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TOXICOLOGY RESEARCH LABORATORY

DP/ROK/82/028

REPUBLIC OF KOREA

Technical report: General Toxicology*

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 Paul G. Brantom,
Expert in General Toxicology

United Nations Industrial Development Organization
Vienna

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EXPLANATORY NOTES

Abbreviations

KRICT - KOREA RESEARCH INTITUTE OF CHEMICAL TECHNOLOGY
GLP - GOOD LABORATORY PRACTICE
SOPS - STANDARD OPERATING PROCEDURES
BIBRA - THE BRITISH INDUSTRIAL BIOLOGICAL RESEARCH ASSOCIATION

ABSTRACT

As part of the expert assistance defined for the Toxicology Research Center (DP/ROK/82/028) a mission is reported in General toxicology, undertaken between 23rd February and 22nd March 1986. Assistance was provided to the staff of the centre consisting of written documents, informal discussions and seminars.
The broad objective of the assistance was to develop experimental expertise necessary for carrying out toxicological screening to internationally acceptable standards. It is conclu that a priority for the laboratory is the development of the necessary documentation, and approach, to demonstrate compliance with GLP. It is also concluded that a continuing relationship with BIBRA may be of benefit to the development of the Center. Action in these two respects is recommended in addition to ensuring that future experts are aware of the GLP requirement before beginning their missions.

CONTENTS

INTRODUCTION

This report covers a mission of one month, commencing 23rd February 1986, during which, 19 days were spent with the staff of the Toxicology Research Center. This center, established with UNDP aid and guidance, is intended to develop as the main facility for contract toxicology in the Republic of Korea. To achieve this goal it is necessary to develop expertise in general toxicology to a standard acceptable to regulatory authorities around the world. This mission aimed to provide advice and guidance, compatible with the current state of development of the laboratory, directed at defining standards that would be acceptable internationally. The original mission objectives were defined as :

1. Advise on the design of protocols for acute, sub-chronic and chronic toxicity tests.
2. Train the veterinarian for the assessment of animal quality and gross signs of diseases during quarantine period.
3. Instruct and train the staff of the Toxicology Center in :
   a) observation of clinical signs during tests.
   b) Procedures and evaluation of gross necropsy and histopathology.
4. Advise in experimental data processing and evaluation of safety limit.

These original objectives were partially redefined after discussions with Dr. Roh the Director of the center. The revised objectives excluded the histopathology component from 3(b) above but added a need to emphasize the importance of GLP (Good Laboratory Practice) in achieving the goal of international acceptability. Advice and guidance would only be provided in the areas defined if the specific need could be identified.

The objectives were achieved through individual discussion, observation, practical demonstration and seminars, as described in more detail in the body of the report.

RECOMMENDATIONS

1. The Director of the Toxicology Research Center must be supported in his efforts to bring the laboratory into compliance with GLP.

2. An arrangement for continuing cooperation should be made between BIBRA and the Toxicology Research Centre and efforts to reach an appropriate agreement should be encouraged.

3. To aid the contribution of future experts it would be valuable to give guidance that compliance with GLP is to comprise part of their mission.

I OBJECTIVES

The broad aim of all the work during this mission was to provide assistance in the development of experimental expertise, necessary for carrying out toxicity screening to internationally acceptable standards. This broad objective was defined after a brief review of the state of development of the laboratory. During this review it became clear that the Toxicology Research Center has made very rapid progress during its brief existence, and has moved a long way towards its goals.

The main contribution that was now needed was advice and discussion directed at ensuring that the science and the practice were in accord with international standards. From the broad objective the following specific tasks were defined :

1. Advise on the design of protocols for acute, sub-chronic and chronic toxicity tests.

2. Provide guidance and training in techniques for :
   Autopsy of rats.
   Observation of clinical signs in rats and mice.

3. Provide guidance on the implementation of GLP.

II ACTIONS

These, carried out in response to the above Objectives fall into the following categories, each of which is considered separately :

Informal Discussions
Seminars
Documentation

The following sections detail the actions under the three categories :

A. Informal Discussions

These were the most frequent and most extensive form of contribution. The aim in each case was to take any area of activity which came to attention and discuss appropriate aspects of the approach, justification and acceptability with those individuals directly involved. Topics covered in such discussions are defined under the following sub-sections.

Animal unit

On a number of occasions the new facility, under construction, was visited and various aspects of design and operation were discussed. Specific discussions related to procedures for visitors to the unit and protection of the unit from wild rodent ingress.

Autopsy procedure

Several autopsy sessions were observed and guidance given on alternative procedures and justification for specific aspects of procedure. As an aid to future practice a copy of the BIBRA Standard Operating Procedure (SOP) for full autopsy of a rat was provided, and an SOP was prepared which described the procedure currently followed for teratology autopsies.

Clinical condition of animals

By a sequence of demonstrations and a practical seminar the principles and procedure for clinical examination of both rats and mice was explained.

Research project

Attendance at two seminars on future research proposals resulted in detailed discussions relating to one proposal. These discussions were the consequence of availability of unpublished data which was directly relevant to that project. During discussions possible alternative approaches were identified.

B. Seminars

During the 19 days at the center three seminars were given as described below :

Experiment Design and Practice

Given on 7th March 1986, this seminar aimed to provide an explanation of the thinking behind protocols for sub-acute and chronic studies, specifying some of the problems and pitfalls of each design. An effort was made to separate the scientific components of design from the need to meet GLP requirements. A full record of all the points made was prepared, for retention by the staff of the center.

Good Laboratory Practice (GLP)

This seminar, given on 13th March 1986, set out the principles and the spirit of GLP, as it applies to the work of a toxicology laboratory. The components of a protocol that would comply with GLP were defined in detail. The SOPS described earlier for autopsy procedures were used to illustrate how these documents should be prepared. In addition, a full list was prepared of all the S. O. P. that would be needed by the

laboratory and all the data sheets that would be required to support them. As with the first seminar, a full record was prepared of the points made, for future reference by the staff of the center.

Environmental Carcinogenesis

A final seminar given on 14th March 1986 was a description of some research undertaken by Dr. Brantom into the effects of Nitrosamine carcinogens in an effort to understand the significance, for man, of low-dose exposure to these carcinogens from many sources. This research was placed in context in the area of environmental toxicology.

C. Documentation

In addition to the detailed documentation of two seminars some guidance notes were prepared on the clinical observation of rats. Notes were also prepared on the procedure and data collection for teratology studies.

III CONSEQUENCES

All the various actions defined in chapter II aimed to improve awareness of internationally acceptable standards and give the benefit of experience to aid avoidance of foreseeable problems in carrying out toxicity screening studies.
The consequences of such actions lie in the quality of the future work of the center. Dr. Roh, the director of the Toxicology Research Center gave a considerable amount of his time to ensuring that the actions described were effective as a contribution to the future work of the center.

Staff who were involved in those areas where practical advice or instruction was given showed great willingness to incorporate new ideas into their existing techniques.

With the willingness of the staff and the understanding of the Director, Dr. Roh, it is certain that the actions described will have a considerable beneficial effect upon the future work of the center. It is hoped that these actions will provide a useful base upon which the more specialist advice, defined for the future, can build.

IV CONCLUSIONS

The main conclusion from the time spent in the Toxicology Research Center relates to the future needs. The laboratory has developed rapidly in a short time and has defined a program of expert advice and staff training which integrates with their future development. This program should ensure that the scientific and technical development of the laboratory keeps pace with its needs. It is vital, however, if the laboratory is to find international acceptance, that the work is carried out in compliance with GLP. During this mission the seeds were sown, and Dr. Roh, the Director, is clearly aware of the need to make progress in this area.

The progress made so far by this laboratory is impressive and justifies considerable support in the efforts to achieve its ultimate goals. It is possible that a continuing relationship can be established with BIBRA to provide consultation and training when this can be identified as necessary, in addition to the program currently defined.