The history of the pyrethroid insecticides

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The synthetic pyrethroid insecticides were developed at Rothamsted Research, which receives strategic funding from BBSRC, in the 1960s and 1970s. Today they account for around one sixth of global insecticide sales[1], and global annual sales of pyrethorids exceed US$1.4Bn. They are also used to impregnate bed nets, which help to reduce the spread of malaria as part of the World Health Organisation's Global Malaria Programme.

The science of pyrethroids

Natural pyrethrins are derived from Chrysanthemums, the same genus as common daisies, and are an important component of plant defences against insect pests. For thousands of years they have been extracted and used to combat insect pests. However, the natural pyrethrins are not particularly effective when used on fields of crops as th y are quite unstable, breaking down quickly when exposed to sunlight.

To overcome their limitations, scientists developed synthetic compounds, called pyrethroid insecticides, based on the chemistry of the natural pyrethrins. Both work by targeting sodium channels in the cell membranes of insect nervous systems. By locking these channels open, the pyrethroids block normal nerve impulses, paralysing the insect and ultimately killing it[1].

The development of the synthetic pyrethroids at Rothamsted was led by Michael Elliott. Elliott joined the institute in 1948 to investigate the link between molecular structure and biological activity in the natural pyrethrins. He used this knowledge to create the synthetic pyrethroids. Elliott won numerous awards over the course of his career, and received a CBE in 1982.

Compared to natural pyrethrins, the synthetic pyrethroids are more stable in direct sunlight. They are also signifi antly more effective against a wider range of insects, so farmers need to apply less insecticide to their crops. This also means pyrethroids are less likely to build up to dangerous levels in the environment[2].

However, pyrethroids can harm some beneficial insects such as bees or the parasitic wasps that prey on pests, and they are also toxic to fish and other aquatic organisms. Because humans possess enzymes that quickly break down pyrethroid insecticides, the pyrethroids are only toxic to people in large quantities or over long periods of time[3].

Early landmarks in the discovery of the synthetic pyrethroids

- Pyrethrin insecticides from pyrethrum daisies (Chrysanthemum cinerariaefolium) have been used in various forms for thousands of years. They were originally discovered in China and imported into Europe as 'Persian powder'.
- Hermann Staudinger and Lavoslav Ružička published a definiti e study on the structure of natural pyrethrins in 1924[4].
- Pest control research at Rothamsted began before the Second World War when other pest control options often relied on arsenic or cyanide. Work on plant breeding near Rothamsted in the 1920s supported the establishment of the pyrethrum industry in Kenya.

1940

1949
The first ynthetic pyrethroids, allethrin and bioallethrin, are developed in America by Milton S. Schechter and colleagues[5,6]. They are around twenty times more effective at killing insects than DDT without the serious environmental or health impacts[7].

1960

1962
In the UK, Michael Elliott creates resmethrin, a 'first gene ation' synthetic pyrethroid, by altering the molecular structure of naturally-occurring pyrethrin. At the time such structure-activity studies were not common practice.

Resmethrin, named in honour of the Rothamsted Experimental Station in Harpenden, UK, where the discovery was made, is much more effective against houseflies than natu al pyrethrins. However, it is still unstable in sunlight and unsuitable for use outdoors[8].

1967
Elliott produces another first gene ation pyrethroid, bioresmethrin, by isolating one of the active compounds from resmethrin.

Bioresmethrin is a single isomer of resmethrin, which exists as a mixture of four different isomers, i.e. compounds with identical molecular formulas but with different shapes. At the time, other compounds with several isomers were produced as a mixture, but the agro-chemical companies, working alongside Rothamsted scientists, were able to manufacture just the bioresmethrin isomer[8].

Late 1960s
The first gene ation synthetic pyrethroids are supported and commercially exploited by the National Research Development Corporation (NRDC), a group established by HM Treasury to commercialise the outputs of UK research, and its successor, the British Technology Group. An initial licensing deal is agreed by NRDC with six companies (Mitchell Cotts, the Wellcome Foundation, Roussel Uclaf, Sumitomo, FMC and Penick) interested in manufacturing and selling pyrethroids[9].

1970

1972
Michael Elliott develops permethrin, the first field- able pyrethroid. It is much more suitable for use in agricultural settings as it does not break down so quickly in sunlight[2]. The development of permethrin leads to a second round of licensing deals with the agro-chemical industry.

1972
DDT is banned in the US following growing concerns about bioaccumulation and its persistence in the environment. Because they break down in sunlight, pyrethroids do not accumulate in the same way.

1976
Japanese chemical company Sumitomo independently discovers fenvalerate. Elliott becomes aware of the development of the work through his colleague Professor Izuru Yamamoto in Japan and through the patents filed y the company. He realises he can build on their success in his own work.

The results are two new pyrethroids, cypermethrin and deltamethrin, the latter in particular is an extremely potent insecticide[8].

1980

1980s
Professor Chris Curtis at the London School of Hygiene and Tropical Medicine begins to investigate the potential of insecticide-treated bed nets to control malaria. He campaigns for aid agencies to distribute the nets for free to communities in affected regions to help reduce mosquito numbers and lifespan[10].

1983
Pyrethroids make up 25.1% of the global insecticide market and 33 million hectares of crops are treated with pyrethroids annually[11]. Pyrethroids developed by Elliott and colleagues at Rothamsted constitute two thirds of the global pyrethroid market[11].

1984
Michael Elliott retires from Rothamsted[11]. Around one quarter of the profits made by UK firm Mi chell Cotts this year are attributed to the sale of pyrethroid insecticides[13]. Mitchell Cotts were one of the original licencees for pyrethroids.

Late 1980s
The World Health Organisation (WHO) recommends using pyrethroids developed at Rothamsted, including deltamethrin and permethrin, for ITNs[14]. Pyrethroids are the only class of insecticides recommended for use in such nets due to their low toxicity to humans and other mammals. Their physical properties also mean manufacturers can easily incorporate pyrethroids into the fibre used to make bed nets.

1990

1991
An MRC-funded study shows that using insecticide-treated mosquito nets (ITNs) in a rural region of the Gambia can reduce the number of deaths of children under the age of fi e by around two-thirds[15]. The ITNs used in the study were treated with permethrin.

Early 1990s
Sales of synthetic pyrethroids reach US$1.2Bn per year[9].

1998
New long-lasting insecticidal nets (LLINs), which use pyrethroids such as cypermethrin, form one of four pillars to tackle malaria in the World Health Organisation's international Roll Back Malaria Programme[16,17].

2000

2002
Deltamethrin is the world's highest-selling pyrethroid with annual sales worth US$208M (around £132M)[18].

2004
BBSRC-funded researchers at Rothamsted, working with Australian colleagues, develop a product to overcome resistance to pyrethroid insecticides that is appearing in several insect crop pests. Their product first release an enzyme inhibitor to disable the insect's resistance mechanism. Several hours later it releases the insecticide, which kills the insect[19].

2007
Pyrethroids account for 17% of global insecticide sales[1]. Total global sales of insecticides are around $8Bn[20].

2009
A Cochrane Collaboration review of earlier trials confirms that ITNs reduce death amongst children under fi e by around one fifth. Th y also signifi antly reduce the incidence of illness caused by malaria[21].

2010

2011
The WHO recommends the use of 12 long-lasting insecticidal mosquito nets to tackle malaria. The nets all rely on pyrethroids developed at Rothamsted[22].

Notes and References

Thanks to Professor John Pickett and Professor Bhupinder Khambay for providing much of the historical information about the work of Dr Michael Elliott at Rothamsted Research, and for their comments on a draft of this case study.

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