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REPUBLIC OF KOREA

Technical report: Animal 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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Abbreviations

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

ABSTRACT

Technical assistance was provided in the area of toxicological pathology to KRICT from October 2 to October 30, 1987, as an UNIDO assignment. Technical assistance included the implementation of GLP and SOP in the area of pathology in KRICT. Lectures on the pathology of spontaneous diseases, especially in aging rats were given to the pathologists and toxicologists. As a training exercise for microscopic diagnosis, microscopic slides of both neoplastic and non-neoplastic lesions that occur spontaneously in aging rats were reviewed with pathologists. Also, as part of practical training, pathology reports and microscopic slides from subchronic studies actually conducted in KRICT were reviewed. Some diagnostic mistakes of lesions were corrected. In addition, technical assistance was given to laboratory technicians involved in animal necropsy, tissue trimming, preparation of microscopic slides, and the staining of tissue sections.

Continuous professional training for technical personnel, especially pathologists at KRICT, is vital in order to satisfy GLP and to establish KRICT as an internationally acceptable toxicity testing

center. It is extremely difficult to conduct a variety of subchronic or long-term toxicity tests in KRICT, since technical staffs do not have practical experience in the conduct or the analysis of such experimental data. Therefore, peer review of pathology data, especially microscopic slides by an experienced pathologist is essential to obtain valid conclusions from toxicity tests conducted in KRICT. Training of a clinical pathologist is also essential for the proper interpretation of clinical pathology data. Pathologists should be trained immediately at one of many toxicology laboratories in the U.S.A. to acquire practical experience in animal pathology and the skill to interpret pathology data from various types of toxicity tests.

INTRODUCTION

This report covers an UNIDO mission to the Toxicology Research Center at the KRICT for a one month period from October 2 to October 30, 1987. The primary purpose of this mission was to provide technical assistance relative to the area of pathology in conducting toxicity tests in KRICT. In addition, the mission included an evaluation as to whether GLPs and SOPs in the area of pathology were implemented as advised in last year's mission.

Recently, Korea has industrialized rapidly and achieved remarkable progress in the steel, electronic, and chemical industries. Along with that progress, there have been concerns about occupational health and environmental contamination in the industrialized regions. Many private chemical and pharmaceutical industries are synthesizing numerous chemicals in an attempt to produce new marketable chemical commodities. Therefore, it is essential to evaluate the toxicity of chemicals in order to avoid potential health hazards relative to factory workers the consumers, and the environment.

Since toxicity data should be provided to users of new chemical products in the international market, it is impossible to develop any marketable new chemicals without toxicity data. The KRICT will play a vital role in providing such toxicity information on new chemical

products in market place. However, unless the KRICT satisfying international quality criteria for laboratory facilities, equipment, and well-trained technical personnel, toxicity data generated at the KRICT would not be acceptable to regulatory agencies in the world. As a result, the KRICT must receive further assistance from the development programme of UNIDO in order to develop acceptable international quality criteria for toxicity testing. The establishment of a reputable toxicity testing laboratory in Korea is essential to continue industrialization, protection of public health, and to a clean environment.

II. ACTIONS

A. Technical Training

1. Animal Necropsy Procedures

Last year, in order to train prosecutors for animal necropsy and for the trimming of tissues, I prepared a booklet that provides written explanations for each necropsy step with illustrative color photographs for detail anatomy and for the various dissecting techniques. Standard necropsy and tissue trimming techniques, which are used currently in Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Inc., were also demonstrated to prosecutors.

After reviewing the animal necropsy area this year, I found following item; (1) prosectors have not followed proper necropsy techniques and harvested irregular vital organs or tissues prior to preparation of microscopic slides. (2) When vital organs are removed from the animal and weighed the organ weights, they apparently dry out before placing them in the fixative solution. The reason is that these organs were not preserved in physiological saline solution during weighing organs. (3) Also, eyes, testes, and epididymides were fixed in formalin fixative instead of the recommended Bouin's solution. Therefore, tissues were shrunken due to dehydration and microscopic slides of these tissue sections were very poor in quality.

2. Tissue Trimming

Although I provided an illustrative booklet and a demonstration of the trimming technique last year, prosectors have not followed uniform tissue trimming according to the instructions. Consequently, it is difficult to assess treatment-related pathological lesions because of irregularly trimmed tissues.

I also provided a demonstration of the proper tissue arrangement of trimmed tissue within tissue cassettes. This procedure will increase both productivity and accountability of the tissue sections.

3. Tissue Processing

The quality of tissue sections was unsatisfactory since the tissues were processed improperly by the autotechnicon. Time setting of the autotechnicon for tissue processing was readjusted according to the particular animal species. Laboratory technicians have not operated the autotechnicon efficiently because they did not have practical experience in operation or maintenance of such an instrument.

4. Microscopic Tissue Sectioning

Both productivity and quality of tissue sections were unsatisfactory since technicians are sectioning the paraffin blocks with a microtome before the blocks are properly cooled in a water bath. A Frigi-Tray (cold water bath) is a necessary piece of equipment that will be needed in this processing area.

5. Tissue Staining

The technicians are not efficiently utilizing the automatic staining machine because of improper installation of the water line to the machine.

B. Lectures

1. General toxicology

This lecture series consist of three parts; (1) general principles, (2) testing procedures, (3) target organs and related pathological changes. The first part covers absorption, distribution, and excretion of toxicants. It also deals with various approaches to toxicologic evaluation, including risk assessment, and the type and amount of data required to carry out such evaluations. The second part of the lecture covers the types of tests needed to evaluate carcinogenesis, mutagenesis, and teratogenesis. Third part deals with toxic effects on specific target organs and related potential pathological lesions.

2. Pathology of Common Spontaneous Diseases of Aging Rats

This lecture covers most common age-related diseases of rats. The incidence of age-related diseases in different strains of rats was discussed. Differential diagnosis of age-related disease by histological observation and the relationship of such diseases to the animal experiments were explained.

C. Practice

1. Review of Microscopic Slides from Spontaneous Diseases of Aging Rats

Approximately 350 microscopic slides showing age-related neoplastic and non-neoplastic lesions were selected from 2-year-old, Charles River CD albino rats (Charles River Breeding Laboratories, Inc., North Wilmington, MA). Microscopic slides were reviewed with pathologists as part of their training in proper microscopic diagnosis.

2. Review of Pathology Reports and Microscopic Slides from Subchronic Toxicity Studies Conducted in KRICT

The pathology reports and microscopic slides of subchronic studies conducted in KRICT were reviewed with pathologists. Diagnostic mistakes made in these studies were corrected.

D. Documentation

Last year a copy of GLPs and SOPs for the area of pathology (animal necropsy, tissue preparation, microscopic sections, paraffin blocks, and microscopic slides) that have been used at the Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours & Co.,

Inc., was provided in order to assist in the preparation of KRICT GLPs and SOPs. However, this year, I noticed that appropriate GLPs and SOPs have not yet prepared. The significance of GLPs and SOPs has been emphasized many times relative to compliance with international standards of toxicity testing.

IV. RECOMMENDATIONS

Because of increasing demand on the limited facilities for toxicologic testing, and because of the short supply of qualified personnel, it is extremely important that toxicity data generated at KRICT be accepted internationally. However, to assure general acceptance, the data must meet certain prerequisites such as "Good Laboratory Practice (GLP)" which is promulgated by the U.S. Food and Drug Administration (1980). If any toxicity testing laboratories fail to meet GLP procedure which requires an adequate laboratory facility, proper equipment, and qualified technical staff, toxicity data submitted from that laboratory may not be acceptable internationally to any regulatory agency.

Following recommendations are proposed to satisfy GLP requirements and to establish internationally acceptable legitimate toxicity testing center:

1. Laboratory facilities are close to meeting GLP requirements, but laboratory equipment is not sufficient. Technical advice is required to purchase the necessary equipment, especially equipment for clinical pathology.
2. Veterinary pathologists should receive practical training to be competent for making diagnosis for lesions of spontaneous diseases and toxicity-related lesions at contract toxicology laboratories in the U.S.A. In addition to advanced veterinary pathology training, 5 or 6 years of practical experience in laboratory animal pathology and toxic pathology at toxicity testing laboratories are also required. Therefore, it will take several years before KRICT can have competent pathologists .
3. Toxicologists and teratologists also need practical training in conducting a variety of toxicity tests in order to acquire knowledge for proper interpretation of toxicity data. Contract toxicology laboratories in the U.S.A. can provide such training.
4. Since toxicologists and pathologists at KRICT have not had sufficient practical experience in conducting or interpreting the data from toxicity tests, especially long-term toxicity

studies, an experienced pathologist should review the experimental data prior to issuing a final toxicology report.

5. Technical staff members and technicians need education concerning the importance of GLPs and SOPs and should practice to comply with these requirements.
6. Technicians are required to have continuous practical training in the preparation of good quality microscopic slides. Also, they need training for the proper operation of machines such as the Autotechnicon and the automatic staining equipment.
7. The technical staff should improve their foreign language abilities, particularly English in order to communicate efficiently. Most of the staff find it difficult to understand English instructions given by consultants dispatched by UNIDO. Trainees who are elected to study in the U.S.A. should take English courses at the university to improve both oral and written communication skills.