Development of Insecticidal Chemicals

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Chemicals employed for insect control have been obtained from three sources—inorganic materials, botanicals, and organic synthesis. There is no proof of what material was first used to kill insects. The Chinese are said to have discovered the insecticidal property of rotenone. The Romans divided poisons into three groups—animal, plant, and mineral—and it can be assumed that some of them were used to poison insects. Recommendations for the use of arsenicals as insecticides date from 1681, and tobacco and its chief alkaloid, nicotine, have been used as insecticides since 1690.

Of the synthetic organic insecticides, it is probable that carbon disulfide, made by the direct combination of carbon and sulfur, was the first such product. It is one of the simplest organic compounds and has been used as a fumigant for more than 100 years. Other early synthetic organic insecticides include paradichlorobenzene and chloropicrin.

The discovery of the insecticidal value of these early materials probably resulted from knowledge of their poisonous effect on higher animals or observation that insects were repelled by them. The information thus obtained was handed down from generation to generation, each adding knowledge gathered during its life. Thus, at the beginning of the 20th century we had a number of inorganic insecticides, including arsenic, antimony, selenium, boron, fluorine, sulfur, and mercury compounds; a few botanical insecticides, of which nicotine and pyrethrum were the best known; and a still more limited number of synthetic organic insecticides.

Roark (1) tells us that new insecticides are developed in two ways. "The first is by determining the structure of the active principles of plants recognized as toxic to insects. Then the principles or other compounds closely related to them are synthesized. The second is by testing compounds of known structure and unknown toxicity upon several species of insects and selecting the ones which are effective. The first method starts with a material of known toxicity but unknown structure. The second starts with a compound of known structure but unknown toxic value."

An example of the first method is the synthesis of allethrin. For more than 30 years chemists studied pyrethrum flowers, attempting to isolate and identify the insecticidally active principles. In 1924 two Swiss chemists, H. Staudinger and L. Ruzicka (2), announced that two compounds, which they called pyrethrin I and pyrethrin II, were responsible for the insecticidal activity of pyrethrum flowers. The chemical structures of these two compounds were described, as were unsuccessful attempts to synthesize them. Between 1934 and 1947, F. B. LaForge and associates (3)(4)(5) of the U. S. Department of Agriculture discovered two additional insecticidally active esters in pyrethrum flowers, which they named cinerin I and cinerin II. Cinerin I, being the simplest of these four compounds, was taken as a pattern for synthesis of the related compounds. One of them, the allyl homolog of cinerin I, was found to be insecticidally active. The name "allethrin" was coined for this material, and it is now being manufactured on a large scale for use in aerosol bombs.

The second method for developing insecticides, that of testing compounds of a known structure, is more of an empirical process. Some chemical manufacturers submit samples of all products made in their plant or chemical research laboratories to entomological screening laboratories to determine whether or not they are insecticidal. Phenothiazine is one insecticide developed by this process. It was first tested against mosquito larvae and found toxic. Subsequent tests showed it to be highly toxic to a number of agricultural pests, including the codling moth. Today it is used extensively to control intestinal worms in animals. The chlorinated hydrocarbon insecticides DDT and BHC and the organic phosphorus insecticides were developed in the same manner.

The steps in the development of a new insecticide are well defined. First, the chemical must be synthesized in the laboratory. It may be the product of the intense study of a botanical with the ultimate synthesis of a principal part, it may be one of a series of related chemicals, or it may be a byproduct of a chemical process. It is then sent to the screening laboratory, where it is tested against a number of insects and against insects in several stages of development.

If the chemical is found to be insecticidal, and about 1 in 30 are, it is taken to the entomological laboratory for further tests. Here the compound is compared as precisely as possible with available standards. In addition, its stability and compatibility and various formulations may be investigated. On an average 1 in 10 compounds taken to this stage succeed.

Following the laboratory tests chemicals are usually passed to a toxicologist, who gives them an initial appraisal for acute oral toxicity, irritation, and vapor hazard. Initial field tests are also warranted at this stage. They are usually made on small plots in which the chemical in three or more formulations and at several concentrations is compared with a standard insecticide. Not more than 1 of 3 candidate materials is successful in these tests.

For materials found effective in the initial field tests patent applications are usually made. The toxicological tests are extended to cover the chronic hazards (usually 2-year feeding tests.) Additional chemical work to develop methods for assay of formulations and analysis of spray residues is also required. Large-scale experiments are set up in several geographical areas to test the material on all insects for which it has shown insecticidal value. The field experiments are usually continued for at least two years. Analyses are made of treated crops to determine the presence of the compound within edible portions. The data on toxicology and residue analyses are used by the Food and Drug Administration of the U. S. Department of Health Education and Welfare to establish tolerances of insecticide residues which may be permitted in food products without deleterious effects upon the consumer.

During this period of study of the insecticidal properties of the material, there is a parallel study of manufacturing processes. The product that was first prepared in small laboratory equipment is next made in larger batches in large laboratory equipment. The process is next moved to the pilot-plant stage, and finally, if successful, to plant manufacture and processing.

Wellman (6) has estimated the cost of marketing a new agricultural chemical as between 1 and 2 million dollars, as shown below.

Costs Chargeable Against a Successful Agricultural Chemical

Synthesis	$ 150
Initial screening	200
	350
1 in 30 succeed	X 30
	10,500
Further laboratory and greenhouse work	1,000
	11,500
1 in 10 succeed	X 10
	115,000
Initial field tests	900
	115,900
1 in 3 succeed	X 3
	347,700
Company development	250,000
	597,700
1 in 2 succeed	X 2
	1,195,400
Company liaison with Experiment Station	37,500
	1,232,900
Cost of State and Federal work	150,000
Total research and development cost of successful chemical	$1,382,900

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