rats	(m)	(k)	6	—	5
	8	220 x 180 x 340	Rectangle/Hinners	200	rats	(m)	(k)	6	—	2,5,6
Young and Bertke Co.	0.33	70 x 70 x 200	Square/Hinners	30	rats	(m)	(k)	3-6	1.8[f]	3,5
	1.3	90 x 90 x 300	Square/Hinners	108	rats	(m)	(k)	3-6	2.0[f]	5
	2.9	140 x 140 x 330	Square/Hinners	144	rats	(m)	(k)	3-6	3.6	5
	3.3	150 x 150 x 340	Square/Hinners	15	monkeys	(m)	(k)	3-6	4.4[f]	5,6

(a) Blank spaces in table indicate information not collected.
(b) Does not include any time for special design.
(c) For chamber with special features 1, 2, 6 and 8.
(d) Nose-only exposure.
(e) Stainless steel/lucite — heat transfer problems and solvents might react with lucite.
(f) Approximate price, not a quoted or catalog price.
(g) Hazelton 100 design by Dr. Owen Moss at Battelle Northwest.
(h) Operating — some concern about getting homogenous particle distribution within chambers.
(i) Chambers designed by Dr. Basil Leong at Upjohn.
(j) Ready for manufacturer — no manufacturer at this time.
(k) Operating.
(l) Design stage.
(m) Stainless steel/glass.
(n) Stainless steel.
(o) Stainless steel/lucite.

SPECIAL FEATURES LIST

1. Designed to run with animal waste catch pans in place during exposures.
2. Cage racks can be rolled into and out of chambers.
3. Designed to be movable. These are either self-contained units or have quick disconnects.
4. Designed to be cleaned in tunnel type rack washer.
5. Have internal spray rings for cleaning and flushing.
6. Available as knockdown units for construction in selected location.
7. Designed to fit into rooms with ceiling heights of 10 feet.
8. Available as a complete system with air handling and filtration (input and exhaust)(does not include monitoring equipment).
9. Modular construction.
10. Transfer of animals to temporary housing unit without exposing handlers to test agent.
11. Atmosphere generating equipment contained inside chamber.
12. Built-in exhaust air handling system.

TABLE A5-2 INHALATION CHAMBER OPERATING PROCEDURES

Parameter	Facilities Providing Information[a]															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Temperature °C (range)	22	22	22	22 (21-24)	22	22	22	22	22	—	22	22	22	22	—	22
Relative Humidity % (range)	50 (45-55)	—	50 (60-70)	50 (40-65)	50 (40-65)	50 (50-65)	50 (30-70)	50 (60-70)	50 (60-70)	— —	— —	— —	50 (20-80)	— —	— —	— —
Pressure cm H_2O (range)	-1	—	-2.5	0.25-0.5	-1	—	-0.5	-1.2 (-1to-2.5)	-1	—	—	-0.5 (-0.5to-1)	-2.5	—	—	-0.5 (-0.25to-1)
Light Intensity (ft candles)			Optimal for species	—	—	—	—	—	—	—	—	—	—	—	—	(100)
- internal lighting	No	—	Yes	No	—	—	No	No	No	—	—	—	—	—	—	Yes
Air changes/hr.	—	—	15-20	12-18	15	≤60	—	20	15	—	—	10-15	17	—	—	10-15
Computer monitoring	Yes	—	Yes	No	—	—	Yes	No	No	Yes	No	Yes	No	Yes	—	No
Computer feedback control	Yes	—	Yes	No	—	—	No	No	No	Yes	No	Yes	No	Yes	—	No
Cleaning - Time (min)	15	—	15-30	10-15	—	—	—	5	15	—	—	—	10-15	—	—	15
- Equipment	Hose	—	Press. hot water Solvent	Hose				Hose	Hose Cage Washer			—	Hose Solvent	—	—	Press. hot water
- Connections	Water Drain	—	Water Electric Drain	Water Drain			—	Water Drain	Water Drain			Drain	Water	—	—	Water Electric Drain
Input air - Source	Prepared	—	Prepared	Room air	Room air	Room air	Room air	Room air and prepared	—	—	—	Prepared	—	—	Prepared	
- Type filters	HEPA Charcoal	—	HEPA Charcoal	HEPA Charcoal	HEPA Charcoal	HEPA Charcoal	Charcoal HEPA	Charcoal HEPA	—	—	—	Charcoal HEPA	—	—	—	
Exhaust air - Separate system for each chamber	Yes	—	Yes	No	No	No	No	No	—	—	No	—	—	No	—	Yes
- Type filters	Electro-static precip. and scrubber	— —	Charcoal HEPA	Charcoal	Charcoal HEPA	Charcoal HEPA	Charcoal HEPA	Charcoal HEPA	—	—	Charcoal HEPA	Charcoal	Charcoal	— HEPA	—	Scrubber
Personnel required to operate[b]. No./chambers	2/4	—	2/8	2/8	—	—	—	—	—	4to6/27	2/4	4/8	2/4	—		3/10
- Training period (mo.)	3-6	—	—	—	—	—	—	—	—	—	—	—	—	3	—	—

(a) See Sources of information table for names of facilities.
(b) Supervisory and maintenance personnel not included.

APPENDIX 6

A LIST OF TITLES FOR QUALITY ASSURANCE STANDARD OPERATING PROCEDURES

Specific titles of SOPs are given under the following major headings:

- Facilities Specification
- Facilities Inspection and Sanitation
- Equipment Inspection
- Equipment Maintenance
- Equipment Calibration
- Consumables Acceptability
- Automatic Data Processing Equipment
- Record Storage
- Traceability
- Test and Control Article
- Performance Audit
- Corrective Action
- Study Planning and Conduct
- Personnel
- Animal Care

Facility Specification SOPs

- Analytical and Synthetic Chemistry Laboratory
- Animal Care Facility
- Animal Care Supplier Facility
- Animal Surgery Facility
- Animal Quarantine Area
- Cage/Rack Washing Area
- Control Article Storage Facility
- Control Article Handling Facility
- Feed Mixing and Blending Area
- Glass Washing Area
- Inhalation Exposure Area
- Pathology Laboratory
- Radiochemistry Laboratory
- Refrigerated Food Storage Area
- Showers/Dressing Room
- Test Article Storage Facility
- Test Article Handling Facility
- Waste Handling and Disposal Area
- Veterinary Medicine Area

Facility Inspection and Sanitation SOPs

- Analytical and Synthetic Chemistry Laboratory
- Animal Care Facility
- Animal Care Supplier Facility
- Animal Surgery Facility
- Animal Quarantine Area
- Cage/Rack Washing Area

- Control Article Storage Facility
- Control Article Handling Facility
- Feed Mixing and Blending Area
- Glass Washing Area
- Inhalation Exposure Area
- Pathology Laboratory
- Radiochemistry Laboratory
- Refrigerated Food Storage Area
- Showers/Dressing Room
- Test Article Storage Facility
- Test Article Handling Facility
- Waste Handling and Disposal Area
- Veterinary Medicine Area

Equipment Inspection SOPs

- Aerosol Generation System
- Animal Cage
- Animal Rack
- Atomic Absorption Spectrophotometer
- Autotechnician Tissue Processor
- Automatic Titrator
- Analytical Balance
- Constant Temperature Bath
- Gas Chromatograph Autosampler
- Gas Chromatographs and Detectors
- Gel Permeation Chromatograph
- Infrared Spectrophotometer
- Inhalation Chamber
- Liquid Chromatographs and Detectors
- Microscope
- Miscellaneous Glassware
- Muffle Furnace
- pH Meter
- Thin Layer Chromatograph Scanner
- Top Loader Balance
- UV Visible Spectrophotometer
- Vapor Generation System

Equipment Maintenance SOPs

- Aerosol Generation System
- Animal Cage
- Animal Rack
- Atomic Absorption Spectrophotometer
- Autotechnician Tissue Processor
- Automatic Titrator
- Analytical Balance
- Constant Temperature Bath
- Gas Chromatograph Autosampler
- Gas Chromatographs and Detectors
- Gel Permeation Chromatograph
- Infrared Spectrophotometer

- Inhalation Chamber
- Liquid Chromatographs and Detectors
- Microscope
- Miscellaneous Glassware
- Muffle Furnace
- pH Meter
- Thin Layer Chromatograph Scanner
- Top Loader Balance
- UV Visible Spectrophotometer
- Vapor Generation System

Equipment Calibration Standard Operating Procedures

- Aerosol Generation System
- Analytical Balance
- Atomic Absorption Spectrophotometer
- Automatic Titrator
- Gas Chromatograph
- Gas Chromatograph Automsampler
- Gel Permeation Chromatograph
- Infrared Spectrophotometer
- Inhalation Chamber
- Liquid Chromatograph
- pH Meter
- Top Loader Balance
- UV Visible Spectrophotometer
- Vapor Generation System

Consumables Acceptability SOPs

- Animal Quality Testing - Dogs
- Animal Quality Testing - Guinea Pigs
- Animal Quality Testing - Hamsters
- Animal Quality Testing - Non-Human Primates
- Animal Quality Testing - Mice
- Animal Quality Testing - Rabbits
- Animal Quality Testing - Rats
- Chemical Quality Testing
- Gas Quality Testing
- Reagents and Solvents Quality Testing

Automatic Data Processing Equipment SOPs

- Data Entry Operator Identification
- Data Storage and Retrieval
- Operator Training
- Inspection and Maintenance
- Audit
- Error Correction Authorization
- Data Checkpoint

- Error Notification and Correction
- Data Cross Verification
- Data Input Verification and Editing
- Data Collection and Transcription
- Data Format Input
- Data Format Output
- Instrument Diagnostic
- Statistical Analysis Test Verification

Record Storage SOPs

- Computer Tape and Disc Storage
- Data Storage and Retrieval
- Data and Specimen Retention Requirement
- Data Transfer to Repository
- Data Storage (Repository) Security
- Preserved Tissue Storage and Retrieval
- Tissue Block Storage and Retrieval
- Tissue Slide Storage and Retrieval

Traceability SOPs

- Control Article
- Data Trail Audit
- Test Article
- Test Aminal System

Test and Control Articles SOPs

- Control Article Handling
- Control Article Dose Preparation (Weighing and Mixing)
- Determination of Control Article Identity
- Determination of Control Article Strength, Purity and Composition
- Determination of Control Article Stability
- Determination of Control Article Dose Homogenity
- Determination of Test Article Identity
- Determination of Test Article Strength, Purity and Composition
- Determination of Test Article Stability
- Determination of Test Article Dose Homogeneity

Performance Audit SOPs

- Preparation of Performance Audit Sample
- Performance Audit Sample Identification and Routing
- Performance Audit Sample Traceability
- Reporting of Performance Audit Results of Quality Assurance
- Reporting of "Out of Control" Performance Audit Results to Management

Corrective Action SOPs

- Report to Management
- Corrective Action

Study Planning and Conduct SOPs

- Computer Data Entry Operator Identification
- Master Study List Maintenance
- Notebook Data Recording and Initializing
- Notebook Data Entry Change
- Protocol Preparation
- Protocol Change
- Pre-Study Personnel Training and Instruction
- Specimen Identification
- Study Director Designation
- Study Director Replacement
- Study Inspection
- Study Credit
- Test System Animal Identification

Personnel SOPs

- Background Summary Preparation
- Illness Notification to Supervisor and Exclusion from Study
- Personnel Training
- Personnel Clothing and Safety
- Personnel Health and Sanitation

Animal Care SOPs

- Animal Bedding and Cage Changing
- Animal Cage Identification
- Animal Identification: Mice, Rats, Guinea Pigs and Hamsters
- Animal Identification: Rabbits
- Animal Identification: Dogs
- Animal Identification: Non-Human Primates
- Animal Handling, Feeding and Watering: Rats and Mice
- Animal Handling, Feeding and Watering: Rabbits
- Animal Handling, Feeding and Watering: Dogs
- Animal Handling, Feeding and Watering: Non-Human Primates
- Animal Room Sanitation
- Animal Cage and Rack Cleaning and Sanitizing: Stainless Steel Cages
- Animal Cage and Rack Cleaning and Sanitizing: Plastic Cages
- Animal Cage and Rack Cleaning and Sanitizing: Stainless Steel Cage Racks
- Animal Feeder Cleaning
- Animal Drop Pans Cleaning and Sanitizing
- Blood Sampling in Rats, Mice and Rabbits
- Blood Sampling in Dogs
- Blood Sampling in Non-Human Primates
- Determination of Animal Health
- Euthanasia - Rodents and Rabbits
- Euthanasia - Dogs

APPENDIX 7

PROJECTED AVAILABILITY OF LAIR MODULES

No.	Module Title	Availabilty at LAIR, % 100	75	50	25
1	Acute Oral Exposure Area, Rodent		X		
2	Subchronic Oral Exposure Area, Rodent		X		
3	Chronic Oral Exposure Area, Rodent		X		
4	Subchronic Oral Exposure Area, Dog		X		
5	Acute Inhalation Exposure Area, Rodent				
6	Subchronic Inhalation Exposure Area, Rodent				
7	Chronic Inhalation Exposure Area, Rodent				
8	Acute Inhalation Exposure Area, Primate				
9	Subchronic Inhalation Exposure Area, Primate				
10	Chronic Inhalation Exposure Area, Primate				
11	Dermal Testing Area, Rabbit				
12	Ocular Testing Area, Rabbit				
13	Behavioral Studies Area				
14	Metabolism Studies Area				X
15	Pharmacokinetics/Pharmacodynamics Studies Area				X
16	Oncogenic Studies Area				X
17	Respiratory Physiology Studies Area				
18	Reproduction Studies Area				X
19	Teratology Studies Area				X
20	Food Preparation/Blending Area	X			
21	Non-radioactive Waste Handling/Disposal Area				
22	Refrigerated Food Storage Area	X			
23	Quality Assurance Laboratory		X		
24	Animal Quarantine Area	X			
25	Pathology Laboratory			X	
26	Clinical Chemistry Laboratory		X		
27	Animal Breeding Area			X	
28	Veterinary Medicine Area				
29	Analytical/Synthetic Chemistry Laboratory			X	
30	Automated Data Processing Area	X			
31.	Radiochemistry Laboratory		X		
32	Cage/Rack Washing and Storage Area	X			
33	Chemical Storage Area			X	
34	Showers, Lockers and Toilets Area			X	
35	Glassware Washing Area		X		
36	Library Area	X			
37	Technical Offices Area		X		
38	Shipping and Receiving Area	X			
39	Luncheon Room Area		X		
40	Record Archives Area	X			
41	Specimen Storage Area	X			
42	Linen Storage Area	X			

No.	Module Title	Availabilty at LAIR, % 100	75	50	25
43	Janitorial Storage Area	X			
44	Central Cylinder Gas Storage Area	X			
45	Equipment Maintenance Area		X		
46	Laundry Area				
47	Central Power Area	X			
48	Central Standby (Emergency) Power Area	X			
49	Central Water Supply Conditioning Area		X		
50	Central Wastewater Conditioning Area				
51	Central Air Handling Area			X	
52	Central Heating Area	X			
53	Central Compressed Air/Vacuum Area	X			
54	Central Communications Area	X			
55	Central Refrigeration Area	X			
56	Central Toilet Area	X			
57	Central Vacuum Cleaning Area				
58	Dermal Testing Area, Rodent				
59	Central Automated Facility Systems Control Area				
60	Administrative Office Area		X		
61	Neurotoxicology Studies Area, Chicken				
62	*In Vitro* Genetic Toxicology Studies Area				
63	*In Vivo* Genetic Toxicology Studies Area				

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