SAFETY IN PESTICIDES PRODUCTION

The organization and execution of a sound toxicity evaluation program and the thorough application of industrial hygiene practices in manufacture and formulation should be given high priority by every producer of pesticides

Toxicity Studies of Pesticides And Their Formulations

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THERE IS NO LONGER ANY QUESTION that a safety evaluation program plays a significant role in pesticide development. The suggested references at the end of this paper all have dealt with some aspects of the problem. The ideas involved are directed primarily to pesticide development, but most of the principles apply equally to chemicals for other end uses.

The first and most important problem to be faced is that of personnel. There are many aspects of a toxic material, not the least important of which is its safety. The terms "toxic," "poisonous," and "deleterious" defy definition without qualifying clauses on quantity, time, and conditions of use. It is sufficient to say that all three branches of our government —legislative, executive, and judicial—at state and/or federal level, have labored this point without avail.

The only productive avenue is to consider toxicology for what it is: a melange of sciences applied to a specific objective. This objective may be variable and often indefinite. It is too much to expect, therefore, that any one person could qualify as a toxicologist. The execution of an adequately designed toxicological program will obviously involve the talents of more than one scientist, and so our most important problem is born.

The basic or applied sciences most intimately associated with toxicology are pharmacology, biochemistry, pathology, biology, and analytical chemistry, not necessarily in that order. Technically

trained assistants in clinical laboratory techniques, tissue fixation, x-ray, animal care, and nutrition provide invaluable services. In specific types of studies radioactive tracers and engineering are indispensable, as are statistics.

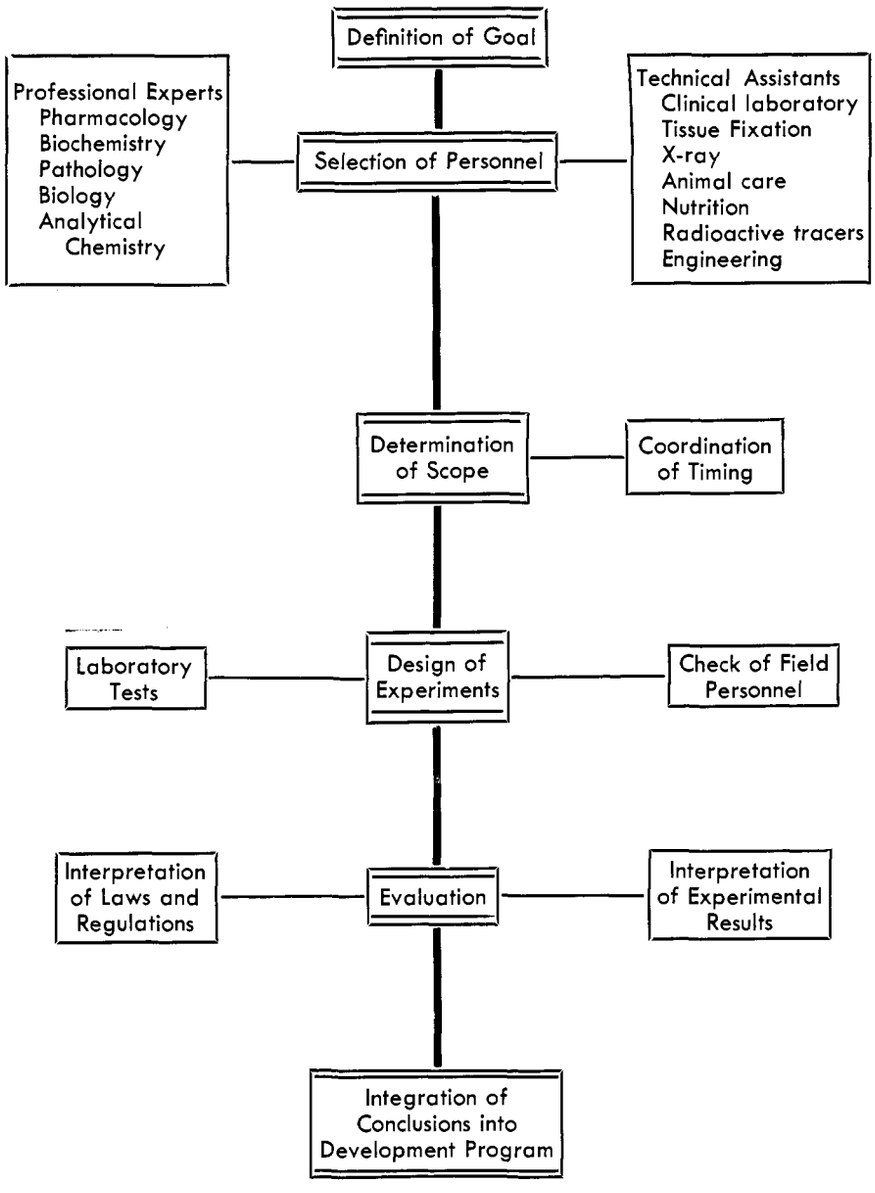
The key person may be selected from any of the professional experts in the biological sciences, provided he is willing and able to perform additional duties quite aside from the scientific aspects. In actual practice pharmacology provides the basic discipline most applicable to the problem of safety evaluation and the responsible investigator will be referred to as the "pharmacologist." To design and supervise a comprehensive investigation successfully he must understand fully and adequately the objectives to be sought, the pertinent regulations and standards for evaluation, the significance and adequacy of data, the specific contribution to be made by each specialist, and in addition he must have a fine sense of timing and personnel relations. As can be readily appreciated, these talents come not from formal discipline alone, but also from experience and personal devotion to the task of acquiring this collateral background. As applied to agricultural chemicals, this is a relatively recent and highly fluid era, and the selection and training of such personnel is a serious responsibility.

Scope and Timing

The second major problem is the scope and timing of the investigation, a relatively simple problem since the objective is so clear cut. The scope need include only those studies which will determine the safety or relative hazard of the pesticide in question under conditions of use. In practice this usually involves a careful, stepwise procedure closely integrated with the other developmental aspects of the material. Consideration is given to the preliminary tests necessary for protection of personnel who are making, formulating, and applying the agent in test quantities. If early laboratory and field tests are encouraging, additional studies are immediately in order. These must evaluate the above hazards more carefully under extensive use conditions and begin the comprehensive phase of subacute and chronic evaluation by various routes of exposure and in several animal species. At this time consideration must also be given to both pure and technical grade material, and to formulations. Adequate analytical methods applicable to biological material must be developed in cooperation with the chemists. With the entomologist the exposure of personnel under conditions of use and abuse must be determined and experiments designed to evaluate the hazard. As is well known, these may include oral, dermal, and inhalation toxicity problems. Methods of application may dictate special inhalation tests if the formulations or equipment tend to produce aerosols, since the inhalation hazard from these free floating particles may be quite different from that of vapors.

If the pesticide is sufficiently toxic to cause personnel hazard, a program of diagnosis and treatment must be worked out with the medical staff in order that an adequate industrial hygiene program may be inaugurated. The problem of residue hazard should receive continuous attention to assure experiments adequately designed to evaluate this hazard at the earliest possible moment. Much of the design is determined by the adequacy of analytical methods, the residue levels encountered, and whether the metabolic fate of the chemical can be traced in the animal. Each bit of data developed by the analytical chemist thus becomes important to the safety evaluation program.

DEVELOPMENT OF A SAFETY EVALUATION PROGRAM



In pesticide development, time is money and the timing of each phase of the biological study is the responsibility of the supervisor. With adequate cooperation one or more years may be saved on the program without any loss of scope. This can only be accomplished in laboratories where research and development are the primary objectives and where control work, routine testing, and teaching are kept at a minimum.

Design of Experiments

The third problem, that of the intimate details of experimental design, must be treated either rather briefly or in great detail. Brevity will best serve the purpose at this time. Intimate detail involves decisions on the number, sex, and species of animals, dosage levels and routes of administration, duration of

exposure, frequency and extent of hematological investigations, clinical-type laboratory tests, organ function tests, and physical examinations while the studies are in progress. Biochemical techniques must be selected and applied to elucidate the metabolic fate, whether by excretion, disintegration, or storage. Terminal evaluations of gross or microscopic pathology, organ weights, and other criteria must be carefully planned far in advance.

It cannot be stressed too strongly that intimate design for safety evaluation must not be stereotyped. Each candidate material requires consideration based on the chemical involved, its potential use, and data previously available. Experience and judgment must be dominant factors throughout the entire project. No design can be inflexible. Few things could more adversely affect the future of pesticide development than the acceptance of the philosophy of "more and more" of a prescribed and dogmatic set of tests based on predetermined feeding levels, safety ratios, time intervals, group numbers, and the like.

Evaluation

Nowhere in the safety evaluation program is the training, ability, experience, and integrity of the responsible investigator more paramount than in the next problem, that of evaluation. He is responsible for the interpretation of data and determination of their adequacy at each phase of the program. The logical question at this point is "adequate for what?" This was briefly outlined under the discussion of scope as protection of research and production personnel, experimental and testing staff, formulators, applicators, and finally the public. It is the objective of management and research personnel and the principle of the applicable written law.

W. Hazleton founded Hazleton Laboratories in 1946, after holding professorships in pharmacology at George Washington University and Georgetown University. Dr. Hazleton took his B.S., M.S., and Ph.D. from the University of Washington. Now chairman designate of the pesticides subdivision of the ACS Division of Agricultural and Food Chemistry, Dr. Hazleton is interested in the safety evaluation of agricultural chemicals, food additives, drugs, and cosmetics, with special emphasis on those which affect the autonomic and central nervous systems or are cholinesterase inhibitors.

Recent papers by Oser, a biochemist speaking before the Food, Drug, and Cosmetic Law Section of the New York Bar Association, and by Bartenstein, a lawyer speaking before the American Association for the Advancement of Science, may be cited to illustrate the complexity of evaluating natural laws in terms of statute law. For those aspects not specifically covered by law, the evaluation can be made by the pharmacologist. Residue data in particular are subject to interpretation under federal laws and regulations. Under these circumstances the responsible pharmacologist must integrate his evaluation and interpretation with those of officials charged with the enforcement of the applicable laws. This is the area of a new frontier.

The problem of evaluating safety in compliance with a law might well be considered and discussed as a separate problem but, for our purposes, can be included in the over-all major problem of evaluation. Probably the most challenging and least understood aspect of the problem is the building of a new concept within a democratic framework of government. It is the responsibility of each scientist concerned with safety evaluation to guard against extreme interpretations in either direction. If the public is to benefit from the legal protection provided, great care must be exerted to avoid science by regulatory edict. Such a condition is encouraged, first, by the appealing nature of the phraseology "in the public interest," and second, as Bartenstein has indicated, "the government thus assumes a sole burden of responsibility so great as to risk negative decisions without appropriate regard to accepted scientific opinion and judgment." On the other hand, there remains much educational work to be done within industry before an adequate appreciation of the evaluation problem is developed. In the meantime progress is being made all along the way and, most important of all, the public is being adequately protected while reaping the many benefits derived from agricultural chemicals.

Role of Biological Sciences

As a final problem, brief mention should be made of the role of biological sciences in the development of pesticides and other chemicals. This is an indispensable role and the earlier thought is given to the safety evaluation program the more time and money are saved. The pharmacologist should be an integral part of the planning team. He cannot make up time lost before he is consulted; neither can he recover other costs needlessly incurred because the toxicity of a compound was not investigated early and adequately. Much progress is being made in this field, and when management and chemists start learning by authority rather than by bitter experience much more rapid progress will be made.

These, then, are the major problems of the toxicity studies on pesticides: personnel, scope and timing, intimate experimental design, evaluation and interpretation, and finally the appreciation of its place in the development program. As has been pointed out, most of the problems relate more directly to safety evaluation than to toxicity. None of them is insurmountable, but each requires tact, perseverance, and above all, a broad, tolerant perspective. Evaluation of safety for a chemical under various conditions of use is a new frontier in applied science and is indispensable if our current rate of progress is to be maintained or accelerated. At present its specialists are few and the training of new personnel is a serious responsibility. Those of us in the field who have come up through the drug development counterpart appreciate the vast and significant differences which exist between the two fields.

In this review every effort has been made to discuss only the broad aspects of the problem. Partisanship, personalities, specific laws, conflicting viewpoints, and controversial topics have been avoided as much as possible. Our progress in this country has been outstanding and will continue to be so long as we are aware of the fact that there is being developed in a democratic manner a basic legal and scientific philosophy designed to encourage progress while at the same time providing continuously higher and safer standards of living.

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