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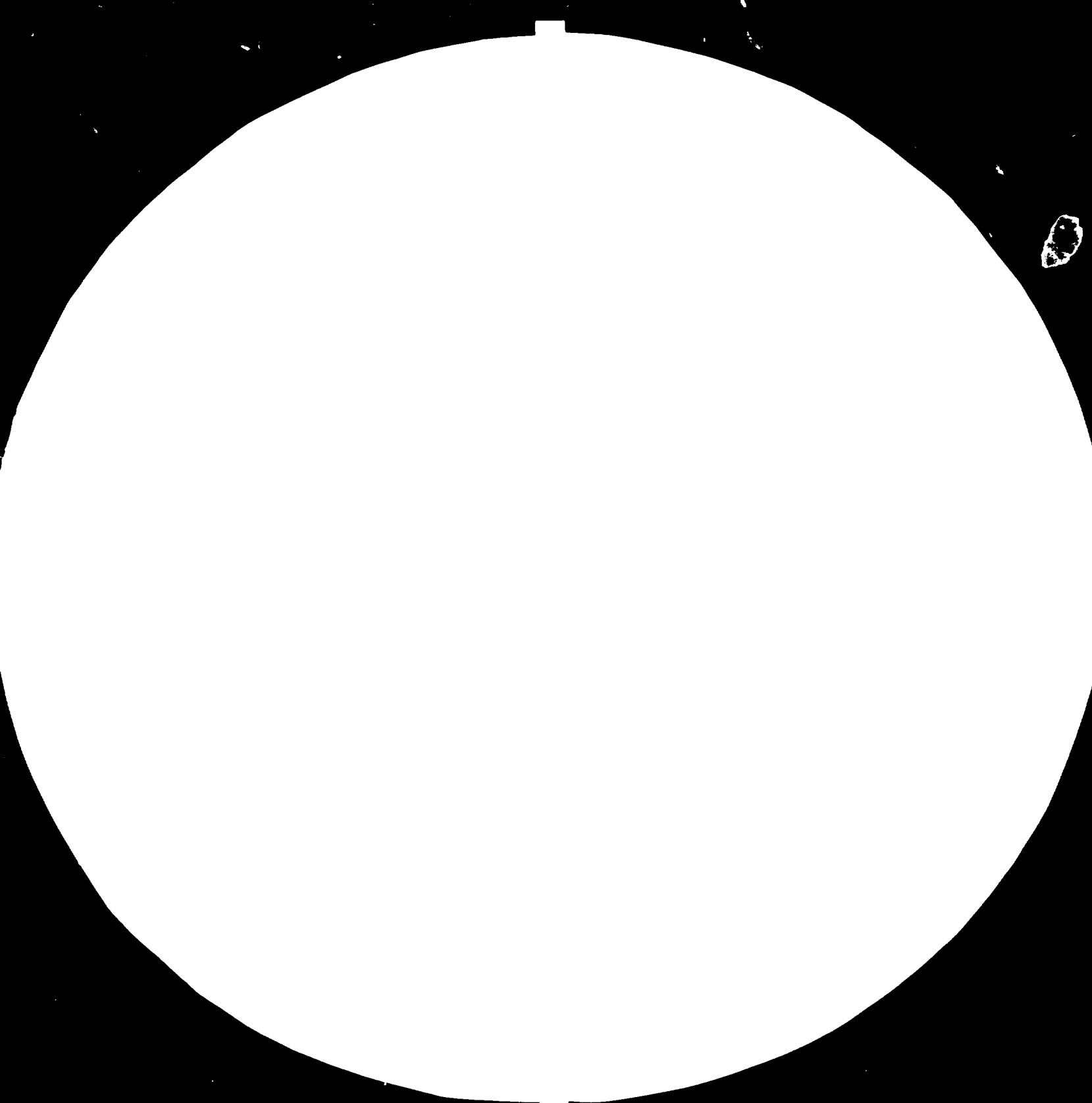

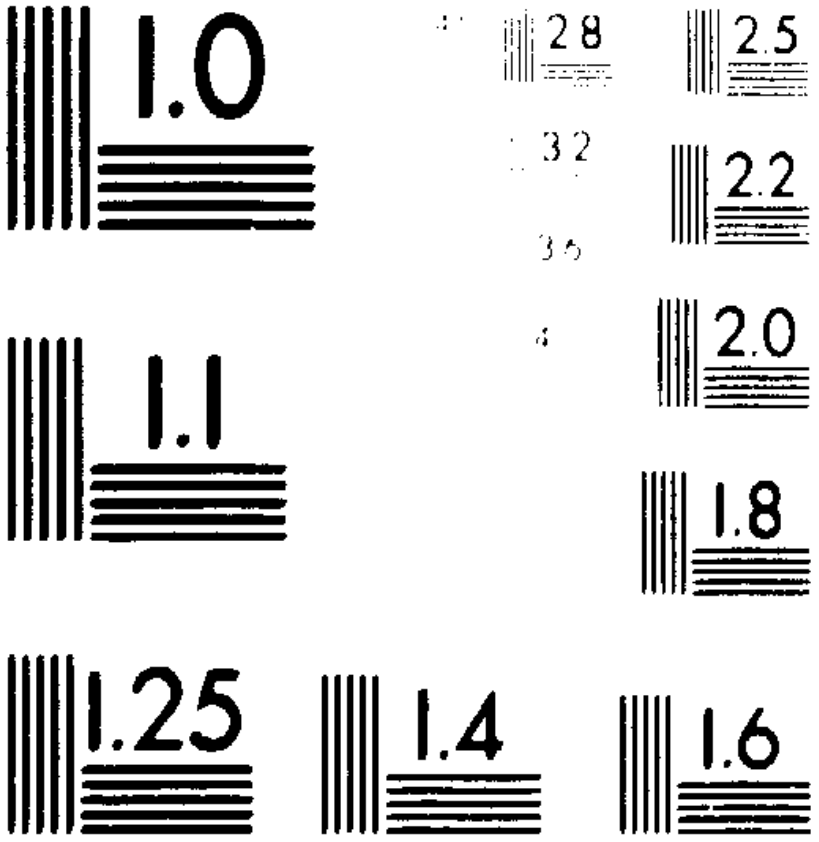

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31 January 1984
English

PREPARATORY ASSISTANCE FOR TOXICOLOGY RESEARCH LABORATORY

DP/ROK/82/028

REPUBLIC OF KOREA

Terminal report*

Prepared for the Government of the Republic of Korea
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Masao Nakazawa, Ph.D.
Expert in Toxicology

United Nations Industrial Development Organization
Vienna

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CONTENTS

PART I. - THE MISSION

1. OBJECTIVES AND ACTIVITIES

1.1 Mission objectives

The expert carried out the mission from 2 to 31 August 1983. The purpose of the mission is described in the Preparatory Assistance Document and may be summarized as follows:

a) Assessment of capability of toxicology research in Korea.

b) Assessment of the necessity for toxicology research in Korea.

c) Review the preliminary work plan for the establishment of a toxicology laboratory.

d) Propose a work plan for the toxicology program in terms of facility, man power and equipment, and asses the need for external technical assistance.

e) Define the basic elements for a UNDP project of assistance undertaken.

1.2 Activities

To assess the present status of toxicological research capacity of Korea and to further evaluate the necessity for such a capability, the expert has visited and talked to the key personnel of the following organizations:

a) Government regulatory agencies and research institutes,

b) Research institutes supported partially by Government,

c) Industry,

d) University and others.

For the fact finding part of the mission, the expert has covered the following areas:

a) The regulatory mechanism and testing requirement for registration of chemicals in Korea;

b) Present animal facilities and manpower if any;

c) Present and future R & D plans and anticipated problems;

d) Understanding of safety evaluation of chemicals and related products;

e) Intention and future plan for animal experiments including safety evaluation.

Following is the list of organizations and persons met during the fact finding and assessment part of the mission:

a) Governmental regulatory agencies :

. National Institute of Health :

Dr. K. H. Yong	Director of Safety Evaluation Division
Dr. H. W. Moon	Chief of Toxicology Laboratory

. National Environmental Protection Institute:

Dr. Y. S. Suh	Director of Water Quality Research Division

. Office of Rural Development, Agrochemical Research Institute:

Dr. Y. S. Park	Chief of Pesticide Chemistry
Mr. G. S. Kim	Chief of Safety Evaluation

b) Government supported Research Institutes :

. Korea Advanced Institute of Science and Technology:

Dr. J. K. Roh	Head of Toxicology Lab.
Dr. C. S. Kim	Director of Foreign Relations
Dr. M. H. Han	Head of Genetic Engineering Center
Dr. W. H. Park	General Director for Research
Dr. T. W. Kwon	Director for Biological Research Division

. Korea Research Institute of Chemical Technology:

Dr. Y. B. Chae	President

. Korea Research Institute of Ginseng and Tobacco:

Dr. I. Huh	President

c) Industrial Sector :

(1) Multi Chemical Industry:

. Luckey Central Research Laboratory, Luckey Group:
Dr. W. H. Kim Chief of Genetic Engineering Division

. Oriental Chemical Company:
Mr. H. W. Shin Manager of Project Division
Dr. H. S. Hann Director of Research Center

(2) Pharmaceutical Industry :

. Dong A Pharmaceuticals:
Dr. S. H. Minn Director of Research and Development

. Chongundang:
Mr. Y. H. Lee Vice President

. Yuhan:
Mr. K. H. Ann Animal Laboratory

(3) Agrochemical Industry :

. Hannong Company:
Mr. K. C. Shin Executive Director Research and Development

. Kyungnong Company:
Mr. M. B. Kim Director of Research and Development

d) University and Others

. Myung Jin Co. (Supplier of Laboratory Animal Equipment)
Mr. K. T. Kim President

. Seoul National University, College of Vet. Science:
Dr. C. Y. Lee Vet. Pharmacology and Toxicology

2. FINDINGS

2.1 Assessment of Present Capability

The present status of toxicology capability in Korea has been assessed and findings from each organization are as follows:

a) Government regulatory sector

Authorities must have knowledge and experience of the experiments when assessment of the safety of compounds from experimental data is made. KNIH (Korea National Ins. of Health), as a regulatory agency, is building a center for safety research for the purpose mentioned above. The KNIH facility may cover all systematic toxicology research but it may take another year to start their activity. KNIH may only carry out studies on national projects. Due to their regulatory function, they can not carry out independent R & D for the industry. NEPI (National Environmental, Protection Inst.) is more concerned about environmental research, and they have no plan to carry out animal toxicology research. Office of Rural Development, ACRI (Agrochemical Research Inst.) is in charge of toxicity and efficacy evaluation of agrochemicals for registration. ACRI has been testing only acute toxicity, and has a plan to build a new semi-barriered animal facility but only two animal rooms are being planned. This may not be enough to carry out systematic toxicology. NILS (National Inst. of Labor Science) has no animal facility nor any plans for it.

b) Government Supported Research Institutes

KAIST (Korea Advanced Institute & Science and Technology) has been active to establish a safety evaluation laboratory. Acute toxicity, mutagenicity and aquatic toxicology studies are made and they maintain germfree rats to prepare the production of specific pathogen free rats for toxicology research. However, this laboratory has not enough capability in either facility and manpower at present. KRIGT (Korea Research Inst. of Ginseng and Tobacco). An animal facility for pharmacology studies

is planned for only ginseng and tobacco but not for other chemical compounds. For carcinogenicity, an additional facility for long term animal experiments may be necessary. KRICT (Korea Research Inst. of Chemical Technology) does not have any animal facility but they plan to have a biology team to cover the bioactivity of new compounds.

c) Industry sector

Among the many companies, as a model case of research activity on animal experiments, top ranking companies in important sectors have been assessed.

Luckey Central Research Institute (general and fine chemicals)

Four conventional animal rooms for pharmacology, endocrinology and genetic engineering are being maintained. No systematic toxicology is planned, and they are looking for a contract toxicology laboratory.

Chong Gun Dang (Pharmaceutical), Dong A (Pharmaceutical)

No animal facility, and the companies have no plan for their own toxicology laboratory. They also expect a contract toxicology laboratory to be established in Korea.

Hannong, Kyungnong (Agrochemical)

Both have no plans for their own toxicology laboratory and are looking for a contract toxicology laboratory especially to evaluate their products for expert.

Dongyang Chemical (Chemical), Yuhan (Pharmaceutical)

Both of them recognize the necessity for their own laboratory of toxicology but have only plans for animal experiments for pharmacology and efficacy screening in house. They expect an independent toxicology laboratory to be established in Korea.

As a summary, at present there is not one toxicology laboratory in Korea able to carry out systematic toxicity evaluation in accordance with international standards and requirements in government, research institutes and industry in Korea. However, KNIH has started to build a safety research center for a regulatory purposes. KAIST has been preparing systematic toxicology research for 5 years independently.

2.2 Assessment of needs

Nowadays the safety evaluation of chemicals and pollutants on human as well as the environment have become an important subject in modern society. Advanced countries and international organizations have launched various programs for the safety evaluation of various chemical compounds. Besides the government, in house research centers of industry are also actively engaged in this research. For example most of Japanese pharmaceutical companies provide more than 70% of their R & D staff for the safety and efficacy evaluation of their products and approximately 60% of them are specially engaged in toxicology. In addition, there are more than 30 independent contract laboratories for toxicology in Japan alone. Budget wise, they provide 5 to 10% of their total turn over for research and development of the products, of which 50% are only for safety evaluation. Annual turn over of the Japanese pharmaceutical industry is approximately 15 billion dollars and that of the agrochemical industry is 1.5 billion dollars. Comparatively, annual turn over of the Korean pharmaceutical and agrochemical industry is approximately one tenth of that of Japan and there are about 300 pharmaceutical companies and 12 agrochemical formulator-technical compound producers. However, in Korea only 1 to 2 percent of the total turn over is invested in R & D. Also there is no effort to evaluate the safety by their own research staff. Therefore, there is, at present, no research laboratory which could carry out systematic toxicology experiments in Korea neither in government organizations nor in industry. There are two main reasons, first, the industry in Korea imports bulk and formulates and distributes its products only in Korea or exports to countries which have no regulation, and the government is assessing the safety and efficacy of imported compounds by the data provided by the foreign supplier. Up to now, the Government did not require toxicology data carried out by scientists in Korea. Second, there were not many new compounds synthesized in domestic institutes in the past, therefore, there was less requirement for evaluation of their toxicity in Korea.

However, since research into new compounds in some research institutes as well as in industry in Korea is rapidly increasing, the necessity to establish domestic toxicology research capability is now recognized. Advanced research centers such as KAIST or KRICT utilize foreign test laboratories to screen their compounds, but are not satisfied due to inconvenience of communication and discussion of test results. High cost and secrecy of new compounds etc. have also become a serious problem. Even only to evaluate the toxicity data from abroad needs some toxicology expert in Korea with experience and knowledge gained through his own toxicology experiments.

Many advanced countries and international organizations such as OECD have specified so called Good Laboratory Practice (GLP) for toxicological studies. To assure reliable and reproducible results of experiments, Good Laboratory Practice covers not only the quality of animal and experimental facilities but also the design and performance of experiments and the quality of technique during the experiment.

To Korean industry the demand for safety evaluation will increase more and more from domestic customers as well as from foreign countries for the registration and export of the chemicals. Because of lack of capability in management of toxicology research and required neutrality of the data, the industry may prefer to utilize an independent contract laboratory. Generally in-house research of industry is more oriented towards fundamental research. Also, newly synthesized compounds from research institutes are increasing year by year. For example KRICT (Korea Research Inst. of Chemical Technology) starts to synthesize new compounds and expects to reach several thousands of compounds per year in a few years. For example 10% of those new compounds may need to be tested for acute toxicity and 1% may go into systematic toxicity evaluation.

3. CONCLUSIONS

During the last decade, Korea has achieved rapid economic growth and remarkable progress in the field of science and technology and in the development of its industry, in particular of the electronic, machinery and chemical industry. In the fifth five-year economic and social development plan, the Government cites the chemical industry as one of the key areas to be developed for the second takeoff of the Korean economy, and a national program has been launched in support of the fine chemical industry.

The Korean fine chemical industry has already established a certain base and has accumulated some capacity to synthesize or produce pesticides, drugs, dyestuffs and other industrial chemicals. Already, some chemicals such as pesticides and pharmaceuticals are exported in limited quantities. Within the frame of the national project, it is expected that the development of new chemicals will be intensified. During the research and development stage on new chemical compounds for use as pesticides, pharmaceuticals, dyes, food additives and other industrial applications, evaluation of their toxicity, and bioactivity is essential, in order to concentrate on those with optimum properties and thus best commercial potential. However, although Korean technology and physical sciences have made rapid progress in the past, the development of the life sciences and notably toxicology has fallen considerably behind. At present, Korea lacks the capacity, manpower, facilities and experience to perform the screening of biological activity and safety of newly developed chemicals as well as existing compounds. Research institutes and industry has to send newly synthesized compounds to a toxicology laboratory abroad for screening. This is not only undesirable because of the cost and time involved, but also because it makes it difficult to keep new developments proprietary.

Therefore, to meet the demand of the society and also to support the fine chemical industry to proceed into international markets, Korea urgently needs an independent toxicology laboratory for systematic safety evaluation of chemical compounds, which meets international standards and also complies with CLP.

PART II. - PROPOSAL FOR THE ESTABLISHMENT OF A TOXICOLOGY RESEARCH CENTER

1. SUMMARY

In order to carry out systematic toxicological research and to build the necessary capacity to meet international requirements, a proper facility with a minimum of trained staff and equipment is essential.

The presently existing toxicology department at KAIST can form the core for the proposed toxicology research facility. It has a staff of 12 (1 manager, 7 researchers and 4 technicians), and has been engaged in acute toxicity, mutagenicity and aquatic toxicology studies, and laboratory animal science. The work plan for the recommended toxicology laboratory assumes the assignment of a minimum staff of 11 (including technicians) at the beginning of operations. The proposed staff development (training) plan is based on the presently existing capability of KAIST staff. Additional 12 staff members (plus 3 technicians) will have to be recruited during the course of the project in order to make the laboratory fully operational.

The following steps are propcsed:

a) Construction of animal experimental facility:
The facility with barrier system will perform various types of toxicology research with rodents. The size would be approximately 500 m^2.

b) Establishment of laboratory facility for the systematic analytical laboratory work for animal experiments: The laboratory will accomodate and perform clinical chemistry, pathology, hematology, mutagenicity, data processing, office space etc. Approximately 400 m^2 of area is necessary.

c) Training of manpower for the systematic toxicology research:
About 70 man/months of training over 3 years are recommended in the area of general toxicology, reproductive toxicology, pathology, histology, clinical chemistry mutagenicity etc.

d) Utilization of foreign experts: 16 man/months of consultancies are felt to be necessary to build up capacity in the area of the above mentioned disciplines.

e) Acquisition of equipment to perform systematic toxicological research.

f) To fully operate the above research center, the optimum number of scientists necessary would be about 26.

g) It may take at least one and half years to set up the above mentioned items. Thus, routine toxicology research may start approximately after 2 years from the beginning.

h) After accomplishment of the above mentioned first stage, as a next step toxicity evaluation by rabbit, dog and monkey may become necessary a few years after starting the rodent experiments.

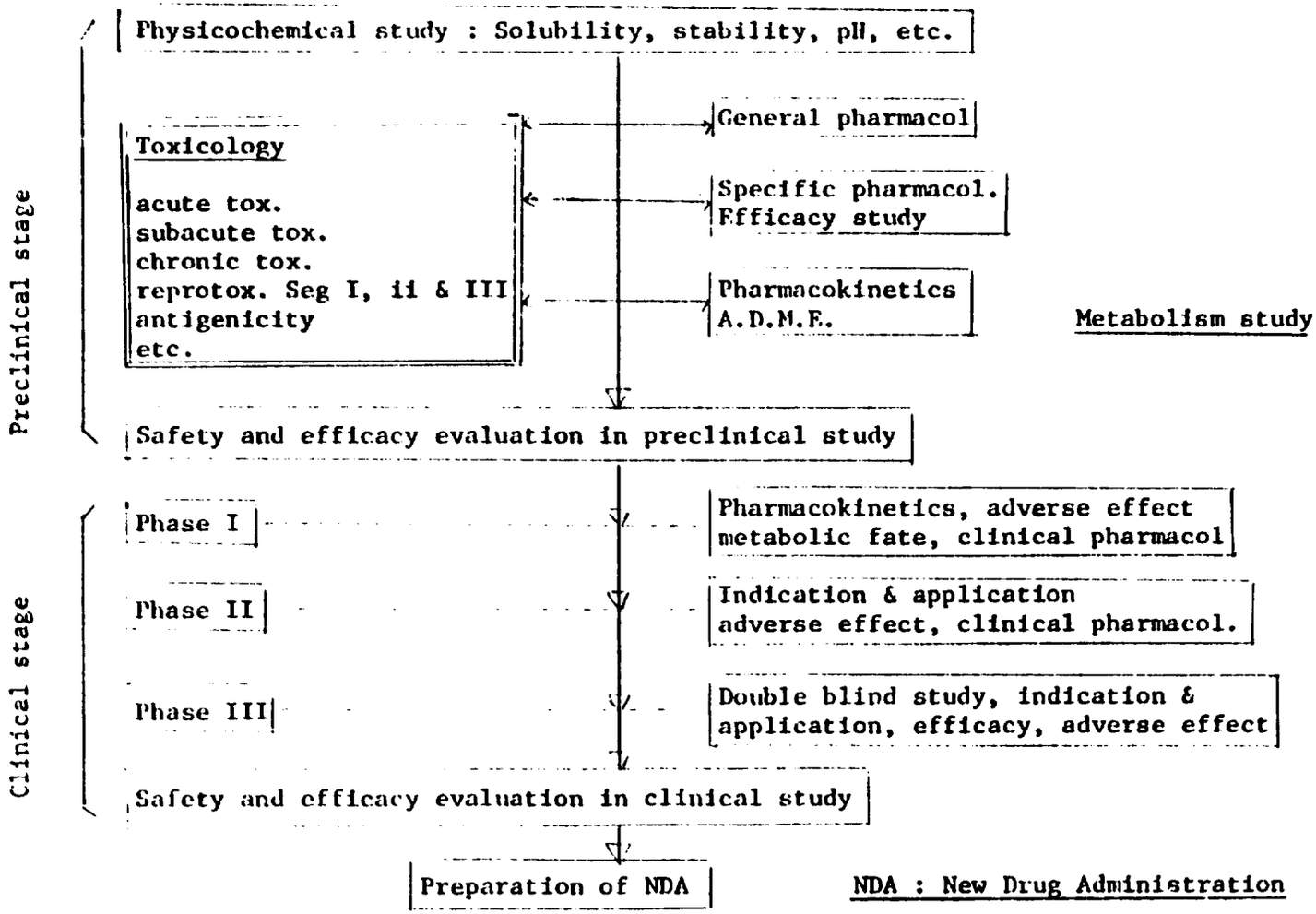
i) Beside the toxicology and efficacy studies, metabolism studies are also important in parallel for assessment of the total bioactivity of chemicals. However, establishment of a laboratory for metabolism (Absorption Distribution Metabolism and Excretion) should be discussed separately in the near future.

j) After the proposed rodent facility, laboratory, and manpower has been secured, the laboratory will have the capacity to manage annually the following experiments:

- 3-4 acute toxicity studies with 3 routes (both rat and mouse study)
- 4 subacute studies
- 1 chronic toxicity study
- 2 reproductive toxicity studies
- Screening of mutagens: 100 compounds year.

The position of the toxicology laboratory within the complete safety and efficacy evaluation cycle (from experimental compound to registration as a new product) is shown in the following table.

RECIPROCAL INFORMATION FLOW IN SAFETY AND EFFICACY EVALUATION STUDIES



2. DETAILED WORK PLAN

2.1 General description

A detailed work plan has been prepared for the establishment of the laboratory which is considered of optimum and suitable size for Korea. The plan will cover the minimum necessary experiments for next few years in Korea.

The work plan includes a time table (Appendix I, II, and III) for

a) New building construction.
b) Laboratory establishment.
c) Utilization of consultants in each field of manpower development and expertise to be generated.
d) Training program according to the scheduled experiments to be carried out within the facility.
e) Equipment acquisition in accordance with the experimental capability.
f) Toxicological experiments in the major fields which could be performed in reasonable capacity.

The size of animal facility and laboratory is estimated both from

a) Approximate estimate of one third of necessary capacity for toxicology research in the next 3 years in Korea.
b) Staff to carry out this program: 26 scientists will be needed to maintain the proposed research center. Half of them are already available within KAIST and 13 more are expected to be recruited. Recruitment and training of the researchers may take one and a half years and just meet with the completion of the new facilities.

2.2 Manpower development and training

The subjects, and duration of the manpower development necessary to meet the minimum requirements are as follows (ref. Appendix II):

a) General Toxicity : 24 man/months (1 x 12 and 2 x 6 months) to get experience and knowledge on the job in clinical hematology and related techniques as well as in some data processing.

b) Reproductive Toxicity : 24 man/months (1 x 12 and 2 x 6 months) to cover teratology related techniques. Also the fellows will obtain the necessary data processing experience.

c) Mutagenicity : 3 man/months to cover mutagenicity from bacterial to cell culture level

d) Histopathology : 6 man/months to get experience on the job in this field.

e) Aquatic Toxicity : 6 man/months to cover the various typer of aquatic toxicity.

f) Hematology : 3 man/months to cover various techniques in hematology.

g) Animal Science : 6 man/months to cover the breeding, production, and management of laboratory animals.

2.3 Expert Program

The following are the requirements for the consultants and the duration of their missions considered necessary to reach optimum results (ref. Appendix III):

A) Toxicology consultant - 4 missions of 1 month each

Duties:

a) First mission: Assist in the planning and design of the facility. Work together with the architect on building plans. Review the equipment list and assist in manpower planning and definition of training requirements.

b) Second mission: Assist in the first stage of operation of the laboratory; adivse in procedures to be set up for toxicology research; review the work program and re-assess the subjects of training programs.

c) Third and fourth mission: General consultation for the management of the laboratory. Assist in finalization of procedures and performance requirements, advise in practical aspects of operations and in conducting toxicology research.

Qualifications: A senior level expert with a minimum of 10 years experience in general toxicology. Experience in planning and management of toxicology programs is required.

B) Architect - 1 month

Duties:

Survey local conditions for building construction and lay down basic requirements and plans for the animal facility and laboratories in accordance with CLP requirements. Work together with the toxicology consultant and local architects in finalization of building plans.

Qualifications: A senior level architect with a minimum of 10 years experience and knowledge of the construction requirements for a toxicology laboratory to CLP standards.

C) Consultant in aquatic toxicology - 1 month

Duties:

Assist in defining work programs in aquatic toxicology. Help establish a screening system together with staff already trained in this field and provide advice on optimum research procedures and latest methods used in this field.

Qualifications: A senior level expert with a minimum of 7 years experience in aquatic toxicology and related areas at a University and/or Industry.

D) Consultant in laboratory animal science - 2 missions of 1 month each

Duties:

a) First mission: Advice to and training of local staff in laboratory animal science related to general toxicology and reproductive toxicology. Introduce optimum procedures and work methods.
b) Second mission: Evaluate results from previous recommendations and provide further advice.

Qualifications: A senior level expert with a minimum of 10 years experience in animal breeding, production, and management of laboratory animals.

E) Consultant in mutagenicity - 1 month

Duties:

Advise local staff on the present status of research in this field. Work together with trained staff members in establishing a screening system and recommend standard work procedures to be introduced at the laboratory.

Qualifications: A senior level expert with a minimum of 7 years experience in a University and/or Industry in mutagenicity and related areas.

F) Consultant in animal pathology - 2 missions of 1 month each

Duties:

Support domestic pathologists and assess the validity of diagnoses made for individual animal experiments. Assist in efforts to establish a national teamwork in animal pathology for mutual consultation.

Qualifications: A senior level expert with a minimum of 10 years experience the University in academic and/or industrial environment. Experience with pathology of laboratory animals is required.

G) Consultant in reproductive toxicology - 2 missions of 1 month each

Duties:

a) First mission : Establish a system for reproductive toxicology experiments in the new facility. Evaluate the existing knowledge in this field and provide information on the latest advances in reproductive toxicology research.

b) Second mission : Evaluate progress achieved since the consultant's first mission. Give further advice on independent experiments and suggest further work and additional training requirements.

Qualifications: A senior level expert with a minimum of 7 years experience in a University and/or industry. The experience should include teratogenicity and other related areas.

H) Consultant in data processing - 2 missions of 1 month each

Duties:

a) First mission: Assist in establishing procedures for the laboratory's own data processing program according to the intended protocol for the experiments. Advise on the most suitable methods of statistical evaluation and correlation of toxicology test results.

b) Second mission: Evaluate the data processing system implemented as a result of the consultant's previous recommendations as to its effectiveness for obtaining the required results. Provide further advice on refinements of the system to achieve sufficient flexibility for easy adaptation to different series of experiments in the future.

Qualifications: Expert with good background in statistical data processing with specific experience in data processing of toxicology.

2.4 Equipment

The following equipment is considered to be necessary for the operation of the laboratory:

a) Formulation

Clean bench for balance	2
Clean bench for formulation	2
Cold stock room + 4°C (2 m^2)	
Refrigerator	1
Freezer	1
Chemical balance (Digital)	3
Blender mixer	1
Shelf for glass wares	
Shelf for reagent	
Power mill (Bench type)	1
Homogenizer	
Magnetic stirrer	

b) Clinical chemistry room

Autoanalyzer	1
Chloride counter	1
pH meter	
Gas chromatograph	
Spectrophotometer	
Chromatogram scanner	
Electrophoresis equipment	
Aspirator	
Waterbath	
Homogenizer	
Cold centrifuge	
Super cold freezer (-85°C)	
Blood platelet counter	
Liquid chromatograph	
Automicro counter	
Coagulation time counter	
Experimenter bench	1
Shelf	1
Sink	2
Ice box	2
Fume hood	1
Automatic blood cell stainer	

c) Mutagenicity

Clean bench	1
Incubator	1
Colony counter	1
Shelves	1
Ice box	1

d) Pathology and histology

Automatic fixation and embedding	
Paraffin expender	
Ice box with freezer	
Slide desk with draft x3	
Slide table	
Shelf for chemicals	
Shelf for paper	
Sink	
Bedding center	
Waterbath	1
Paraffin melter	
Experimental bench	4 + 1
Drier (glass ware)	1
Workdesk	
Paraffin bath	1
Water bath	1
Slide microtome	2
Microscope	4
Desk	2
Shelf for glass	
Digital hemograph	
Electro microscope	1
High pressure tank	1
Oil rotary pump	1
Vacuum evaporator	
Ultramicrotome	
Sink	
Working desk	
Shelf	
Drier	
Ice box	
Shock absorber	

e) Dark room

Developer
Sink
Shelf

f) Washing room

Standard autoclave
Auto water distiller
Shelf
Sink

g) Computer

Personal computer, CPU, Console typewriter, Printer
Graphic display and platter

h) Data locker

i) Stockroom for specimen

j) Special toxicology

Soft X-Ray	
Multiwater T maze	1
Shuttle Box	3
Rotor load	
Body weight balance	1 balance / 2 room
Cage	400/room 150% extra for rotation
Cage rack	

k) Animal facility

Automatic watering system
Autoclave
Cage washer
Pass box
Air shower
Ultraviolet sterilizer for water
Air conditioning system
Incinerator

l) Energy center

Standby generator

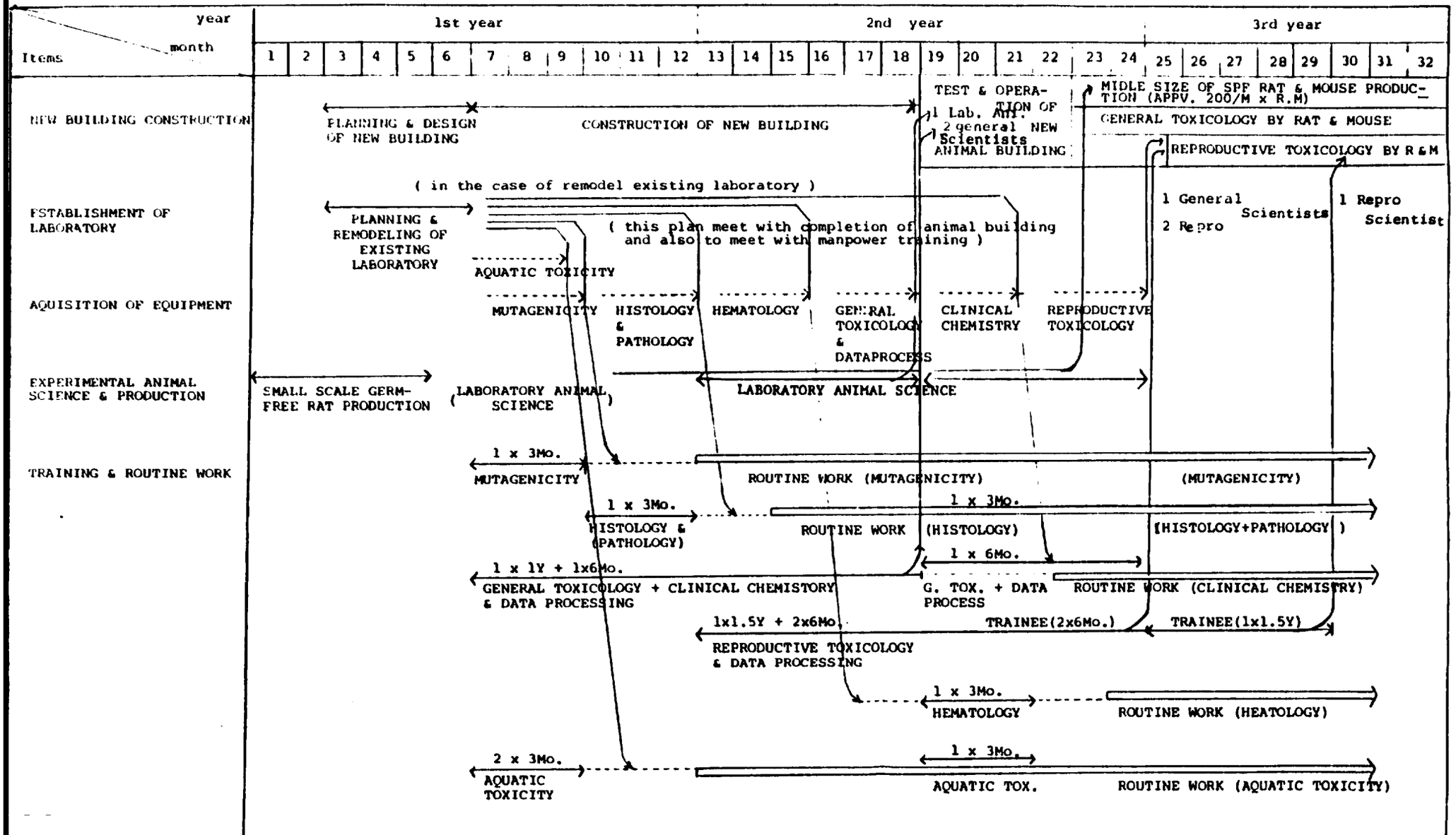
2.5 Institutional framework

The development plan for the toxicology laboratory presented in this report assumes that the laboratory will be self sufficient in personnel, facility and equipment. However, establishment of the facility within the framework of an existing institute will have the advantage of common administrative support and easier access to additional manpower when needed. General chemistry capability within the host institute, although not a requirement, will be of advantage.

An institute of this type is best supported by a strong clientle able to provide continuous projects to the laboratory. This is an important factor when considering the physical location of the toxicology laboratory and the institutional framework within which it should be established. Proximity of the chemical industry or other institutes in need of toxicology services will be an advantage. However, as a goal, the laboratory should be a separate entity and not be dependent financially on a particular client in order to preserve its impartiality.

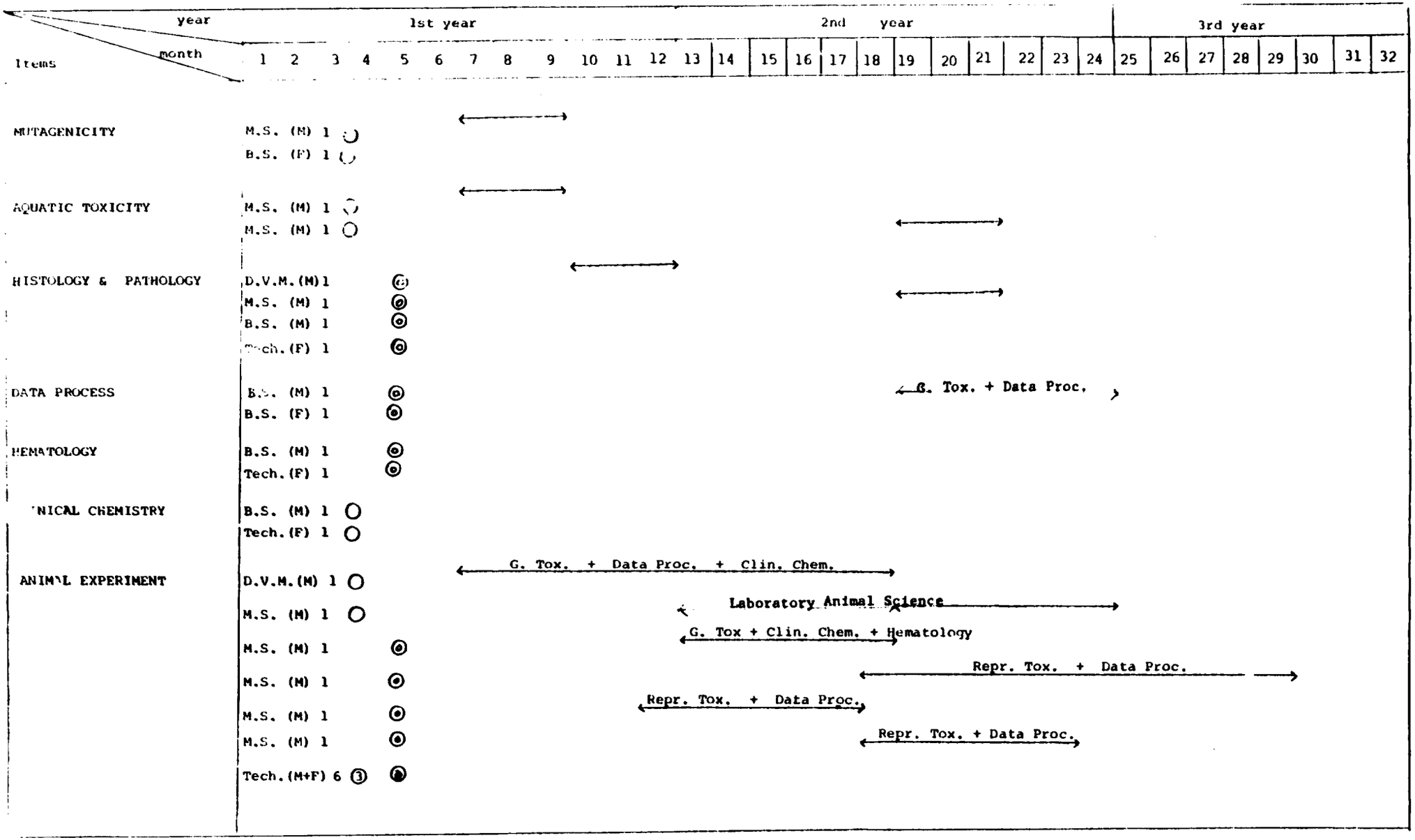
The institutional framework within which the toxicology laboratory will be established should be well defined before the start of the project.

APPENDIX I. TOTAL WORK PLAN



(M) MALE STAFF
(F) FEMALE STAFF
○ EXISITING MANPOWER IN KAIST
◎ RECRUIT MANPOWER
←---→ TRAINING

APPENDIX II. MANPOWER & TRAINING PLAN



APPENDIX III. EXPERT PLAN

Items \ year / month	1st year												2nd year												3rd year							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
TOXICOLOGY (More then 10 y expert)						1 M/M										1 M/M											1 M/M					1 M/M
ARCHTECT (Specialist for Tox. Lab.)						1 M/M	GENERAL CONSTRUCTION																									
LABORATORY ANIMAL SCIENCE (More then 10 y)									1 M/M													1 M/M										1 M/M
MUTAGENICITY (More then 5 y)														1 M/M																		
PATHOLOGY (More then 10y)																							1 M/M									1 M/M
REPRODUCTIVE TOXICOLOGY (More then 7 y)																										1 M/M						1 M/M
DATA PROCESS (At least 3 y)																							1 M/M									1 M/M
AQUATIC TOXICOLOGY (More then 7 y)											1 M/M