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TOXICOLOGY RESEARCH LABORATORY

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REPUBLIC OF KOREA

Technical report: Toxicologic pathology*

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

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I. EXPLANATORY NOTES

Abbreviations

KRICT - KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY
TRC - TOXICOLOGY RESEARCH CENTER
GLP - GOOD LABORATORY PRACTICE
SOP - STANDARD OPERATING PRACTICE

II. ABSTRACT

As an expert in toxicologic pathology, I provided technical assistance to KRICT from November 6 to December 8, 1986. Technical staffs received instruction on setting up GLPs and SOPs for animal necropsy, tissue processing, and microscopic observations by pertinent GLPs and SOPs. In addition, other technical assistance was extended to personnel in animal necropsy, microscopic tissue preparation, and histopathology of laboratory animals by means of slide illustration, lecture, and direct supervision in each of these processes.

An ongoing training program is necessary for the technical staffs at the TRC in order to develop professional competency, especially in pathology, toxicology, and teratology. Since technical staffs lack practical experience in conducting a variety of long-term toxicity studies, it will be difficult to conduct such studies with the present technical man power. Technical staffs should be trained immediately at toxicology laboratories in the U.S.A. or other industrialized nations in order to obtain practical experience necessary to conduct and interpret animal toxicity tests.

III. INTRODUCTION

This report describes an UNIDO mission to the Toxicologic Research Center at the KRICT for a one month period from November 6 to December 8, 1986. The primary purpose of this mission was to provide technical assistance to the Toxicology Research Center relative to conducting various types of toxicity studies, especially in the area of toxicologic pathology. The Institute is the main toxicity testing laboratory in Korea. It has expanded rapidly in the last few years with the development program of UNIDO to conduct safety assessment of new chemical products which have synthesized in KRICT, pharmaceutical or chemical industries.

Since toxicity data must be generated for users of new chemical products, the Institute will play a vital role in providing such information on new chemical products. However, unless the Institute satisfies international quality criteria for laboratory facilities, equipment, and well-trained staffs, toxicity testing generated at the Toxicology Research Center would not be acceptable to regulatory agencies in the world as legitimate data. Considering this view, the Institute deserves to receive further assistance from the development program of UNIDO in order to comply with the international quality criteria for toxicity testing. The establishment of a reputable toxicology laboratory in Korea would be beneficial relative to industrialization, public safety, and a healthy environment.

IV. RECOMMENDATIONS

1. The toxicity Research Center should rapidly expand the laboratory facilities, purchase equipment, and train technical staff in order to build the international reputation as a legitimate toxicity testing center.

2. Technical staffs, especially veterinary pathologists, should be trained and provided with opportunities to obtain practical experience in making diagnosis for spontaneous diseases and toxicity-related pathological lesions at contract toxicology laboratories in the U.S.A. or the other industrialized nations.

3. To facilitate the technical training of the staff in the Toxicology Research Center, it is desirable to contract long-term toxicity tests with commercial contract laboratories in the U.S.A., contingent upon practical training of the staff in the Toxicity Research Center.

4. There is no reliable commercial supplier of experimental animals in Korea. When production of specific pathogen free (SPF) rats is fully operational at the Toxicology Research Center, it may be feasible to consider sales to medical schools, pharmaceutical companies, and other research institutes as another means of financial support in-house research. Therefore, budgetary allocations for laboratory animal production should be maintained on a regular basis.

V. OBJECTIVES

The UNIDO mission to the Toxicity Research Center in the KRICT was to provide technical assistance to animal pathology in conducting toxicity tests. After an evaluation of laboratory equipment, facilities, and man power, the mission was extended to providing advice on other needed pieces of equipment, the arrangement of laboratory facilities, and recomendation on man power distribution in order to increase productivity.

Based on an analysis of documents and procedures used in animal necropsy, tissue processing, and preparation of microscopic slides, the objectives of the mission were established as follows:

1. Technical assistance to personnel involved in necropsy, tissue processing, preparation of microscopic slides.

2. Preparation of GLPs and SOPs in the three proceding areas.

3. Training of veterinary pathologists on the histopathology of laboratory animal diseases.

4. Assitance to veterinary pathologists in the interpretation of results from animal tests.

VI. ACTIONS

A. Technical Training

1. Necropsy Procedure

A booklet that consists of illustrative color photographs for each necropsy procedure with detail on anatomy and written explanations, was prepared to train the veterinary pathologists and prosectors.

2. Tissue Processing

A booklet was prepared to illustrate the procedures involved in tissue trimming. Time setting of the autotechnicon for tissue processing was readjusted according to animal species because of the unsatisfactory quality of microscopic slides. Tchnicians have utilized new tissue trimming techniques and processed the trimmed tissues through readjusted autotechnicon. Consequently, the quality of the microscopic slides produced is satisfactory.

3. Microscopic Tissue Sections

The technique of paraffin tissue sectioning by the microtome was demonstrated, and technicans were trained to use the new techniques. The quality of paraffin tissue sections has been markedly improved. Also,

proper tissue arrangement within the paraffin section itself was demonstrated in order to increase both productivity and accountability of the tissue sections.

4. Tissue Staining

A demonstration of basic tissue staining and special staining techniques was conducted. The quality of tissue staining has shown significant improvement after training.

B. Lecture

1. Common Spontaneous Diseases of Rats and Mice

This lecture covered common spontaneous diseases of rats and mice with special emphasis on the clinical signs, causes of disease, and related pathology. Gross and microscopic findings were demonstrated by using color projection slides.

2. Pathology of Aging Rats and Mice

This lecture was concentrated on common age-related diseases of both rats and mice. Detailed gross and microscopic observations were explained by using color projection slides. The incidence of age-related disease in different strains of rats and mice was given according to various ages. Differential diagnosis of age-related disease by

histopathological observation and its implication in the animal experiment were explained. Common neoplastic lesions were demonstrated by gross and microscopic observation with color projection slides. Incidence tables of non-neoplastic and neooplastic lesions in old age rats and mice were provided as basic references of comparison. In addition, literature references were provided to help explain the pathological and/or toxicological significance of the lesions observed.

3. Significance and interpretation of Carcinogenicity in Animal Toxicity Tests

Regulatory decisions concerning the carcinogenic potential of chemicals are often based on the results of chronic toxicity test conducted in both rats and mice. The study results have shown that carcinogenicity is not simply an all or none phenomenon.
Five interpretative conclusions used in toxicology and carcinogenicity studies were explained. The five categories were (1) clear evidence of carcinogenicity, (2) some evidence of carcinogenicity, (3) equivocal evidence of carcinogenicity, (4) no evidence of carcinogenicity, and (5) inadequate study for carcinogenicity. In determining the carcinogenic potential of chemicals, several other factors must be considered. These factors include the dose-response relationship, the variability of the end point, the effects on tumor latency, and the types of tumor produced. Also, the significance of evaluating malignant and benign tumors both separately and combined was explained.

C. Documentation

1. GLPs and SOPs for Animal Necropsy, Tissue Preparation, Tissue Sections, Paraffin Blocks, and Microscopic Slides.

The significance of GLPs and SOPs was emphasized in terms of compliance with international standards of toxicity testing. If any toxicity testing laboratory fails to meet the necessary requirements for international standards of toxicity testing, toxicity data submitted from that laboratory may not be acceptable to regulatory agency.

To assist in the preparation of GLPs and SOPs (animal necropsy, tissue preparation, microscopic sections, paraffin blocks, and microscopic slides), a copy of GLPs and SOPs for these processes that are used currently in Haskell Laobratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc., was provided. Preparation of the GLPs and SOPs for these processes is currently underway at the Toxicology Research Center.

2. Format of the Pathology Report and Lesion Tables

In an attempt to comply with GLPs, formats for pathology reports and lesion tables which have been used in commercial toxicity testing laboratories in the U.S.A. were provided. In addition, veterinary pathologists received training in the preparation of pathology report and lesion tables for various types of toxicity tests.

VII. CONSEQUENCES

All the actions defined have taken to improve the workmanship of tissue preparation, microscopic slides, and pathology report in toxicity tests. Dr. Roh, the director of the Toxicology Research Center was keenly aware of the importance of pathology in the animal experiments. He has supported enthusiastically to incorporate the actions into existing system.

Staffs and technicians who were involved in the training were enthusiastic about new ideas and methods for preparation microsocopic slides. They supported the concept and methodology of GLP and SOPS in the area of pathology. The technical assistance provided by the UNIDO mission will improve the quality of microscopic slides. Also, lecture on the pathology of laboratory rodents will bring considerable benefit to veterinary pathologists for understanding of spontaneous diseasesof aging laboratory rodents and interpretation of animal experiments exposed to new chemical products.

GLP and SOPS of pathology section in Toxicology Research Center are cosidered to be compatible those of international standards, provided new version of GLP and SOPS are compiled following incorporation of new GLP and SOPS into existing ones.

VIII. CONCLUSIONS

The Toxicity Research Center has progressed remarkably within a short period of time under the leadership of director, Dr. Roh. The staffs and technicians have acquired the basic skills to run short-term toxicity tests as a result of the UNIDO development program. The program has contributed significantly in terms of improved techniques and increased scientific knowledge for proper interpretation of toxicity screening experiments. Since philosophies and methodologies of toxicology are advancing rapidly, continuous education and training of staffs are critical to maintain high quality standards of toxicity testing.

Because staffs have not had practical experience in conducting various types of long-term toxicity tests, current program should be structured to provide opportunity for practical experience and training at commercial toxicity laboratories in industrialized nations. It is necessary to continue the UNIDO development program at the Toxicity Research Center in order to comply with GLPs and to achieve international recognition as an acceptable toxicity testing laboratory. Since it is impossible to develop any new chemical products without validated toxicity information, the establishment of a reputable toxicology testing laboratory will play an important role relative to further industrialization in Korea.