INSECTICIDE DEVELOPMENT WORLDWIDE

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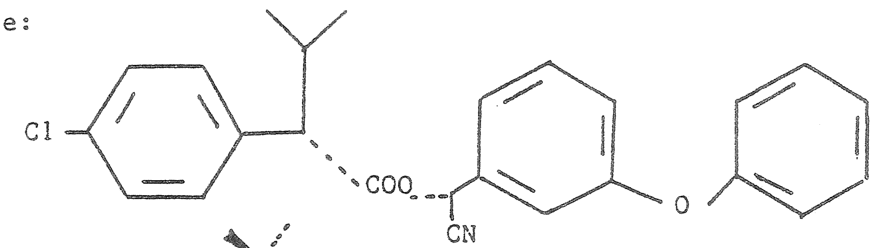
In many areas of the world, a primary limiting factor in agricultural production is insect pests. Further economic hardship in many of the countries are imposed by insect pests vectoring serious human diseases such as malaria, sleeping sickness and typhus. For many years insect control in most countries was the domain of a group of insecticides called organochlorines. Classified as the first generation insecticides because they represented the first group of organic hydrocarbons synthesized specifically for use as an insecticide, the success of the organochlorines was due mainly to one product - DDT. In many countries DDT was synonymous for many years with insect control. Later advances in organic insecticide synthesis saw the introduction of two groups of insecticides known as the organophosphates and the carbamates. Known as the second generation insecticides the organophosphates and carbamates are the most commonly used insecticide throughout the world. Malathion, parathion and dimethoate are some of the best known of the OP's with carbaryl, carbofuran and methomyl popular carbamates.

During the 1970's a new group of insecticides was discovered that were absent of problems of bioaccumulation in the food chain seen with some organochlorines or problems of high mammalian toxicity associated with many of the second generation insecticides. This group of insecticides were known as the third generation insecticides and were referred to as the synthetic pyrethroids. The basis of their activity as an inseticide was noted in the ancient knowledge of the insecticidal properties of the monocarboxylic acid ester called pyrethrum, that is derived from the chrysanthemum flower. The discovery of light-stable synthetic analogues of pyrethrum made use in agriculture possible.

A unique property of the pyrethroids is the varying insecticidal properties of the differing stero isomers produced during its synthesis. The number of possible isomers varies depending on the number of rotational bonds within the pyrethroid molecule (Figure 1). Synthetic pyrethroids with the cyclopropane ring of chrysanthemic acid have 2 chiral centers which generally result in 4 stereo isomers. Substitution of a hydrogen atom of the benzyl methylene group of the phenoxybenzyl with a cyano group forms another chiral center and another 4 possible isomers. The 4 major pyrethroids registered in Canada either have 2 or 4 chiral centers resulting in the formation of 4 or 8 stereo isomers (Table 1). Advances in the production of synthetic pyrethroids have enabled the isolation of the most active isomer in some formulations.

FIGURE 1. The stereochemical structure of fenvalerate and deltamethrin.

Fenvalerate:



Deltamethrin:

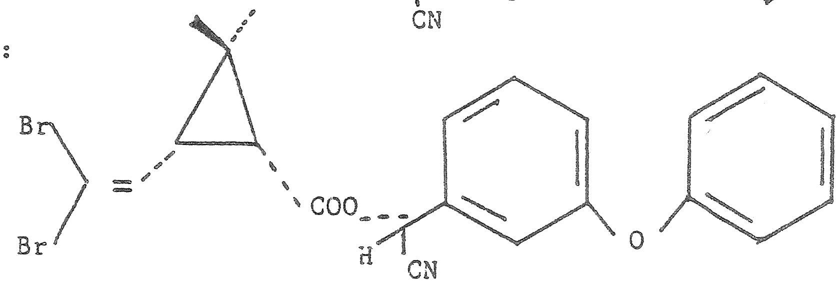


TABLE 1. The number of possible isomers of the agricultural pyrethroids in Canada.

CHEMICAL NAME	NUMBER OF POSSIBLE ISOMERS
Permethrin	4
Cypermethrin	8
Fenvalerate	4
Deltamethrin	8

When applied to control insect pests, synthetic pyrethroids like pyrethrum provide fast contact kill. They are not translocated to any significant extent. The translocation that does occur is metabolites of the degraded acidic portion of the molecule. Use of pyrethroids improves the safety to the farmer because of their low mammalian toxicity. Pyrethroids have been shown to be rapidly metabolized and excretued when fed to rodents. The importance of safety is of increasing concern in many countries, where the major method of application often is still the single nozzle backpack sprayer. Another concern of increasing importance, that of pesticide residues in food and the environment, are also lessened by pyrethroids. In most environments pyrethroids are hydrolyzed by soil micro-organisms or plants. Applied to metabolically active food crops, pyrethroids become only marginally detectable within 10 days. This reduces the minimum days to harvest, allowing safe control of many insect pests late in the crops development. Besides the nature of the product, a major reason for the positive attributes of pyrethroids is their low rate of product used (Table 2). No longer do rates have to be expressed in kg/ha, as for the 1-2 kg/ha recommended rate for DDT, but instead in g/ha.

TABLE 2. Recommended rates of application for insecticides in each insecticide group.

INSECTICIDES		PRACTICAL APPLICATION RATES (g/ha of active ingredient)
Organochlorines	DDT	1000 - 2000
Organophosphates	Parathion	250 - 800
Carbamates	Carbaryl	750 - 1500
Pyrethroids	Permethrin	60 - 250
	Fenvalerate	50 - 200
	Cypermethrin	30 - 150
	Deltamethrin	5 - 20

The use of synthetic pyrethroids has increased rapidly since its inception in the marketplace in 1976. From its start in Central America, use has spread to nearly all major agricultural regions of the world (Figure 2). In countries where significant marketing of pyrethroids began in 1980, there is projected to be a near doubling in use within 5 years (Figure 3). If so-called new countries are included - countries where pyrethroid use had or is expected to commence after 1980, the increase is predicted to be even more significant. Projected worldwide growth of pyrethroids is expected to continue in not only acres treated, but also market share from 12% in 1981 to 22.5% in 1985 (Figure 4). In some countries, growth in total market share of insecticides has proceeded even quicker - particularly in countries where residue and human health concerns dominate. For example, market growth of pyrethroids in the United States reached 50% by 5 years after its introduction in 1976.

FIGURE 2. Estimated agricultural use of pyrethroids worldwide excluding Japan and China.

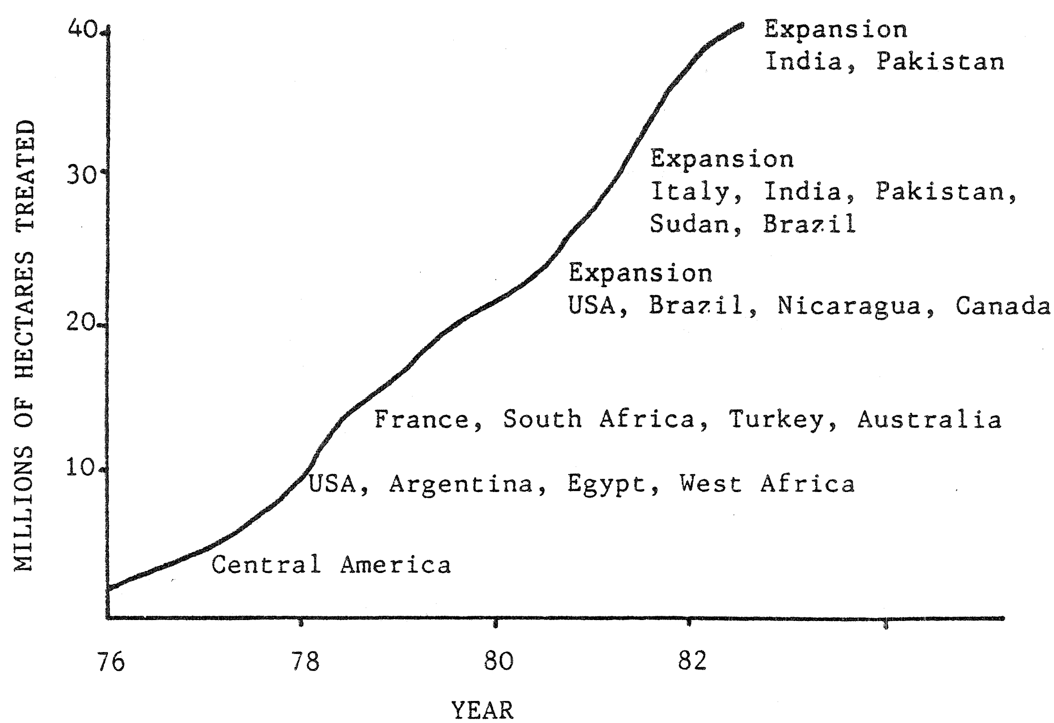


FIGURE 3. Forecast of pyrethroid use in agriculture for 1981-85

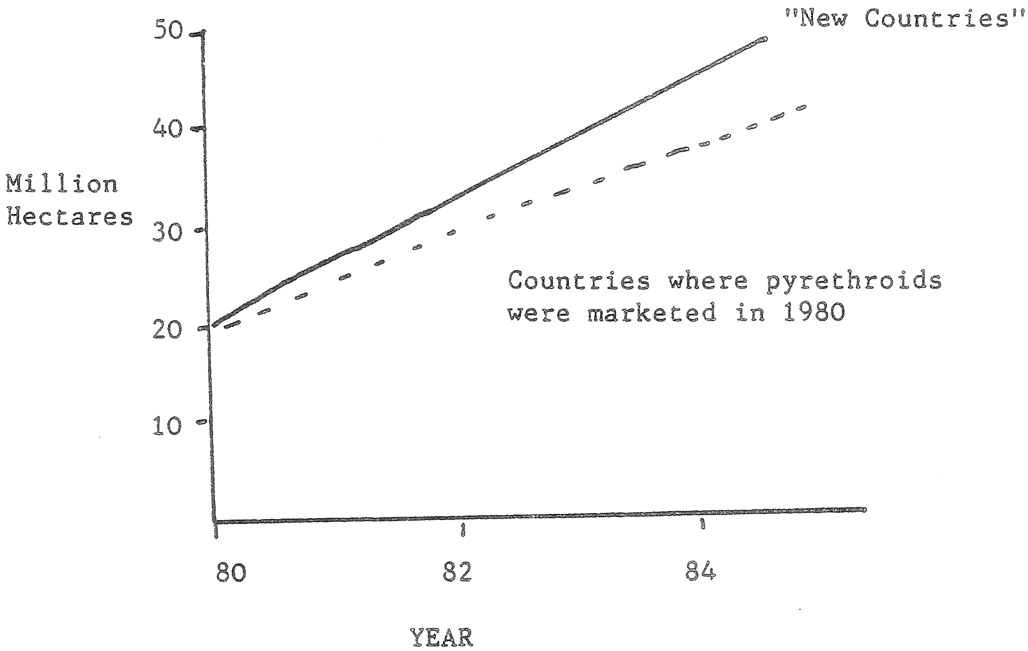
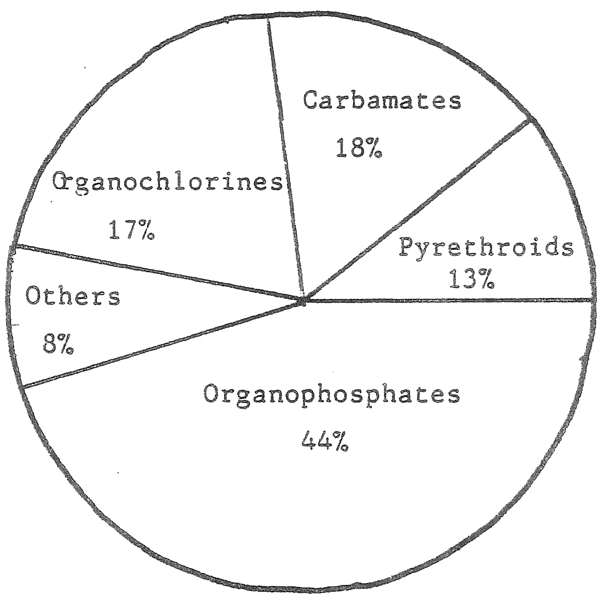
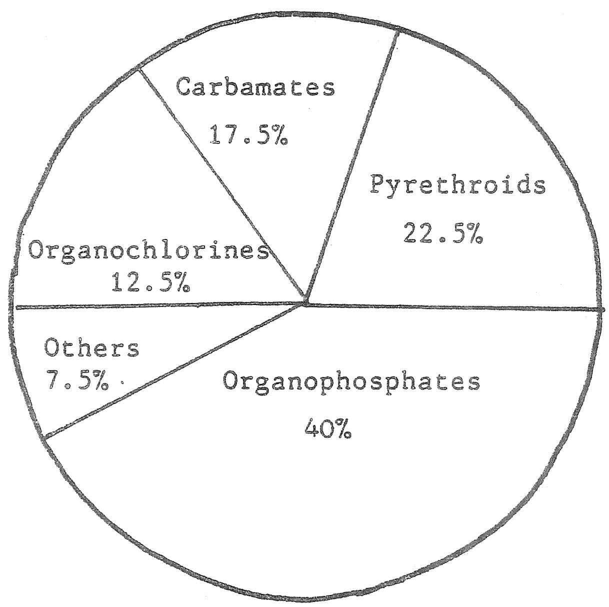


FIGURE 4. Projected change in insecticide use worldwide from 1981 to 1985.



1981 - 220 Million Ha



1985 - 245 Million Ha

Expansion of synthetic pyrethorids in nearly all major markets is reflective of their excellent activity against most serious insect pests. Pyrethroids have a broad spectrum of activity and are particularly effective against lepidopterous, coleopterous and most heteropterous insect pests.

Although synthetic pyrethroids represent the major change in insecticide use worldwide in recent years, further developments in effective bioinsecticides have been made in a number of countries. Strains of the commonly used bacterium Bacillus thuriengensis have been produced for control of specific insect pests. One strain, which has been registered for use in Canada, called B.t. israelenis has proven to be effective against Simulium sp. larvae. Similar to this has been the development of formulations of specific insect diseases. Most noteworthy of these are formulations of nuclear polyhedrosis viruses for use against specific insect pest species in forestry. Insects treated with the virus typically die late in their larval development. Their applicability in high value agricultural crops is less than that for forestry since damage to the crop can occur during the time from host infection to death. In Canada, recent registrations were granted for nuclear polyhedrosis viruses against the Douglas fir trussock moth and the red-headed sawfly.

INSECTICIDE DEVELOPMENT IN CANADA

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The development of insecticides in Canada has become increasingly difficult due to the weight of escalating costs of registration on small market size and price competitiveness of existing products. Recent changes in registration have made this problem more acute, as Canada has the distinction of being the most difficult country in which to register pesticides. This has placed greater emphasis on pursuing insecticides of maximum possible market penetration.

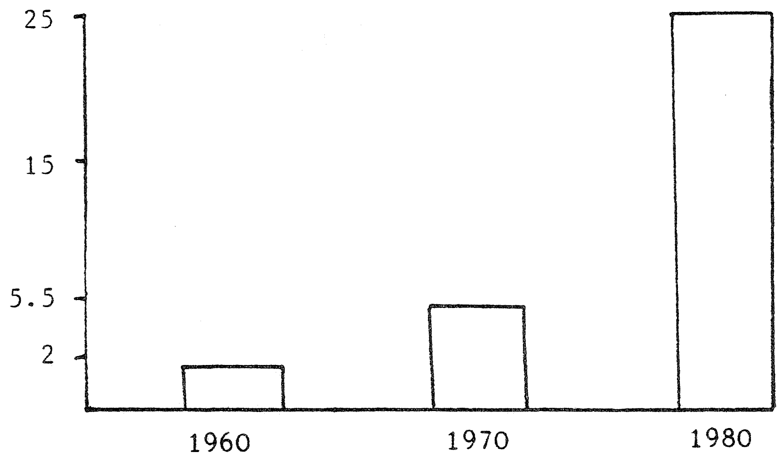
In Canada, the requirements for the registration submission of a pesticide are divided into 8 major parts (Table 1). Residue, environmental, and efficacy tests have to be done in Canada with tests in the other categories accepted if they meet registration guidelines. These other studies generally are done in laboratories located at the company's parent plant. In Canada specific studies on toxicological and environmental concerns are also required. For insecticides, these studies extend into concerns associated with application. Registration for aerial application for example has to include studies on potential environmental effects of pesticide drift. These added studies reflect the increasing impact of environmental tests on registration--a product of Canada's large and diverse geography. Delays imposed by these additional studies have had a greater effect on insecticides, as many important pest markets rely solely on aerial application; i.e., Bertha armyworm in rapeseed.

Table 1. Data required for a pesticide submission.

1. Label
2. Product Chemistry
3. Toxicology
4. Metabolism Studies
5. Food, Feed and Tobacco Residue Studies
6. Environmental Chemistry
7. Environmental Toxicology
8. Efficacy

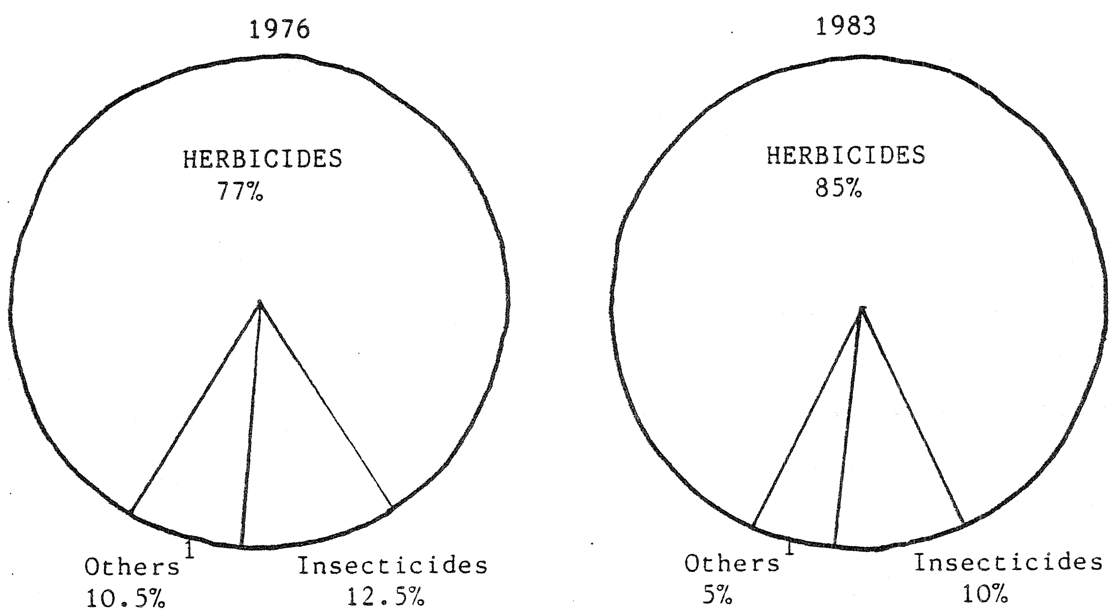
Fulfilling all registration requirements in Canada has become a very expensive undertaking. High rates of inflation in recent years, coupled with the proliferation of registration studies, has increased the costs of developing an insecticide to 25 million dollars (Graph 1). With insecticides occupying a decreasing share of the pesticide market--10% in 1982 and dropping due to the expansion in herbicide use (Graph 2), and registrations of new compounds since 1980 being limited to agriculture, the pursuance in Canada of new insecticides is becoming increasingly difficult (Table 2).

GRAPH 1. Increasing costs of insecticide registration from 1960 to 1980[1].



[1] Production plant design and construction costs excluded.

GRAPH 2. Relative percentage of pesticide market share of pest control products in 1976 and 1983.



[1] Others refer mainly to fungicides, rodenticides, and mollusicides.

TABLE 2. Number of new insecticide registrations in Canada from 1961 - 1983[1]

YEARS	NUMBER OF INSECTICIDES REGISTERED
1961 - 1965	24
1966 - 1970	21
1971 - 1975	14
1976 - 1980	15
1981 - 1983	3

[1] From Agriculture Canada Plant Products and Quarantine Directorate and Scientific Information Retrival Section

Faced with these problems, added importance is placed on the suitability of the product to be used in as many markets as possible. With rising costs, the development of a product for 1 market has become outdated. To be suitable for use in many markets requires a product with a broad spectrum of activity. At the pest management level, this places more emphasis on selectivity in time of application rather than selectivity in product of application.

In order to be successful in achieving maximum market use, an extensive efficacy and residue program in Canada is critical. Since the development of new insecticides are not done with Canada in mind but for use in crops such as cotton and tobacco, new insecticides tested in Canada often already are registered in other countries. Determinations of potentially Canadian markets is made easier by equating market similarities. Also, much of the time-consuming toxicological studies have been completed, leaving mostly environmental, residue and efficacy studies to do. Identifying and coordinating the studies needed is then needed to minimize the time lag between initial testing and registration. In Canada at least two years of testing at source sites are required for which rates, methods and times of application have been established and performance has been consistent. As a result, the benefits of an effective efficacy program on the success of an insecticide in the marketplace can be categorized in three ways:

A) Widespread testing determines market potential.

Success in many areas of pest control open the possibility of not only maximum use, but also of more competitive pricing. An establishing of a wide use pattern improves a product's acceptance at the distributor level. Inventory concerns are lessened and market stability is increased through reduced reliance on periodic pest outbreaks. An expanded label opens greater opportunities through price competitiveness. In the area of pest control, insecticides are one of the most affordable of all control measures. Being able to price competitively with older established products is easier if its potential in important markets such as grass-hopper or flea beetle control are known.

B) Rapid and orderly testing hastens product introduction into the marketplace.

Years "lost" in research can quickly make a product unprofitable. In Canada, multi-million dollar investments in the pesticide market are tied to 17 year marketing patents. The beginning of the patent life usually coincides with the initiation of widespread insecticide testing. Coordinating testing at the government and industry levels is important in hastening the product introduction, since, despite a wide diversity in market testing, only 1 or 2 research personnel conduct tests in specific markets.

C) Thorough testing can extend market duration.

In many crops, programs have been established in which a number of insecticides are recommended at different times for different pests. Determining where the product is most suitable in that program can reduce potential problems such as pesticide resistance. Although this is not a primary concern in most of the larger markets, localized markets such as the Colorado potato beetle in Quebec and the tentiform leaf miner in Ontario have been lost due to continued use of a single product line.

In conclusion, the inherent problems of small market size in Canada and added registration requirements and costs of development can best be overcome through efficient, widespread testing of the insecticide to quickly determine its maximum market suitability. Since most insecticides developed in Canada already have a defined control spectrum in other countries, preliminary evaluations of its possible Canadian use patterns can be made. Efficient efficacy testing can then improve the product's chances of success by maximizing market determination, speeding market introduction, and assuring proper product incorporation into the marketplace to enhance market duration.