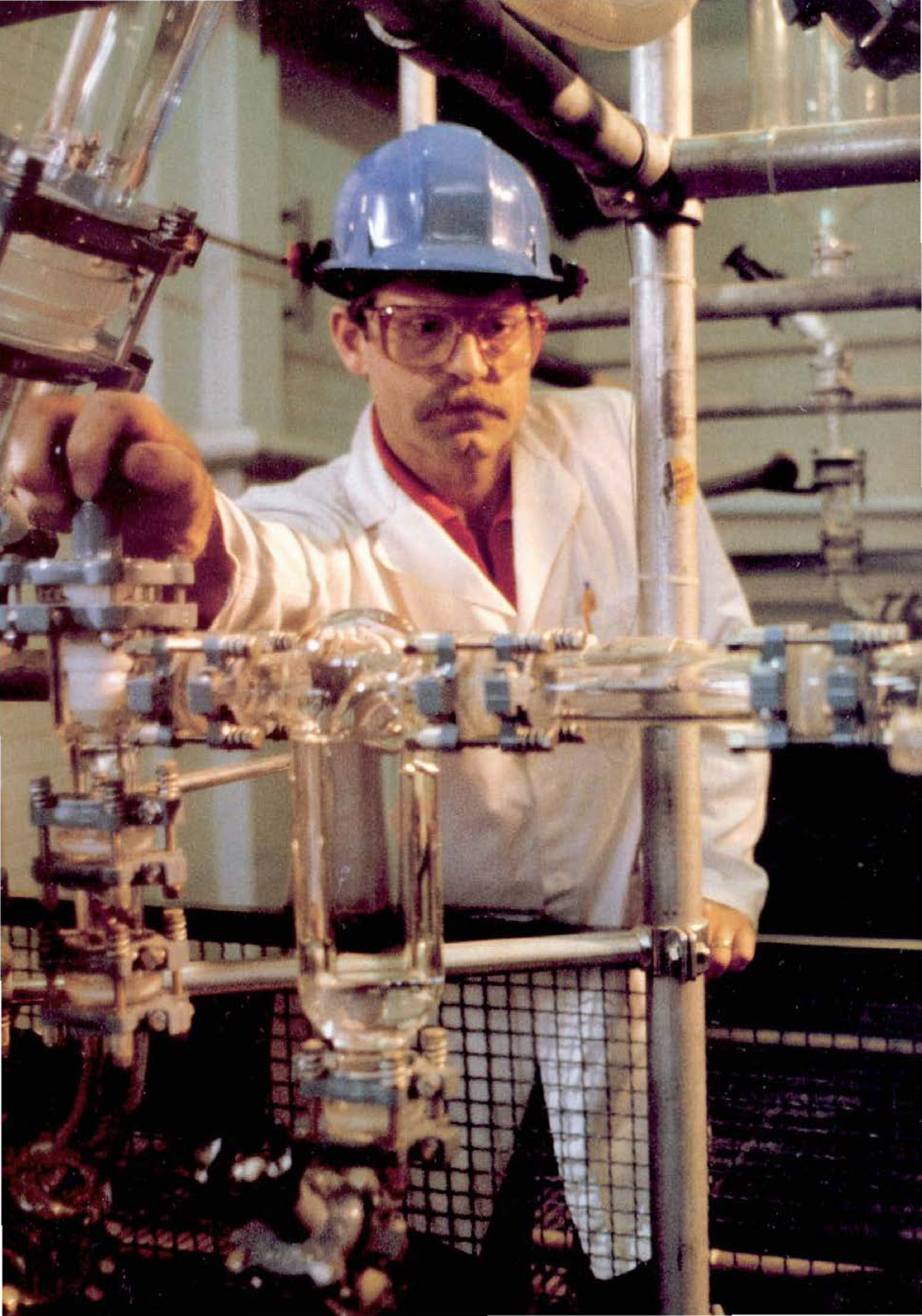

THE DUNLENA PROJECT

Environmentally friendly agrichemicals

Like it or not, the economic truth is that Australia could not support the standard of living — in particular, the choice of foods and the quality of nutrition—to which it has become accustomed without agricultural chemicals. Many of our most economically important plant and animal species are affected by pests, diseases and weeds; without chemical control of their depredations, crop losses would, according to some estimates, increase by as much as 50%.

The concept of organic farming is attractive, but it cannot be applied on a large enough scale to feed the world's rapidly growing population. Almost half the agrichemicals sold today are employed to protect the world's staple foods: wheat, barley, rice and similar grains.

On the other hand, our need for agrichemicals — a $20 billion a year industry around the world – stems to a great extent from the promotion of monocultural farming, which in turn has promoted the spread of particular pests, weeds and diseases. And there is no doubt that, in many instances, too many agrichemicals have been applied with too little discrimination, leaving dangerous residues in the very foodstuffs they were meant to protect.

Persistence (the tendency of many agrichemicals to remain, still active, in soil or water) and resistance (which, ironically, is a consequence of chemicals doing their jobs, initially destroying large numbers of susceptible pests but through natural selection allowing less-susceptible individuals to survive and breed, eventually rendering chemical controls ineffective) are the greatest problems associated with the thousand-odd pesticides and hundreds of herbicides presently used in agriculture.

Researchers involved in designing and testing new agrichemicals now have to work within severe scientific, environmental and social limits: their products must be effective, yet they must not persist in soil or water, must not place non-target species at risk and must leave either no residues in food or residues that are below internationally agreed levels.

There is also an ethical element involved in the production of new

by Carson Creagh

agrichemicals: many hazardous, older-style herbicides and pesticides are still in use, primarily in the Third World, so researchers are seeking to replace these with effective yet environmentally friendly agrichemicals that can be manufactured and marketed at competitive prices.

'Traditional' ways of synthesising and releasing agrichemicals involved either producing analogues of chemicals with known pest-killing activity, or conducting almost a parody of the heuristic technique of trial-and-error. In the latter case, using random screening methods, scientists tested a range of chemicals for potential pesticide application before they found a specific use — rather like medical researchers developing a cure, then looking for a disease it would fit. For example, DDT — dichloro-diphenyl trichloroethane — was identified during random screening for insecticidal properties in a program to develop new dyes.

Approaches began to change in the 1960s and 1970s, with the synthesis of isosteres (molecules of similar size and shape) of DDT, which was being withdrawn from widespread use partly because many pests had become resistant to it, but primarily because of its persistence and harmful side-effects.

However, the way in which DDT killed pests (the wedge shape of the molecule interferes with an insect's nerve function, exhausting and eventually destroying nerves and, ultimately, the whole nervous system) was of immense value.

Researchers developed hundreds of DDT isosteres based on a similar-shaped molecule, pyrethrin-1, the most potent of the natural insecticidal esters isolated from Chrysanthemum flowers. Pyrethroids, as the synthetic compounds are called, are among the most active insecticides known: in the case of deltamethrin, for example, synthetic modification of the active parts of the pyrethrin-1 molecule has led to a thousandfold increase in toxicity to houseflies.

Unfortunately, while pyrethroids are immensely powerful insecticides they are also highly toxic to fish and aquatic invertebrates, so researchers began looking for ways to modify pyrethroids to reduce their toxicity. Scientist Dr George Holan, of what was then the CSIRO Division of Applied Organic Chemistry, noticed that an essential part of the pyrethroid structure—a cyclopropane ring—was duplicated in some of the DDT isosteres with which he had been working. He reasoned that the similarity of structure implied a similar mode of action and, after several years of research with colleagues David O'Keefe, Reimund Walser and Chris Virgona, he combined parts of the DDT isostere and the pyrethroid to create an insecticide with increased stability, greater potency and enhanced biodegradability.

One of the results of those experiments was cycloprothrin, which does not work in the same way as DDT does in the laboratory, but which is no less effective in the field. In some insect pests — for example the sheep blowfly — in addition to its insecticidal activity cycloprothrin also paralyses the female's ovipositor and prevents egg-laying.

Even more significantly, cycloprothrin exhibits zero toxicity in mammals and fish. This is of particular importance in Asia, where fish raised in rice paddies form a major protein source — and where organophos-phates and conventional pyrethroid insecticides kill fish as well as insect pests.

In contrast, cycloprothrin is so safe that it has been approved for use in the rice fields of Japan (where the government bans the use of any persistent or fish-toxic insecticide) and is being marketed throughout Asia by Nippon Kayaku, following a licensing agreement with CSIRO in 1978.

The rational approach to agrichemical design pioneered by Dr Holan has evolved further; today, researchers tend to examine the biology of plant and insect pests and, through knowledge of their anatomy and physiology, gain a better appreciation of which kinds of chemicals are most likely to be effective.

The 'traditional' technique of random screening resulted in five to ten active chemicals from every 10 000 compounds tested. The rational method, which can be applied to herbicides and fungicides as well as pesticides, means far fewer compounds need to be tested, since biological activity can be monitored resulting in fewer false starts and less 'wastage' of research facilities and funds. During the 1960s and 1970s, 20–25 new agrichemicals were introduced onto the market each year, but rising development costs and a decline in the number of new active compounds discovered by random screen-ing have seen this number drop to between five and ten new agrichemicals a year.

The cost of development is an important consideration: the synthesis, formulation and commercial production of agrichemi-cals takes up to eight years, costs at least $40 million per individual product and involves close cooperation between entomologists, toxicologists, chemists, market analysts, economists, engineers, field development teams, government regulatory authorities, lawyers and marketing personnel.

In the late 1980s, the high costs and equally high potential profits of agrichemical development led the former Division of Applied Organic Chemistry, through the initiative of then Chief, Dr Dave Solomon, to establish a joint-venture firm called Dunlena Pty Ltd. Du Pont Australia, of the international chemical conglomerate E I du Pont de Nemours & Company, has a 49% share in Dunlena.

Through the technology transfer company Sirotech Ltd, CSIRO owns 35% of the shares, while the remaining 16% is held by Australian financial institutions including the Australian Industry Development Corporation.

Dunlena intends to stimulate an agrichemical manufacturing industry in Australia, working with Australian firms to perform product-development work for low-volume, high-quality biologically active compounds destined for local use and for export to the world market. The joint venture calls for CSIRO to conduct initial studies, with Du Pont handling field and laboratory testing in consultation with CSIRO's 'fine chemicals' program. Du Pont provides Dunlena with world-wide marketing and development expertise, and helps organise manufacturing in Australia and overseas.

The CSIRO contribution to Dunlena is based at the its laboratories in Clayton, Melbourne, which also permit scaling-up of experimental work well beyond the level previously available in Australian research efforts. The fine chemicals program, managed by Dr Greg Simpson, also uses computer facilities to 'model' molecules on-screen to test their size, structure and other properties, ensuring that the only compounds to be synthesised are those likely to be biologically active. Once a compound's biological activity has been identified, Dunlena chemists establish its 'process chemistry'—the manufacturing processes and development costs for patentable groups of chemicals — and prepare samples for field trials. Secondary and tertiary screening trials confirm and quantify each compound's potential market niche, then a provisional patent application is filed. It's a painstaking process, but Dunlena expects that its products—a number of selective herbicides are currently undergoing field trials—will generate sales worth $150 million a year to Australia, providing significant export earnings as well as making a range of low-toxicity, environmentally friendly chemicals available to Australian agriculture.

More about the topic

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A quest for selective toxicity in the synthesis of insecticides. G. Holan. *Chemistry in Australia*, 1984, **51**, 185–90.

Further information on Dunlena Pty Ltd is available from Dr Greg Simpson, Fine Chemicals Program, CSIRO Division of Chemicals and Polymers, Private Bag 10, Clayton, Vic. 3168, phone (03) 542 2519.