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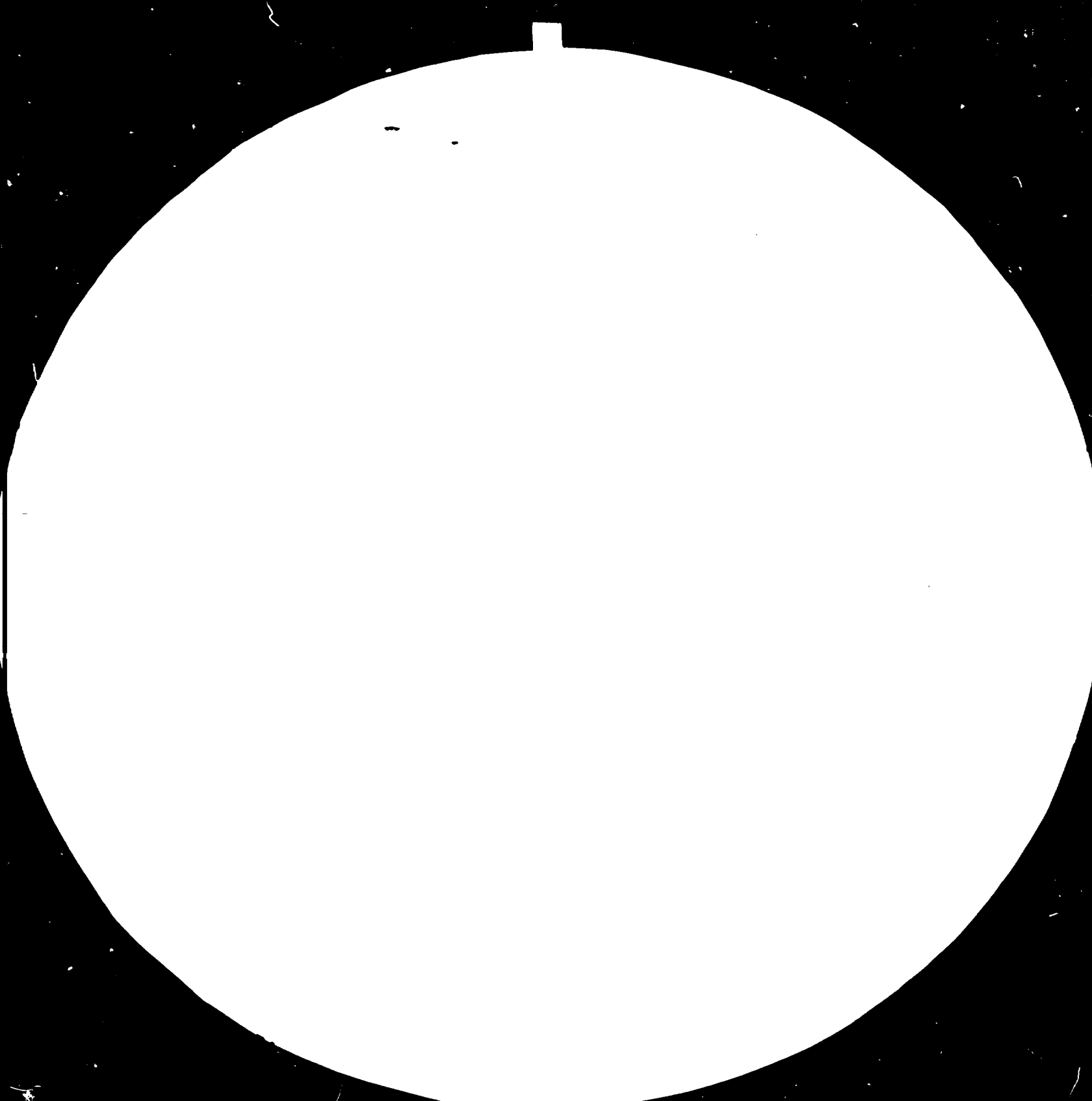

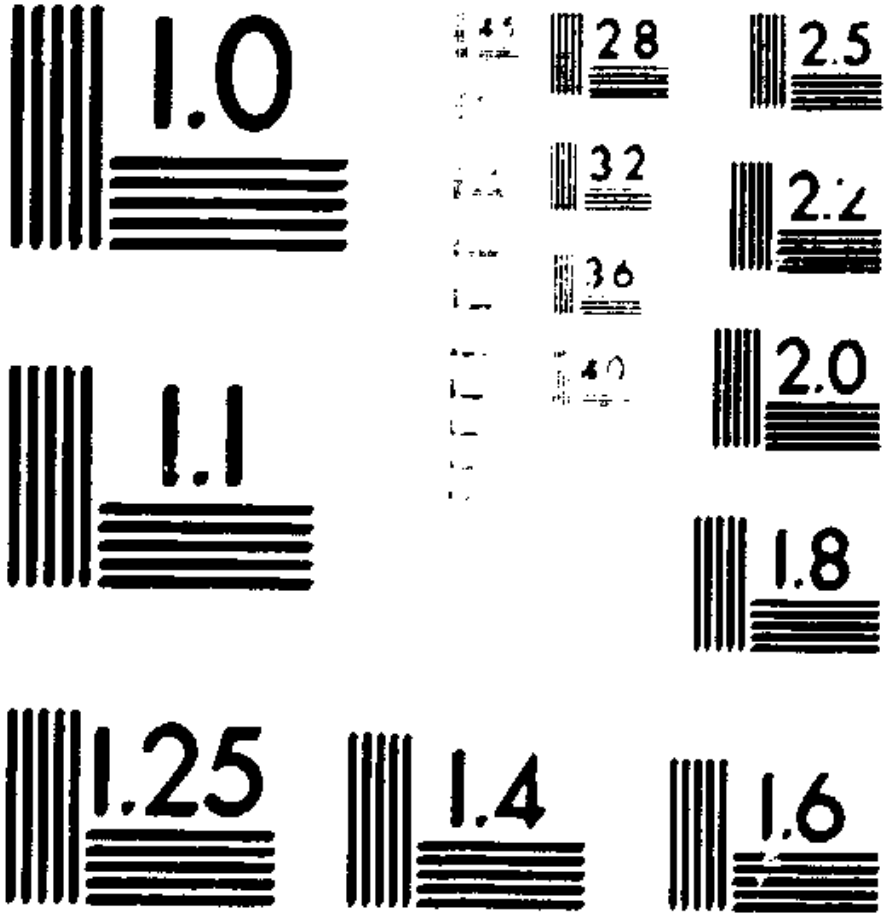

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REGIONAL NETWORK FOR PRODUCTION MARKETING AND CONTROL OF PESTICIDES IN ASIA AND THE FAR EAST

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REPUBLIC OF KOREA

Technical report: Consultancy on toxicology of pesticides*

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 Sayed S. H. Qadri,
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United Nations Industrial Development Organization
Vienna

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I. PURPOSE OF VISIT

The main ob. ective of the visit was to interact with staff at the toxicology group of Pesticide Biology Division, Agricultural Chemicals Research Institute, Office of Rural Development, Suweon, Republic of Korea. To this lectures, group discussion and seminars were to be given on general schemes for pesticide toxicology evaluation, test animal case and maintenance, practical considerations of acute toxicity tests, subchronic toxicity testing methodology, bio-chemical methods for pesticide toxicity evaluation, method and evaluation of fish toxicity, to suggest improvements to and full utilization of existing toxicology laboratory facilities and to recommend methods of developing toxicology laboratory management skills; practical exercises were to be arranged to study the acute toxicity tests - skin, mucous membrane irritation tests, bird toxicity test and inhalation toxicity test to rat.

II. THE CONSULTANCY

The eight weeks were spent at Suweon mainly in the Pesticide Biology Division, ACRI (ORD) except four days from October 30 - November 2, 1984 at Inland Fisheries Research Institute, Gyeong Nam, Jin Hae; Department of Agriculture, National Fisheries University, Namgn, Busan and Dong-oH Chemical Co., Ltd., Ulsan. Whilst at Suweon I had regular contact with Dr. Kim Gwang Po and his group of toxicology and also had a number of meetings with the Director General, Dr. Yong Hwa Shin and with the co-ordinator UNDP of ACRI, Suweon, Dr. Yong Sun Park.

Regarding the formal programme, I gave twelve lectures (detailed attached) which were attended by staff of toxicology group and a few scientists from other groups and neighbouring institutions. These were followed by often quite lengthy informal discussions with agronomists, plant pathologists, chemists and entomologists. At the request of Dr. Kyong Hee Lee, Head Pesticide Biology Division, ACRI (ORD), Suweon I gave a seminar on "Toxicological evaluation of new chemicals/bioactive components from plant as pesticides". Two more seminar talks on "Pesticide Research in RRL (Hyderabad), India" and on "Practical consideration in evaluation of pesticide Toxicology" under the schedule of consultancy issued by Dr. Shin, which were attended by workers from the Institute and the Secul Agricultural University, Suweon.

The practical work involved the blood collection, dissection of animals to study the location and safe removal of various tissues and organs for examination and biochemical analysis. Dr. Shin and Dr. Kim planned to study acute toxicity of pesticide to mucous membrane and skin irritation tests against rabbit, MLD of pesticide against chicks and inhalation toxicity of pesticide against rats. A series of tests were arranged with parathion, paraquat, monocrotophos and fungicides to bring into practice the protocols for the above-mentioned tests. A large number of pertinent slides were projected to explain the salient features of acute, subacute, sub-chronic, chronic and long term tests, which were copied and given to Dr. Kim as a record for future guidance. A large number of reading materials were provided consisting of reprint copies of the consultants research publications directly in the line and xerox copies of the concerned literature. Another exercise involved the compilation of notes on protocols with practical considerations for acute sub-acute, sub-chronic, chronic, metabolism, neurotixicity, synergism and potentiation, animal care and maintenance, toxicity to fish, inhalation toxicity, detection of chemically induced liver injury, blood and urine physiology and histology, lectures and discussions during the period of consultancy were prepared and two xerox copies were given to Dr. Shin and to Dr. Kim one copy to each as a guide for generating data on toxicity of pesticide as per the requirements of licencing board (detailed attached).

Whilst at the ACRI (ORD) I visited various secitons - the Entomology Seciton, the Pesticide Chemistry, Formulation and Residue Analysis and plant Pathology laboratories. Through Dr. Shin I met a number of Senior Researchers who are concerned with the pesticide research.

At the end of last week of October and at the beginning of first week of November I met a number of workers in Inland Fisheries Research Institute, Jin Hae including Mr. Chang Gye-Nam and Miss Sun. The Institute is trying to breed in large scale different types of carps, eels and edible bull frogs by artificial insemination, feeding and pathology. I also met with Professor In-Bae Kim, Department of Aquaculture, National Fisheries University of Busan, who is rearing eels, carps and other edible fishes based on indigenously prepared feed, growth rate and the use of pesticide to control microbes in water system. I had a detailed discussion on the use of pesticide in aquatic medium and its possible effects on animal growth and on hazards to consumer. Also visited Dong-oH Chemical Co., Ltd., Ulsan and met with Mr. D.Y. Cho who explained the production of technical grade of carbamate insecticide BPMC

and had a discussion with Mr. Cho on the pesticide manufacturing processes developed by CSIR Laboratories, India based on indigenous know-hows, who has shown interest in indigenous processes, especially in the technology developed by RRL, Hyderabad for Phosgene production - an intermediate for carbamate pesticide production.

III. BOOKS AND PERIODICALS

I visited the library at Toxicology Section, ACRI (ORD), Suweon and inspected the books, journals and periodicals in the areas of interest. This subject is relatively new for the Institute and I suggested that they purchase several books and periodicals which are not in stock at present as per the list given by me.

IV. EQUIPMENTS AND MISCELLANEOUS ITEMS

I gave a list of equipment, surgicals and miscellaneous items requried in animal maintenance, breeding and testing for procurement, which are not in stock at present for routine toxicity data generation.

V. SUGGESTIONS TO IMPROVE AND TO FULLY UTILIZE EXISTING TOXICOLOGY LABORATORY FACILITIES

Whilst in Suweon, I made certain recommendations to Dr. Kim and to the Director General, regarding the development of their laboratories, in order to undertake studies on target enzyme interaction, selectivity, species variations, in vitro and in vivo metabolism, effect of impurities, carriers, synergism and potentiation, neuro and delayed neurotoxicity. This is important to them because the Institute is aiming to develop research expertise to study Environmental Toxicology. New compounds must now undergo quite stringent testing procedures before they can meet the safety requirements of the Korean Government, and metabolism studies represent an important part of this work. Furthermore, biochemical studies of this kind are also useful in throwing up ideas for determining biological nature of a pesticidal compound. Such a study would lead to scientific publications of considerable academic standard in the area. I believe it would be useful to maintain contact with the ACRI (ORD), with a view to making a further visit to them later on when they aim to establish facilities to evaluate sub-acute, sub-chronic, chronic and long term toxicity of pesticides.

VI. RECOMMENDATIONS FOR ACTION (METHODS OF DEVELOPING TOXICOLOGY LABORATORY MANAGEMENT SKILLS)

With the approval of the Director General, Dr. Kim and I hope to have further collaboration. I hope that he will be able to visit us to gain expercience in the use of pesticide to generate sub-acute, sub-chronic and supplementary toxicity data. We also hope that the UNIDO, Vienna will be able to support his visit to my Unit for a period of three months.

In discussion with the toxicology group which is concerned with the toxicity data generation, I mentioned the work that we are doing at RPL on the generation of toxicity data as per the requirement of the Indian Government. We hope that this work will provide useful guidelines in toxicity data generation. This is one of the topics which was the subject of consultancy schedule and future collaboration. I recommended the following to develop toxicology laboratory management skills:

Composition of the staff of the Toxicology Laboratory

1. One Toxicologist (Medical/Ph.D. in Pesticide Toxicology)
2. One Veterinarian (Animal breeding, maintenance, diseases & prevention)
3. Biochemist (Enzyme activity, metabolism and biochemical studies)- one
4. One Histopathologist and Chemist
5. One Hamatologist (Blood and Urine biochemistry)
6. Animal Science (Pesticide evaluation against animals) - one
7. Laboratory Technicians should undergo Training Course on animal breeding, nutrition, diseases, health and hygiene. They must be able to diagonise the reason for animal death due to disease, mal-nutrition or due to toxic action.

In the absence of specifically qualified personnel staff on job may be provided a chance to undergo courses/training programmes as specified above to meet the requirement of competence.

In discussion with ACRI (ORD) staff on the problem of animal maintenance and breeding I recommended the provision of more space for breeding on area/animal basis, air changes, illumination, maintenance of temperature and humidity, nutrition and water round the year. Animal health should be periodically checked by examining parasites, pathogens in blood, feces and alimentary tract. Periodical monitoring of workers health by a medical personnel be carried out. Hygenic conditions during animal breeding and health records generation-

wisely be maintained. Laboratory lacks gadgets for proper administration of drugs, surgical studies, metabolic cages, blood/urine and tissue analyser/ microtome.

Animal breeding and preparations for testing should be carried out in separate rooms. Observations on clinical symptoms and behavioural changes have to be recorded as they help in understanding the toxic mode of action of an insecticide against individual test species.

Some of the errors being committed by Toxicology group in evaluating LD_{50}/LC_{50} values were duly corrected and explained.

Dissolved oxygen level in water, clacium and carbonate levels have to be necessarily checked during evaluating fish toxicity as they change the toxic profile of a pesticide.

VII. VALUE OF VISIT

The generation of toxicity data on pesticides is an important aspect of human safety - not only from the point of view of registering a compound but also as a fundamental biological evaluation, which should give guidance in determining the toxic profile of a compound against test animals to interpolate it on human subjects.

VIII. ACHIEVEMENT OF OBJECTIVES

The main objectives of the consultancy (as stated earlier) were met during the eight weeks at Suweon. As things worked out more ground was eventually covered than was originally planned with Dr. Kim. There were some visits to neighbouring laboratories, and also fairly detailed discussions of certain topics not originally in the programme e.g. the fate of pesticides in animal body and when subjected to isolated enzyme system, kinetics of inhibition, vertebrate selectivity ration, standard errors, factors of synergism and potentiation, procedures for urine and bile secretion collections. Also, some time was spent discussing the purchase of apparatus, expansion and training of the staff with Dr. Kim and the Director General.

In addition it was possible to make visits to Busan (NFU), Jin Hae (IFRI) and Ulsan (D-O CCL), all of which were rewarding and stimulating.

Critically examined the acute oral toxicity to mouse dermal toxicity to rat and fish toxicity protocol laid down by Korean Registration Board and gave suggestions for their improvement. The following expertise has been set up for testing routinely as per the requirements:

1. For routine evaluation of pesticides fabricated an inhalation toxicity testing chamber for exposing rat to mist-aerosol;
2. Demonstrated evaluation of toxicity against fish;
3. Demonstrated evaluation of skin irritation;
4. Demonstrated evaluation of mucous membrane irritation;
5. Demonstrated MLD evaluation against bird.

The following lectures and group discussions were held with Toxicology group and illustrated the salient features with slides in carrying out these studies:

1. Dose-response relationship;
2. Procedures/protocols for testing acute, sub-acute and chronic toxicity testing;
3. Inhalation toxicity
4. Irritation to eye and mucous membrane
5. Species variation
6. Metabolism: a) In vitro and b) In vivo
7. Target enzyme interaction and selectivity;
8. Neurotixicity and delayed neurotoxicity;
9. Synergism and potentiation;
10. Mutagenicity
11. Teratogenicity;
12. Carcinogenicity and Cytochrome P_{450}.

The following Seminar talks were given during the period under review at ACRI (ORD), Suweon, Korea;

1. Some aspects of toxicological evaluation of new chemicals/bioactive components from plant as pesticides (talk delivered on 20/10/1984).
2. A brief resume of pesticide research in RRL-H, India (talk delivered on 16/11/1984).

3. Some practical considerations in evaluation of Pesticide Toxicology (talk delivered on 7/12/1984).

Lectures and discussion notes on the following topics have been prepared with protocols for generation of toxicity data as per the requirements of registration:

1. Principles and methods for acute and sub-acute toxicity;
2. Animal care and maintenance (Design environmental criteria, disease prevention, safety and health);
3. Toxicity to fish;
4. Inhalation Toxicity;
5. Conduct of chronic toxicity;
6. Skir and eye testing in animals;
7. Detection and evaluation of chemically induced liver injury;
8. Blood physiology;

One copy of the notes each to Dr. Kim and to the Director General were given for their guidance in generating toxicity data. Xerox copies of Insecticide Act 1968, India and the data requirements for registration of technical and formulaiton grades of pesticides to Dr. Shin, Dr. Park and Dr. Kim as reference material.