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PESTICIDES FORMULATION AND APPLICATION

DF/FOL/87/G02

POLAND

Technical report: Toxicological and Environmental
Aspects of Pesticide Registration*

Prepared for the Government of the Polish People's Republic
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Alan Calderbank, consultant in
toxicology, environmental and regulatory affairs

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Vienna

* This document has not been edited.

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ABSTRACT

Pesticide research and development at the Institute of Organic Chemistry in Warsaw has been relatively successful. Future success in developing new products and formulations, for use mainly in Poland but hopefully abroad, will depend largely on the ability of IPO (Warsaw and Pszczyna) to provide good mammalian toxicology, ecotoxicology and environmental chemistry data which will meet regulatory requirements.

This will need the upgrading of several laboratories and equipment, the reorganisation and improvement of toxicology and ecotoxicology testing and the provision of staff, laboratories and equipment for carrying out environmental chemistry work. There is also the need to introduce procedures for the operation of Good Laboratory Practice throughout the toxicology and environmental testing laboratories.

I INTRODUCTION

Agriculture is a major part of the Polish economy. An increased use of pesticides in the country was considered necessary to improve agricultural productivity with the emphasis on home manufacture, both of active ingredients and formulated products. As a result the Government provided the Research Institute of Industrial Organic Chemistry (IPO) Warsaw, funding to support an extensive research and development programme aimed at discovering and developing new or improved pesticides and their formulations, for use in Poland and possibly for sale elsewhere.

UNDP is supporting this project by providing consultancy, training of personnel and equipment. Full details of the project are described in Document No DP/POL/87/002.

The present assignment, which is part of the above project, is a UNIDO sponsored consultancy visit to Poland for 2 weeks (Nov 13-26, 1988). The objectives of the mission are described in the Job Description Document (Annex 1) and may be briefly summarised as:

Discussing and advising on -

1. Toxicological data requirements for pesticide registration for international markets.
2. Interim data needed at various stages of valuation and development of new products.
3. Relevance of carrying out regulatory tests according to Good Laboratory Practice (GLP) procedures.
4. Relevance of international standards (WHO) and guidelines (OECD) for toxicity classification and testing.

Part of the assignment involved giving a lecture on pesticide registration requirements and the cost elements involved.

II RECOMMENDATIONS

1. More funds should be provided to purchase new and more modern equipment for most departments involved in pesticide development at IPO, but particularly in the analytical and formulation laboratories.
2. The functions of the two toxicology laboratories in Warsaw and Pszczyna should be coordinated. It is recommended that the facility in Warsaw should concentrate mainly on acute and sub-chronic studies to aid decision making and the early development process. That in Pszczyna is better equipped and should be concerned mainly with chronic studies. Both laboratories need to be upgraded and to comply with GLP procedures.
3. Much of the ecotoxicology work at Pszczyna is satisfactory. Some, such as aquatic toxicology, needs reorganising or redirecting to address strict regulatory needs. It is further proposed that facilities be installed for avian toxicology and soil organism testing.
4. Facilities and equipment for environmental chemistry studies - plant and soil metabolism, soil leaching, hydrolysis and photodegradation - needs to be provided at the Warsaw laboratories. This will involve the use of radiochemical techniques and the need for substantial expenditure.
5. A person should be nominated to study GLP laws and to introduce such procedures, initially into the Toxicology Departments and later into the Environmental Sciences and Field Trials Sections.

III ACTIVITIES

Visits and discussions were held with key personnel at the following Institutes.

1. Institute of Industrial Organic Chemistry

Dr W Moszczynski - Director
Dr J Legocki - Deputy Director

Department of Pesticide Application - Prof E Bakuniak
(Manager)

Herbicides - Prof J Ostrowski*
Insecticides - Prof J Kroczyński
Fungicides - Prof J Gorska-Poczopko

Toxicology - Prof A Majda (Consultant)
- Dr Krystyna Chruscielska

Formulation - Mr T Wisniewski
Ms Maria Tuross-Biernacka

Analysis - Dr Krasiejko
Dr Konopski

Synthesis - Mrs Maria Bielska

2. State Institute of Hygiene, Warsaw

Dr Jan K Ludwicki (Head of Registration)

3. Institute of Plant Protection, Poznan

Prof W Wegorek - Director
Dr E J Czaplicki - Head of Registration
Dr J Dabrowski - Pesticide Residues
Dr K Adamczewski - Herbicides

4. ICI Poland, Warsaw

Mr Jan Kleczar - Senior expert in Agro-chemicals

* Principle guide during the tour

5. Poisons Control Centre, Szpital Praski, Warsaw

Dr J Szajewski, Head of Department of Medicine

6. Institute of Industrial Organic Chemistry, Pszczyna

Dr Stanislaw Lakota	-	Manager
Dr Roman Knapek	-	Head of Toxicology
Dr Jozef Hurny	-	Bee toxicologist
Dr S Kobes	-	Clinical biochemistry
Ms Anna Ruzska	-	Aquatic toxicology
Dr Chmiel	-	Residue analyst

7. Academy of Medicine, Warsaw

Prof R Oledzka	-	Food Research
Prof Brzezinski	-	Toxicology
Dr Barbara Tudek	-	Biochemistry

IV FINDINGS

General Situation

IPO Research and Development has been successful in the registration of 3 marketed (or about to be marketed) products from about 12000 compounds tested. Bromfeninfos is for Colorado beetle and animal ectoparasite control.

Methyl bromfeninfos is for flying insect control and public health.

Stymulen is a growth regulator, related to choline, which increases the stem length of flax. It could have a market also in the USSR.

Although these compounds are relatively simple analogues of existing products, nevertheless their discovery illustrates the value of systematic synthesis around an active toxophore with an appropriate properly targeted biological screen.

Thus the Institute has been reasonably successful in its inventiveness and the ratio of 3 successful products from 12000 tested is above the average for the pesticide industry as a whole (1 : 12000).

It was not within my remit to comment on the biological screen, which is of course crucial to success of the whole enterprise. This aspect will be covered by a separate consultancy visit.

Other aspects such as formulation research were visited but not strictly within the present remit. Nevertheless a few comments are made below.

Registration

Registration of pesticides in Poland is relatively straight forward. There is a Temporary Registration for 3 years for which no long term (chronic) toxicology data is needed. This is followed by "permanent" registration which must be supported by a rat 2 years toxicity and carcinogenicity evaluation and at least three short term tests for mutagenicity. No 2 year mouse carcinogenicity study is required, unless there are problems with the rat study.

The authorities are proposing that the rules be changed and the Temporary Registration scrapped, which would be a detrimental step. The full registration would need renewing every 10 years.

Biological efficacy data on new products is usually carried out for three seasons, unless there is supporting data from a country with similar climatic, crop and soil conditions. Trials are organised by the Plant Protection Institute (Poznan). Head of

registration there is Dr E J Czaplicki. Residue analysis is headed by Dr J Dabrowski with a staff of 23 people at the Institute and a further 65-70 in laboratories located in various parts of the country. Their responsibility is routine monitoring of food crops for pesticide residues as well as arranging 20-25 field trials annually, specially for residue analysis of new products undergoing evaluation.

The toxicology and environmental data is reviewed by Dr Jan Ludwicki with a staff of 20 (6 scientists) at the State Institute of Hygiene. Dr Ludwicki said he was not really qualified to review environmental data, but there was nobody else to do it.

Recommendations for approval or rejection are passed to the Ministry of Health for ratification.

Basically the procedure for pesticide registration in Poland is adequate. The system of providing Temporary Registration for a limited period, although disappearing from many countries, has considerable advantages without significantly increasing consumer risks. It would be a retrograde step if this were abolished in Poland. There is a need for more governmental expertise to be available in the area of environmental hazard evaluation. The behaviour of pesticides in soil, their degradability, deactivation by binding and leaching potential in soil are subjects which are receiving increasing attention in recent years. The evaluation of the data on specific compounds in relation to the background information on existing, or established products is a problem for experts in this field. The authorities need to take steps to ensure that they provide adequate expertise to evaluate the environmental, particularly soil, aspects of pesticide behaviour.

Toxicology

The facilities for carrying out toxicological tests at IPO (Warsaw) are minimal and rather primitive. There is a staff of 11 persons with a part time consultant. Additional, rather better, facilities are available at the IPO (Pszczyna Branch) 16 staff (6 scientists and 10 technicians).

Warsaw: General acute tests (rats and rabbits), long term (rodent) studies, behavioural studies and mutagenicity (Ames) tests carried out. Studies are carried out on industrial chemicals as well as pesticides.

The facilities and equipment is very poor and badly needs renewing and bringing to modern standards.

There is not even a simple barrier system to the one 2 year rat study (Ipofos?) in progress. This study was started in June 1988 using a relatively new hybrid (August/Sprague-Dawley) strain of rat, obtained from Dr Alina Czarnomska, Institute of Oncology, Warsaw.

The laboratory does not follow GLP procedures but studies are largely done according to OECD guidelines and the one (long term) study on bromfenvinphos inspected seemed to have been very well recorded with detailed individual animal data.

Support work is done either in the chemistry department of the Institute or elsewhere (eg diet analysis). Tissue preparation and histopathology is usually done at the Academia of Medicine, Department of Pathological Anatomy, Warsaw.

Pszczyna:

Facilities here are rather better than in Warsaw. There is a simple barrier system to rooms kept under constant environmental conditions, with about 6 air changes per hour. Space for about 4 long term rodent studies.

Studies carried out : Acute oral and dermal (rat), skin and eye irritation (rabbit) 90 day and 2 year (rat)-carcinogenicity or combined toxicity. Embryotoxicity / teratogenicity tests (rats) have been carried out there. There is a support clinical biochemistry laboratory and two pathologists, with facilities for tissue paraffin block preparations, slicing, staining and slide reading (shortly to move to improved new building).

Despite all precautions, problems of a high early mortality rate in the long term rat studies is often encountered.

Work is not carried out according to GLP but a certificate of compliance is obtained from Professor Luciak, a pathologist from the Academy of Medicine, Katowice. This Academy also provides the rats (Wistar strain) used in the studies.

Support analytical facilities at the Institute were poor mainly due to lack of modern equipment and separation from residue analysis.

Ecotoxicology

Most of the ecotoxicology work for IPC is done at the Pszczyna Branch.

See toxicity is evaluated very adequately under Dr Hurney. Acute oral, dermal, speed of toxicity and other tests are carried out in the laboratory. There are many colonies in outside hives and there are adequate resources and facilities to arrange large scale trials for toxicity and repellancy at commercially sprayed sites.

The arrangements for studying toxicity to aquatic organisms was less satisfactory in that it seemed to be geared more to studying problems of scientific interest rather than to serving strict registration needs.

Thus the tests for evaluating accumulation, viz algae --> daphnia --> fish are too complicated and difficult to interpret. A direct water --> fish accumulation test according to OECD guidelines should be developed. The OECD guidelines for evaluating aquatic organism toxicity, viz algae, daphnia and fish (flow-through test) should be adopted. I saw little of practical value likely to emerge from the current work in progress on the effects of pesticides on certain enzyme systems.

I did not see any work at the Institute on the effects of pesticides on avian species, nor on the effects on soil organisms.

Environmental Chemistry

This involves studies of the fate of the chemical in the environment and involves residue analysis, plant and soil metabolism, hydrolysis and photolysis and leaching in soil. Much of this work requires the use of radiolabelled pesticides and techniques.

The only subject partly covered by IPO is residue analysis. This was carried out to a limited extent at both the Warsaw Institute and the Pszczyna branch. At both laboratories the work is mainly directed to analysing samples from field plots using established methods (to help registration of new products or new formulations). Some research is also carried out on method development, studying the dynamics of pesticide degradation (loss) and supporting some of the biological departments by analysis of biological samples.

The analytical laboratories at both establishments are poorly equipped by modern standards. Although GLC is available it was purchased many years ago and badly needs replacing and the detectors need updating with modern versions.

There is also a lack of High Pressure Liquid Chromography (HPLC) equipment and good UV detectors in the laboratories. Both laboratories also suffered from shortage of much basic ancillary equipment important for the effective operation of a good residue analysis laboratory.

V ASSESSMENT OF NEEDS

General

Although it is outside the remit of this review it is perhaps worth stating here that it is believed that the objectives are well understood by management but that achievement is hampered by lack of fundamental equipment and facilities.

The limited amount of synthetic work available is not sufficient to compete with the relatively vast resources of the pesticide industry. Consequently IPO management is quite correct in directing the small amount available towards the modification of known active compounds in areas of biological activity (targets) of importance to Poland.

Another important and realisable objective is to make improved formulations of products using indigenous inerts or adjuvants.

However the Formulation Department is seriously handicapped by lack of much basic equipment. This was particularly apparent for the development of suspension concentrates (SCs), which are aqueous based and tend to be safer than the more conventional ECs. Modern equipment for particle size measurement is almost essential before real progress can be made in this field.

Toxicology

The facilities at the Institute in Warsaw, even with the backing of the Pszczna Branch, are inadequate for providing the full toxicological package needed for the registration of a new pesticide. The division of work between the two laboratories also needs better definition and coordination in order to obtain maximum benefit from the existing resource.

The facilities in Warsaw, particularly, are old and badly need refurbishing and equipping.

It is suggested that the limited resources in Warsaw should either be expanded and properly equipped to carry out long term rodent studies, which would be very costly or to limit its activities to supporting Research and Development.

My recommendation would be the latter, namely to concentrate on the following work:

1. Acute studies, rodents, rabbits, guinea pigs, viz. oral, dermal, skin and eye irritation and skin sensitisation studies.

(Pesticides, intermediates and other industrial chemicals)

2. Short term tests for mutagenicity/carcinogenicity.
3. Diagnosis of potential teratogenicity/foetotoxicity - Churvov test.
4. Sub-chronic tests to highlight the target organ or mode of toxic action and to establish approximate maximum tolerated and no observed effect feeding levels.

The toxicological facilities at Pszczyna are more suitable for long term studies but still need further upgrading in order to improve the 2 year percentage survival of the rodents. There is also adequate resource at Pszczyna for clinical biochemistry, tissue and slide preparation and histopathology.

There is, however, a need for this laboratory, and also that at Warsaw, to improve its working practices to GLP (Good Laboratory Practice) standards (see below).

If the Pszczyna Branch toxicology facilities are not upgraded then chronic studies may not be acceptable for registration purposes and would need to be contracted to outside laboratories, better equipped to handle such work, eg. The Toxicology Research Center (TRC) Veszprem, Hungary.

Ecotoxicology

With some reorganisation and introduction of facilities for game bird toxicity testing and soil microbiology, the Pszczyna Branch is suitable for carrying out most of the ecological studies needed for the evaluation and registration of pesticides eg.

- | | | |
|--------------------|---|---|
| Bee toxicity | - | present facilities and organisation of work satisfactory. |
| Aquatic organisms | - | Equipment for flow-through toxicity studies needed.

Some reorganisation of work needed. Use of radiolabelled chemical for fish accumulation studies. |
| Game bird toxicity | - | Space and facilities would need to be created. |
| Soil organisms | - | Facilities and microbiological expertise needed. |

Environmental Chemistry

Apart from residue analysis very little of this essential work is undertaken by IPO. Even for residue analysis the laboratory space is cramped and the equipment inadequate by modern standards. If IPO seriously intends to evaluate and develop new products for sale in Poland and other countries it must ensure that appropriate environmental fate studies can be carried out "in house" or are contracted out to competent laboratories abroad.

In order to provide adequate "in-house" facilities the use of radiolabelled material with all the equipment (scintillation counter, sample oxidisers, radiochemical detectors and scanners etc) must be made available. This would represent a large capital investment, which would be most appropriately spent at the Warsaw laboratories.

A brief summary of the main needs are as follows:

1. Residue Analysis. Replacement of old GLC equipment and detectors and provision of two High Pressure Liquid Chromatograms. More laboratory space to be made available.
2. Soil and Plant Metabolism Studies. Facilities for handling and measuring radiochemicals. Scintillation counter, oxidisers, scanners, radiochemical detectors etc.

Microbiological support for soil degradation studies.

3. Soil Leaching, Hydrolysis and Photodegradation. Facilities as described under item (2).

Good Laboratory Practice

Toxicological studies used to support registration petitions in most of the major countries need to have been carried out according to rules of Good Laboratory Practice, as originally set out by the US F & DA and later by USEPA and OECD, otherwise they will not be acceptable.

GLP rules are also being extended to ecotoxicology environmental and other tests needed for the registration of pesticides.

Consequently it is essential that any work submitted to the authorities by IPO for registration purposes in the future should be of adequate quality and carried out according to the rules of GLP.



Annex 1

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

JOB DESCRIPTION

DE/FOL/87/CGZ/11-52/J 13421

Post title Expert in Toxicological Aspects of Pesticide Registration

Duration Two weeks

Date required Early 1988

Duty station Warsaw, Poland

Purpose of project To develop capability of the Institute of Industrial Organic Chemistry, Warsaw, Poland in the development of new compounds as potential pesticides and develop formulations for biological assessment of both glass house and field trials.

Duties The expert in consultation with the project counterparts should discuss the various stages of toxicological data requirements for pesticide registration for international markets. He is expected to advise on:

- the toxicological data (short term and long term) to be generated for registration.
- the interim data needed during the various stages of the biological evaluation of potential compounds (glass house, field trials, process chemistry, formulation, co-operative trials etc.).
- the significance of Standard Operating Procedures (SOP), Good Laboratory Practice (GLP) needed for international recognition.
- the relevance of ADI, MRL and toxicity classification according to WHO code of practice.
- harmonization of toxicity test/data systems advocated by WHO and other organization like OECD and EPA.

He is expected to give lectures on the present situation regarding data required for registration of pesticides with various cost elements involved. The expert will have to submit a report on his findings and recommendations.

Applications and communications regarding this Job Description should be sent to:
Project Personnel Recruitment Section, Industrial Operations Division
UNIDO, VIENNA INTERNATIONAL CENTRE, P. O. Box 300, Vienna, Austria

Qualification: Organic chemist, biologist or bio-chemist with extensive experience in the toxicological aspects of pesticides and the data required for registration in international market. He must have experience with FAO or WHO code of conduct, EPA and OECD guidelines.

Language: English

Background information: One of the national development strategies for the forthcoming period in Poland is to increase food production and bring it to a level of self sufficiency. The Government will concentrate its efforts on further increasing the industrial inputs to accelerate growth and efficiency of agricultural outputs. Among other measures, the substantial increase of production and application of pesticides is foreseen. The well known fact, that the pests and fungi are destroying about one third of the potential crop every year, was taken into account, and it was decided to increase the pesticides use from 1 Kg/ha/year of active ingredient (a.i) to 2Kg/ha/year in the next plan period. Also important changes of production profile and solutions are foreseen. The chemical industry in Poland is producing nearly 12,000 t/year a.i. and also importing 5,000 t/year a.i. All active ingredients are formulated locally and a full profile of solid and liquid products is available. However, dependence on the imported products is creating bottlenecks in timely supply and distribution of pesticides which are needed at specific agriculture conditions. Therefore, a large-scale Governmental research and development programme in the area of local production of active ingredients, formulation efficient application of pesticides was begun several years ago and will be continued in the next country five-year development plan. The main goals of this programme are to screen new, more effective, but also more safe pesticides of systemic character, and to prepare complex formulations for specific crops and particular agricultural and climatic conditions. For the years 1986-1991 several billions of Zl are planned to support the programme on screening, formulation and application of selected pesticides. Investigations on the behaviour and fate of new pesticides in the environment and on their influence on particular elements of biosystems are also main objectives.

The Institute of Industrial Organic Chemistry is the research centre in Poland carrying out research on pesticides. The Institute of Industrial Organic Chemistry employs about 350 staff members in the pesticides section of whom 130 are graduates and 17 are professors and associate professors. There are departments comprising full research and development cycles (synthesis, analytics, formulation, engineering, environmental protection, pilot scale production) and biological research (e.g. three stages of screening tests, mode of action, metabolism, fate and behaviour in the environment, greenhouse and field experimentation and toxicology).

The Institute of Industrial Organic Chemistry is conducting extensive research on screening pesticides. In the period of the last 15 years approximately 10,000 new chemical compounds were screened. Among others, four new insecticides from enolphosphates group of low toxicity to control Colorado beetle and sanitary pests were patented. To continue this activity, one of the particular research programmes is linked to further selection of active chemical substance level of already established properties of specific molecular structure, preparation of the formulation recipes and to conduct full cycle of biological and toxicological tests and investigations. The pilot scale applications in the field conditions are also foreseen in the Institute farm. Through this programme eight hundred substances should be synthesized and screened for further biological and application studies. As a result, pilot batches of the new pesticides will be formulated and used for further studies under different soil and climatic conditions. UNDP assistance in the realization of this programme will enable the practical training of young researchers as well as allow review of the trends abroad through study tours for senior research staff. Also, important rehabilitation and modernization of scientific instrumentation and pilot equipment will improve the efficiency of the research and development process.