RESIDUE INFORMATION in pesticides development

Residue Studies in the Research Program

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USE OF AGRICULTURAL CHEMICALS has increased remarkably during the past 15 years, and all signs indicate the next 25 are going to be even more remarkable. Among the key ingredients for a successful future will be research and development of new agricultural compounds to promote a higher standard of living. Probably the biggest factor which will curtail this vital research and development is the rising cost of bringing a new product to the marketing stage. Estimated costs of product development in this field are fantastic. One company estimates it requires four years and about $2 million to see a new product reach sales. When this time and money are compared to the average life expectancy of the new chemical, estimated by some to be from five to 10 years, it becomes apparent why a conservative management might view the whole field of agricultural chemistry as unsatisfactory for investment dollars. Those of us engaged in this field of research, whether as active investigators or consultants, must utilize a research budget in the most effective manner. This can be done without restricting scientific ingenuity if some practical thought is incorporated into a development program.

Experience and training in many philosophies are required in any development program. As consultants to industry, our organization has recognized this need and has attempted to bring about the close coordination of biology and chemistry. We find that many times the two groups are unaware of the fundamental concepts involved. Dr. Hazleton (3) has previously discussed the role of biology in the development of new agricultural chemicals. It has become evident that residues are playing an equally vital role and must be given the same considerations in initial planning and in total evaluation.

Basic philosophies change as new information is made available, and this is especially true with residues. The old philosophy that residues should be held to zero has been altered; today we feel that residues should be held to safe levels. The reasons behind this change are numerous, but primarily they are the results of progress made in the fields of entomology, plant pathology, chemistry, toxicology, and education. The chemist has given the entomologist and plant pathologist newer and better tools with which to work. The toxicologist has learned to evaluate the safety of the new chemicals. The general public has been educated on how to use these new chemicals effectively and to enjoy the results through better, bigger, and more flavorful food.

The chemist must accept the responsibility not only of developing the compound but also for providing the analytical method whereby the chemical can be measured on a food crop. This is no small job.

A better understanding of this responsibility is provided by a background of the legal requirements. Prior to 1954, residues of any chemical occurring in foods were evaluated by the Food and Drug Administration under authority of Section 406 of the Food, Drug, and Cosmetic Act. This section permits the establishment of residue tolerances through public hearings for harmful and deleterious chemicals, if it can be shown that the chemical is necessary and that residues cannot be avoided by good manufacturing process. Until 1950, few pesticide chemicals were granted tolerances under this provision because residues were not well understood and the data were rarely adequate to evaluate fully either residues or safety. Of the more than 90 chemicals considered in the 1950 hearings, many of the studies appeared to have been conducted with the obvious thought in mind that residues would be nonexistent. Even in the case of the really persistent compounds such as DDT, efforts were made to keep residue values as low as possible.

In our work we have been asked to assemble the available efficiency, toxicology, and residue data for submission as a petition for tolerances to the regulatory agencies, and have found that much of the residue data are meaningless. This leads us to believe that the importance of residues has been overlooked in the early stages of compound development. It becomes necessary to delay application for the tolerances until such time as adequate data are gathered, often resulting in the loss of a whole growing season. It is impossible to estimate the financial loss to the company that this delay represents.

With passage of the Pesticide Chemicals Amendment, Section 408 of the Food, Drug, and Cosmetic Act, certain basic concepts have become recognized. The first is that the terms "necessity for use" and "necessary in the production" are to be interpreted as "effective for the uses recommended." The second concept is that maximum effectiveness, or efficiency, of a pesticide chemical can be attained only if the chemical is used to control a disease or insect pest at the proper time in the growing sea-

son. With this latter idea, it becomes feasible to apply a chemical when it is most needed, even if that need should arise only a few days before harvest. It has also brought out the real need of understanding what happens to the chemical in or on the plant, not just how long it remains. This can be stated as the most important change of concept we have witnessed, because residues are now removed from straight analytical chemistry and are placed in a category all their own.

It will be some time before a full understanding of residues will be reached and until then the analytical chemist and the biochemist must work closely together. Basically the analytical chemist finds the work of residue analysis esthetically displeasing because he is not prepared by his training to accept the challenge of working with so complex a mixture as blood, feces, urine, or plant homogenates. These substrates are in the realm of the biochemist who has had a great deal more training in separating the various biological chemicals. It is regrettable that a biochemist may not be readily available when residue problems arise, because the job therefore falls on an organic chemist who is usually the one who originally synthesized the compound. Because residue problems involve two systems of thought, they should be brought closely together early in the development program to ensure rapid success.

Many schemes and plans have been published from time to time and are used by many companies to show the steps in the development of a new chemical. Such plans are important if they are keyed to the problems to be faced. The chart on the next page presents one such scheme which, in general, would appear to be satisfactory. It is keyed to the important factors which must be considered, yet it does not include specific problems which may arise. Its most important contribution is the placing of residues in proper perspective, on a par with use tests and toxicology.

The chemist who synthesizes the compound is the logical one to provide the initial analytical key to the residue problem. In other words, the organic chemist, by being aware of his additional responsibility, can direct his thoughts to the analysis as well as to the synthesis of the compound with which he is working without significantly increasing research costs. His ideas should be written down and preserved for future use, should the compound prove useful.

Identifying Residue Problems

Many of the analytical procedures commonly used for relatively pure samples are dismal failures when applied to biological materials. In any residue analytical procedure, one of the greatest problems is the adequate clean-up of the extract by removal of any interfering substances. During the second step in the development program material can be made available on which clean-up methods can be worked out and analytical procedures can be tested. Thus, specific residue problems can be identified at this stage in the development program.

After a chemical has been shown to be effective in the screening program, it is tried under field conditions. Ample material is available for residue analysis when food crops are involved. A residue program designed and conducted to produce the maximal information relating to the end use of the compound in question can yield valuable results and save a great deal of money later.

Up to this point, very little time or money has been wasted on the large number of compounds which have proved unsatisfactory under screening conditions. The concentrated effort is made only on those chemicals which indicate some economic value and which might be expected to show a return on the investment.

Evaluation of a program must be made periodically, and the appropriate timing depends on the particular company involved and the type of development program being followed. It is obvious that a sound decision can be reached only if all the major problems are recognized. Early consideration of residue, toxicology, and efficacy can provide a basis for making a decision which will result in better utilization of a research budget.

"Management evaluation of results" includes many factors such as formulations, production problems, and market analysis which must be considered in terms of capital investments. If all the factors are available for evaluation, it becomes possible to apply for a temporary tolerance under Section 408 of the Food, Drug, and Cosmetic Act, and an Experimental Permit from the USDA. Additional data on efficacy and residues can be gathered on a nation-wide basis by university groups, Federal and State Experiment Stations, farmer cooperators, and independent research groups. At the same time the experimental data necessary for the evaluation of safety for use is being conducted. The company has given adequate assurance that the public health is not jeopardized and is in a position to recover at least a part of the research costs at an earlier date than would otherwise be possible.

This outline oversimplifies the problem and does not take into account the various ramifications of the whole agricultural chemicals industry. It does, however, include the basic principles which show the need for an early understanding of the biological and chemical activity of a new compound. A satisfactory residue program for a given chemical depends upon many factors; it must clearly show what happens to a chemical when applied to a plant, its rate of disappearance, the breakdown products, and their fate. It is no longer adequate just to prove quantities at a given time.

General rules can be laid down, based on previous experience. For the insecticides which exert their action on the surface of the plant, it becomes important to know initial deposits in relation to entomological effect; it is equally important to know how long that effect can persist. By using the approach suggested by Decker (*1*) and by Gunther and Blinn (*2*), a half-life value for a given insecticide on a given crop can be derived. With such information, practical dosages and suitable formulations can be determined. These data are essential for the evluation of the toxicological information; limits of safety will always dictate maximal residues which, in turn, dictate maximal efficiency. Finally, it points out the range in time, from application to harvest, in which to concentrate further residue studies to evaluate fully the chemical in terms of public health.

Systemic pesticide chemicals offer different problems but some of the

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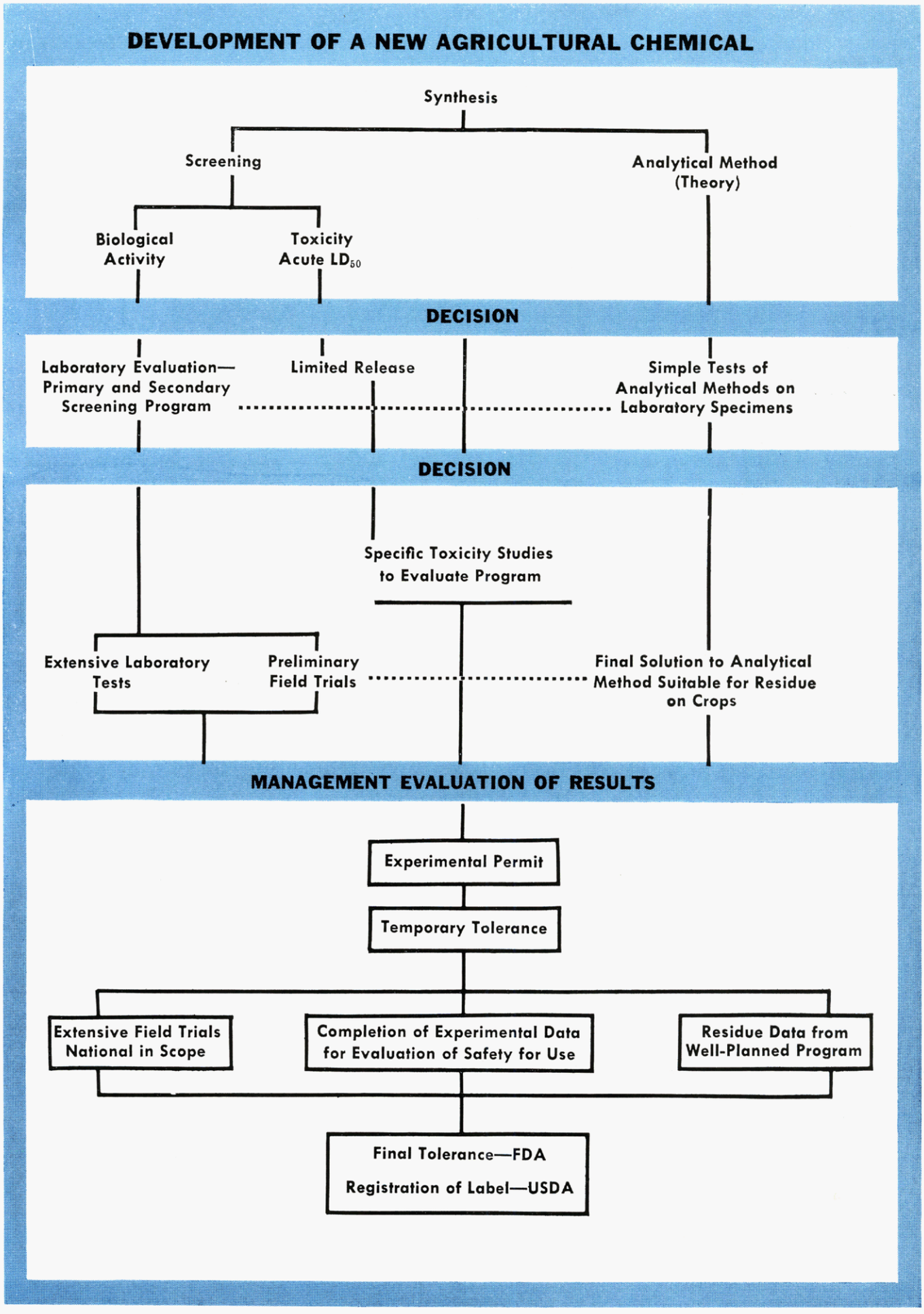
DEVELOPMENT OF A NEW AGRICULTURAL CHEMICAL
Synthesis
Screening
Analytical Method (Theory)
Biological Activity
Toxicity Acute LD_{50}
DECISION
Laboratory Evaluation—Primary and Secondary Screening Program
Limited Release
Simple Tests of Analytical Methods on Laboratory Specimens
DECISION
Specific Toxicity Studies to Evaluate Program
Extensive Laboratory Tests
Preliminary Field Trials
Final Solution to Analytical Method Suitable for Residue on Crops
MANAGEMENT EVALUATION OF RESULTS
Experimental Permit
Temporary Tolerance
Extensive Field Trials National in Scope
Completion of Experimental Data for Evaluation of Safety for Use
Residue Data from Well-Planned Program
Final Tolerance—FDA
Registration of Label—USDA

same considerations apply. The rate of uptake, rate of translocation within the plant, and site of possible concentration, are all vital data if the chemical is to be understood and properly utilized. Metabolism must be studied and metabolites identified and evaluated. These also are the responsibility of the chemist.

Soil fumigant chemicals including nematocides, pre- and post-emergence herbicides, and soil fungicides, must be studied to prove conclusively the questions of translocation, biological concentration, metabolism, and residues in the soil, as well as in food.

To summarize briefly, in order to develop economically a new organic compound which will adequately meet the government demands for safety to the general public, the organic chemist and biochemist must work together on the residue problem early in the development program. This will not only ensure greater financial success to the industry but will promote a better, safer future.

Literature Cited

(1) Decker, G. C., Advances in Chemistry Series, in press.
(2) Gunther, F. A. and Blinn, R. C., "Analysis of Insecticides and Acaricides," Interscience Publishers, New York, 1955.
(3) Hazleton, L. W., J. AGR. FOOD CHEM. 2, 452 (1954).

The Opinion on Residue

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PUBLIC LAW 518, popularly known as the Miller Bill, is an amendment to the Federal Food, Drug, and Cosmetic Act, which empowers the Department of Health, Education, and Welfare to establish tolerances or exemptions from the requirement of tolerances in or on raw agricultural commodities destined for shipment in interstate commerce. This law assigns to the U. S. Department of Agriculture two responsibilities. A certification of usefulness of each pesticide chemical for which a tolerance or exemption is sought and an opinion as to the amount of residue likely to result on specified commodities. These responsibilities have been delegated to the Pesticide Regulation Section, Plant Pest Control Branch, Agricultural Research Service.

In regard to the opinion on residue, Public Law 518 reads as follows: "The Secretary shall submit to the Secretary of Health, Education, and Welfare with any certification of usefulness under this subsection an opinion, based upon the data before him, whether the tolerance or exemption proposed by the petitioner reasonably reflects the amount of residue likely to result when the pesticide chemical is used in the manner proposed for the purpose for which certification is made."

The regulations of the Plant Pest Control Branch include the following statement: "If a tolerance proposed by the petitioner is reasonably to reflect the amount of residue likely to result when a pesticide chemical is used, it must be large enough to include all residue which is likely to result when the pesticide chemical is used in the manner proposed by the petitioner, but not larger than needed for this purpose."

The Food and Drug Administration's regulations for the enforcement of Public Law 518 makes the following reference to the opinion on residue: "The tolerance thereinafter established ordinarily will not exceed that figure which the Secretary of Agriculture states in his opinion reasonably reflects the amounts of residues likely to result."

Information and Data Required in Petitions

Certain information and data are required to be a part of petitions and are necessary before the development of an opinion can be undertaken. This information includes: (1) chemical identity of pesticide, (2) proposed tolerances or exemptions, (3) detailed directions for use of the pesticide, (4) adequate residue data, and (5) a complete description of the analytical method or methods which were employed in obtaining the data.

It should be emphasized at this point that USDA's evaluation of methods and residue data contained in the petition and data otherwise available is solely for the purpose of providing a sound basis for an opinion on residue. In the process of establishing safe tolerances the Food and Drug Administration must recognize factors in addition to those taken into account by USDA in fulfilling its responsibility under the law.

The various types of methods commonly employed in obtaining residue data include biological assay, radioisotope, enzymatic, and chemical methods. The nature of the problem is such that sometimes results by two independent methods may be required. The chief advantages of biological assay and radioisotope methods lie in their sensitivity and relative freedom from interferences. A criticism is their lack of specificity. A number of specific and sensitive colorimetric and spectrophotometric methods have been developed for various pesticides which include insecticides, fungicides, herbicides, and certain antibiotics. Enzymatic methods have been developed and used to determine residues of organic phosphate insecticides or their metabolites. Examples of this type are those based upon the inhibition of acetylcholinesterases by these insecticides.

For a proper evaluation of a residue method, it is necessary to examine data from experiments specifically designed to establish the sensitivity, precision, and accuracy in the application to a particular substrate.

A meaningful way in which the sensitivity may be expressed is in terms of parts per million of sample, units generally employed for stating tolerances. It has been suggested that the sensitivity be stated as the smallest quantity of material that will give a detectable reading for some property such as light absorbance or transmittance, pH, or volume of titrating solution over and above that noted in a control or blank experiment in a total of nine out of 10 experiments. This would appear to be a precise expression of sensitivity.

Precision, of course, refers to the reproducibility of a method or a determination. Poor reproducibility with a method may be due to inherent weaknesses in the method, unusual variation in the composition of control samples, or to losses of the material sought in various steps of the analytical procedure—to mention a few causes.

Accuracy means the extent to which a given quantity of material can be