Agrochemical R&D

hard work and money is not enough

AgrochemEx Conference

CHINA

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Agenda

- Introduction
- Innovation and creativity
- Discovery of the agrochemicals in use today
- Challenges for 21st Century
- Taking up the burden of discovery
- Recent developments in Chinese research

Introduction

- Spectacular progress in the discovery and introduction of new agrochemicals between 1940-1990 has now slowed, essentially because many older actives are still of value and the market entry hurdles are now much higher (especially the development costs)

- “R” (Science) and “D” (Technology) are separate disciplines, requiring different thinking and different resources

- In agrochemical R&D, there are two aspects to the science part (“R”): discovery and characterisation of leads. Discovery is the “wild-card” and hard to manage and predict

*Today’s talk will concentrate upon a crucial aspect of the overall process - the **discovery** of new agrochemical activity*

Fallacies about measuring innovation

- **Money spent**

  Throwing money at a problem rarely achieves the desired effect. No more is this true than in the field of innovation.

  Creative people are rarely driven by the desire to become wealthy. Therefore money cannot stimulate them to greater creativity.

  Reported "R&D spend" mainly measures the cost of "D" and neglects the unpredictable "R"

- **Numbers of patents**

  Often quoted, but really signifying little other than the numbers of patent lawyers active in an organisation/country

  Gartner's law of patents: $d(P)/dt = k \times (N_{PL})$

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Innovation is driven by ideas, technology by implementation of the successful ones

Innovation

- Much is spoken and written about innovation, a subject which is, however, an elusive and unpredictable phenomenon.
- Innovative individuals are born and can only be nurtured. They cannot be created, nor can they be readily ”managed”. Applying the fruits of their labours can lead to triumph or disaster.
- Innovators present a difficult conundrum for any organisation, since (by their nature) they challenge the status quo (received wisdom) and are potentially dangerous. Most organisations are built upon the status quo, hierarchical management and more recently the dead hands of regulation and health & safety.
- Without innovation, no progress would have been made. Even a cursory study of the history of science and the arts will show that innovation creates conflict between the opposing ways of thinking: conventional and radical.

Characteristics of creative people are listed in the next slide - to ease identification

Innovativeness - Creativity

- These two words are alternative descriptions of similar phenomena
- Individuals capable of being creative/innovative generally exhibit many of the following characteristics from an early age:

Unselfconscious non-conformity

Intense enthusiasms

Enjoyment of solitude

Egotistical / temperamental

Tendency to “day-dream”

Impatience with status-quo

Dilettantism

Manic bouts of work

A few examples of innovative individuals illustrate these characteristics, which make such individuals difficult for most of us to live with

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Types of Creativity

• Perceptual innovation:	Art
• Linguistic innovation:	Slang
• Natural philosophical innovation:	Science
• Technological innovation:	Invention
• Biological innovation:	Evolution
• Religious innovation:	Heresy
• Social innovation:	Revolution

Some kinds of innovation are more acceptable to society than others

(thanks to Dr Ellis Gartner for providing the basis for this slide)

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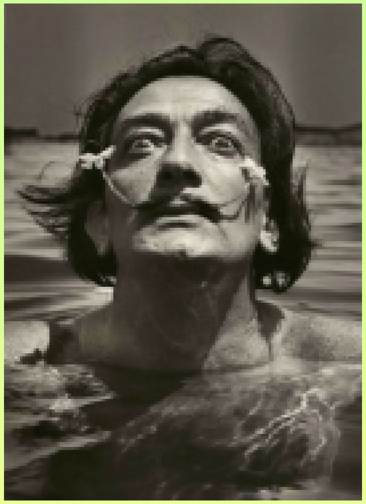
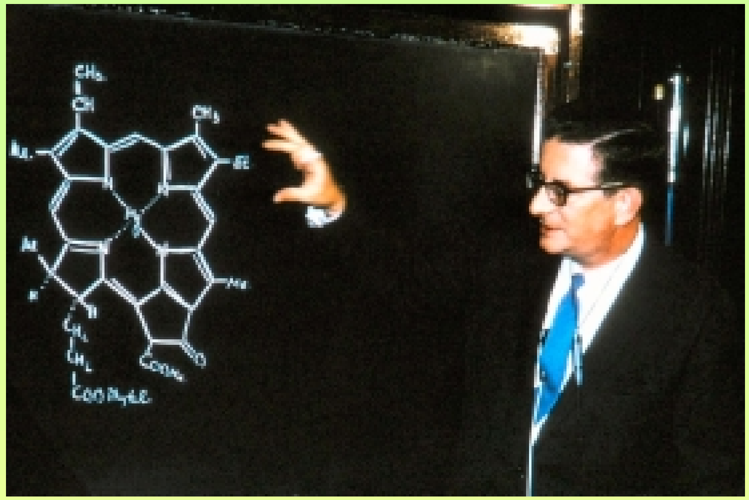
Fostering Innovation - Creativity

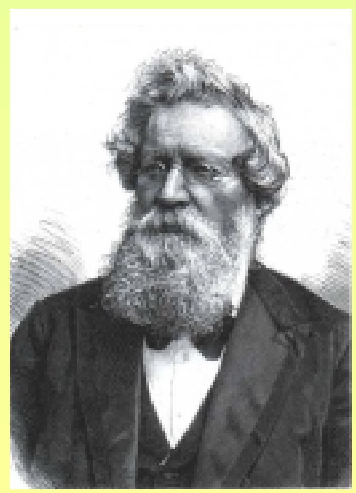
- Many individuals who are capable of inventing lose this ability through poor schooling and lack of encouragement
- Creation of centres of excellence for study and experimentation, where elitism is not considered a “dirty word”. Creatives need to exchange ideas with other like-minded individuals. Not be stuck in an “ivory tower”.
- Within an organisation, creative individual’s enthusiasm should be nurtured and used to encourage others. Performance should not be judged by the usual criteria of everyday work
- Encouragement of interdisciplinary groups is particularly important because most good ideas appear from combining information from more than one area of study

The history of mankind demonstrates that tolerance of creative people has been the exception rather than the rule. Progress has thus been erratic, with many periods of stasis imposed by the reactionary majority.

Creative and Innovative People



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Discovery of the agrochemicals in use today

- Ultimately, the introduction of successful new activity depends upon the discovery of a safe and cost-effective way to selectively block a natural process in a target "pest".
- Initial leads have historically been identified from observation of a possible beneficial effect, followed up by meticulous analysis of ways to augment the effect at will, using man-made solutions.
- Many "serendipitous" discoveries actually fall into the same category as those based upon developing new products from natural products, since in both cases, man is taking his cue from nature.
- Some discoveries have been found purely by chance, as the result of searching for an effect for a newly created chemical compound.
- Attractive though it is, rational design* is still in its infancy, since the natural systems being investigated have so far proved to be too complex for successful creation of an active "*ab initio*".

** Using models of how fundamental processes work as templates for the design of foreign molecules that can disrupt normal processes, allowing a desired result (plant or insect death, for example)to be obtained*

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Discovery of the agrochemicals in use today: fungicides

- In Europe, fungicidal treatments were in use to control bunt (*Tilletia* sp) in cereals as early as the mid-17th century.

- Following the **observation** that wheat grown from seed salvaged from ship-wrecks was free of bunt, the use of brine, followed by lime as a seed treatment became common long before the concept of germs causing diseases was pioneered by Koch and Pasteur in the mid 19th century

- The French botanist, Millardet also **thought about the curious fact** that roadside vines sprayed with a home-made mixture of lime and copper sulphate (meant to deter pilfering of fruit by Bordeaux students) held onto their leaves throughout the season, whereas the main crop, away from the road, lost the majority of their foliage by the time the fruit was ready to pick. Thus was borne the treatment for powdery mildew, Bordeaux Mixture.

This combination of thoughtful study of observations made by many, but considered by few, continues to be the essence of scientific discovery

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Discovery of the agrochemicals in use today: selected fungicides

Fungicide	*Date*	*Discovery*	*Class*	*Date*	*Commercial AI launches*
Sulphur	??	Use as a remedy for mildew had been known for as much as 2000 years			
Brine (aqueous salt)	1637	Useful for sterilising cereal seeds			
Bordeaux mixture	1882	Pierre Millardet first realised that a mixture of lime and copper sulphate killed powdery mildew on vines	copper		
	1934	Dithiocarbamates	dithiocarbamates	1942	thiram
				1943	zineb
				1950 (1955)	maneb
				1956 (1961)	mancozeb
	1940	Bromomethane, 1,2- & 1,3-dichloropropane shown to fumigate soil. Useful for killing nematodes.			
		Chlorinated organics for seed treatment		1940	chloranil, dichlone
	1952	Phthalimides (bacterial toxin, extracted from Pseudomonas syringitabaci)		1952	captan, folpet
				1962	captafol
	1964			1964	chlorthalonil
			morpholines	1965	dodemorph
				1969	tridemorph
	1964		benzimidazoles	1964	thiabendazole
				1968	benomyl
				1960	thiophanate methyl
"mucidin"	1969	Musilek et al (fungal antibiotic)	strobilurins	1996	kresoxim-methyl (BASF)
Strobilurin A	1977	Anke & Steglich		1997	azoxystrobin (Zeneca)
pyrrolnitrin		Extract from Pseudomonas pyrrocinia was shown to have fungicidal properties, but was too light-labile for use as an AI	Blocks glycerol synthesis	2004	fludioxonil (Scholar) Syngenta

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Discovery of the agrochemicals in use today: herbicides

- The discovery of the phenoxy herbicides is credited to both British and US groups working during the 1940s.
- It seems that the initial leads came from natural PGRs isolated from rice seedlings suffering from bakanae disease (*Giberella fujikaroi*), which was causing excessive seedling growth (1928)
- Although scientists at Stauffer discovered the compound later to be called glyphosate, a **key observation** that a spilled sample of a test rubber additive killed a patch of grass, eventually led to the massively successful total herbicide.
- The red bottle brush plant (*Callistemon citrinus*) produces a secondary metabolite that offers useful herbicidal properties. In 1977, an **observant** researcher at Stauffer noticed this and extracted a heap of soil from under such a bush. He found that an active principle, leptospermone, had strong herbicidal activity and this lead to the development of mesotrione

Prepared minds see what many, many others miss!

Discovery of the agrochemicals in use today: selected herbicides

Herbicide	***Date***	***Discovery***	***Class***	***Date***	***Commercial AI launches***
Copper salts	Late 19th C	Bordeaux Mixture was found to selectively kill broad-leaved leaves in cereals	Heavy metal toxin		
Potassium dinitro2--cresylate	??	First synthetic pesticide	Phenolic	1892	
Gibberellin	1926	Isolated from bakane disease (Giberella fujikaroi) of rice, which was causing excessive seedling growth	Plant Growth Hormone		
Indole-3-acetic acid	1928	Natural growth regulator	Natural auxin (plant hormone)		
Phenoxy herbicides	1940-1942	Independently developed by Templeman (ICI, UK) and Jones (American Chemical Paint Company, USA)	Hormone weed-killers	1942-1948	2,4-D, MCPA and 2,4,5-T
glyphosate	1970	John Franz	Non-selective weed-killer (inhibits aromatic acid bio synthesis)	1976	
leptospermone	1977	“biologist” at Stauffer noticed weed suppression under bottle-brush shrubs (AI isolated, leptospermone, was originally described in 1921 by Penfold)	Callistemones (bleach weed leaves)		Mesotrione (Syngenta)

Discovery of the agrochemicals in use today: insecticides

- Many important insecticides work by disrupting nerve impulses in target insects, often with poor selectivity “between foes and friends”.
- Organophosphates were originally identified as part of the war effort targeted at developing nerve gases by British and German scientists. Bayer’s early lead in insecticides stems from early success with such OPs as parathion.
- Ryania extracts were marketed in the USA as light-stable treatments for insect pests, but were similar in toxicity to nicotine and other natural extracts. It was not until the early 2000s that research on the molecular basis of the interaction of the active ingredients of ryania with calcium channels, that some idea of its mode of action was obtained.
- However, the earliest ryanodine receptor lead, which led to the develop -ment of flubendiamide, was discovered by researchers at Nihon Nohyaku *accidentally*.

Natural product leads have often been useful in the development of modern insecticides, but close attention to unusual findings is vital ingredient for success.

Discovery of the agrochemicals in use today: selected insecticides

Insecticide	*Date*	*Discovery*	*Class*	*Date*	*Commercial AI launches*
Pyrethrum	unclear	Probably introduced by the Persians. Selective heptatic toxin in insects	Pyrethroids	1884	Zacherlin: pyrethrum soap (US 308,172)
Lime/nictotine	1763	Mixture of tobacco and lime marketed as a remedy for "plant lice"	Nicotinoid		
Nicotine	1828	First extracted from the tobacco plant by Posselt & Reimann.	Nicotinoid		
Arsenic salts	1867	First use to kill Colorado beetle on potatoes in the USA.			
Rotenone	1895	In French Guiana, Emmanuel Geoffroy discovered the activity of an extract from Robinia nicou, which he called nicouline.	Insecticide, piscicide.		Derris (extracted from the jicama vine)
DDT	1873	First synthesised. No applications recorded.	Chlorinated organic		
	1939	Paul Mueller first showed effectiveness as an insecticide	(interects with sodium-channel)	1949	DDT (Geigy Pharmaceutical)
Organophosphates	1932-1949	Lange and von Krueger showed activity on human nervous system. Later IG Farben's Schrader showed neurotoxic effects in insects. However, discoveries used for war effort by Germans and British (nerve gases) before use in agriculture developed.	Organo-phosphates	1938-1946	TEPP (1938), schraden (1941), sulfotep (1944), parathion (1946) – all Bayer OPs.
Carbamates		Choline esterase inhibitor	Carbamates		
Neo-nicotinoids	1970	Shell early leads (eg SHI-71, nithiazine) failed in greenhouse tests	Neo-nicotinoids	1985	Imidacloprid (Nihon-Bayer)
Ryania	1942	A crude eextract from Brazilian shrub was marketed as a non-specific insecticide by Penick, using Ryanex brand-name (owned by Merck & Co.)	Ryanodine receptor agonists	2007 2008	Flubendiamide (Bayer-Nihon Nohyaku) and Chlorantraniloprole (DuPont) Rynaxypyr

The oxime carbamate, aldicarb, which was introduced in 1965, was apparently developed using *in vitro* acetyl chloline assays that helped to define and design the molecule.
An exceptional example of rational design (thanks to Dr Tom Sparks for pointing this out).

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Challenges for 21st Century

- Bringing new agrochemical solutions to market has become much more expensive as public distrust of the industry has increased.
- The fact that some of this mistrust is irrational can neither be ignored, nor easily overcome. The issue of GMOs in Europe demonstrates this well.
- In Europe and the USA, many older registrations have been withdrawn because they are too expensive to maintain. This is starting to create treatment gaps, especially for minor crops.
- As well as new problems that emerge, resistance to diseases, insect and weed resistance continues to emerge.
- Not all such challenges can be met by reformulation and combinations of active ingredients.

Demand for new active ingredients will continue, but where will they come from?

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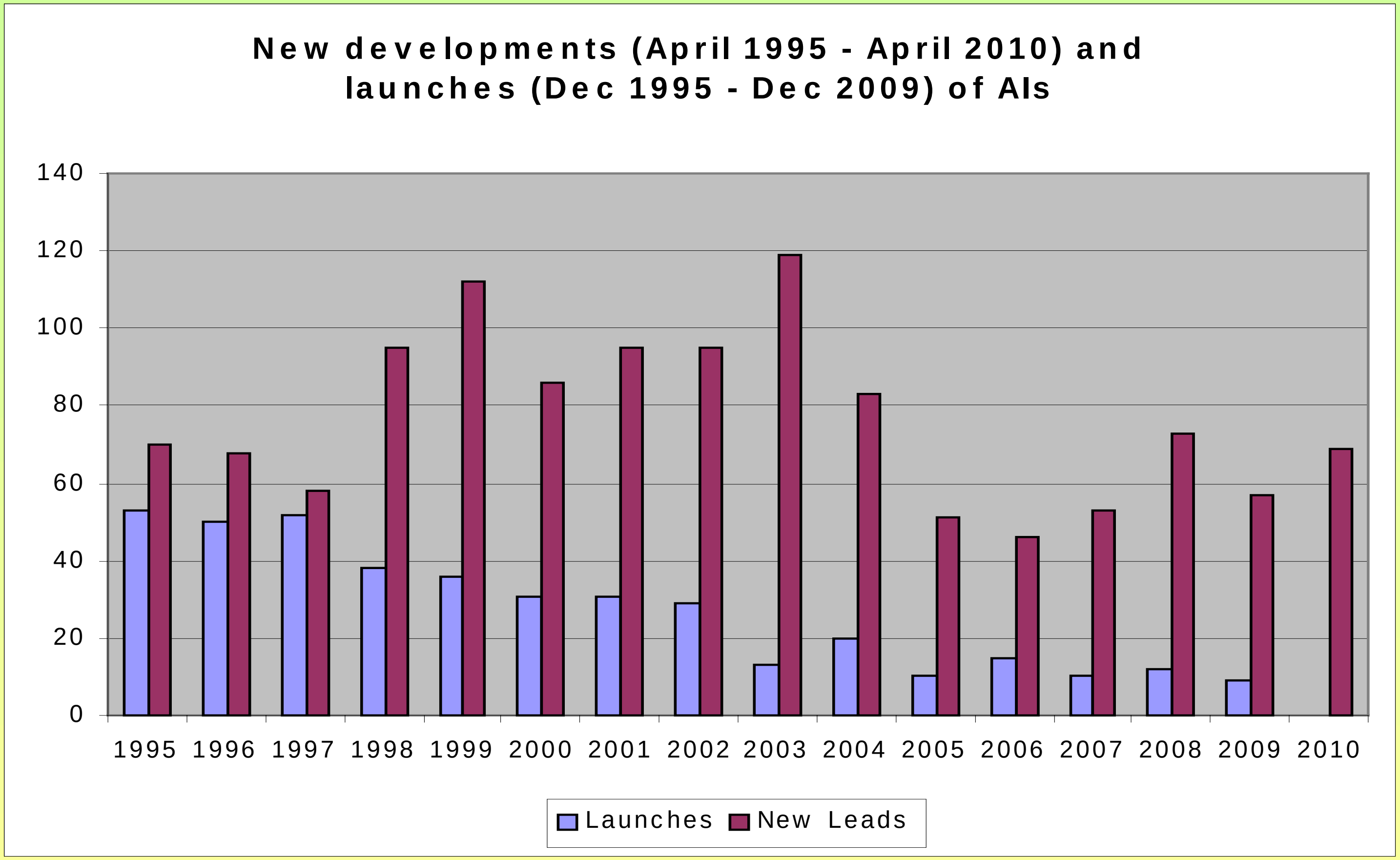
Recent history of new AIs and launches



Source: Ag Chem New Compound Review (Vol 28) 2010 (Agranova)

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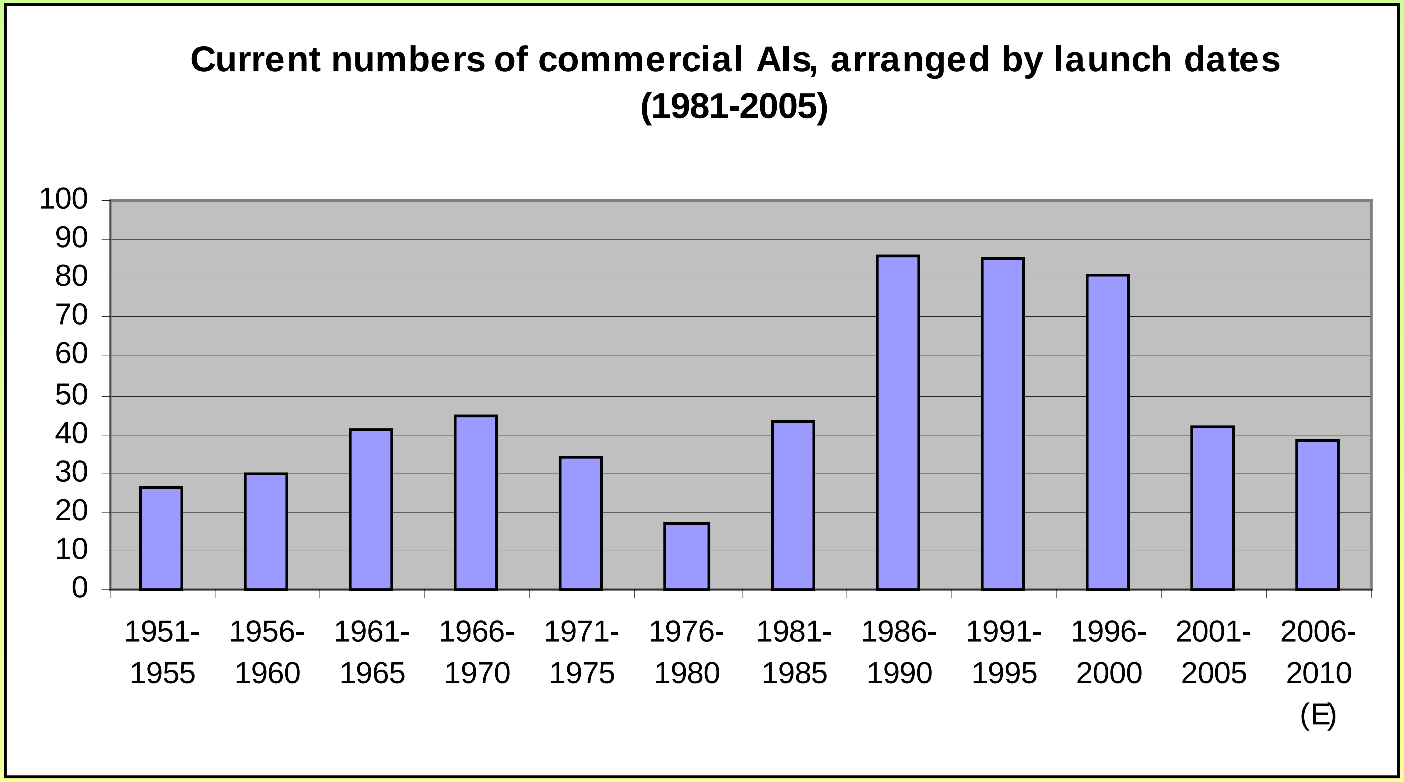
Many new launches ultimately lead to failure and withdrawal. In the next slide, the numbers of launches that have stood the test of time are shown.

Recent history of new AIs and launches



Source: Crop Protection Actives 2010 (Agranova)

*Since 1950, there have been an average of **5-8** sustained commercial new actives per year, except during 1986-2000, when the average increased to 16 per year. The most productive years to date were thus 1978-1992 (assuming 8 years from discovery to market)*

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Taking up the burden of discovery

NEW LEADS (agrochemicals) 2009-2010			
USA	13	Herbicides	10
Europe	10	Insecticides	28
Japan	19	Fungicides	16
China	12	Other	3
RoW	3		

Source: Ag Chem New Compound Review (Vol 28) 2010

- In the late 1990s-early 2000s Japan took over from the USA and Europe as a major source of new leads
- China's R&D effort emerged in the mid-2000s as a new centre for discovery

Research into insecticides has become dominant, as a result of these changes

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Recent developments in Chinese research

- Pesticide use in China was under-reported up to the end of the last century and the West's understanding of the region was generally poor.

- Since 2002, Agranova has steadily developed a better network of contacts in China and visits the country 2-3 times a year.

- Entries in the Ag Chem New Compound Review have reflected this catching up of the rapidly developing crop protection research effort in China.

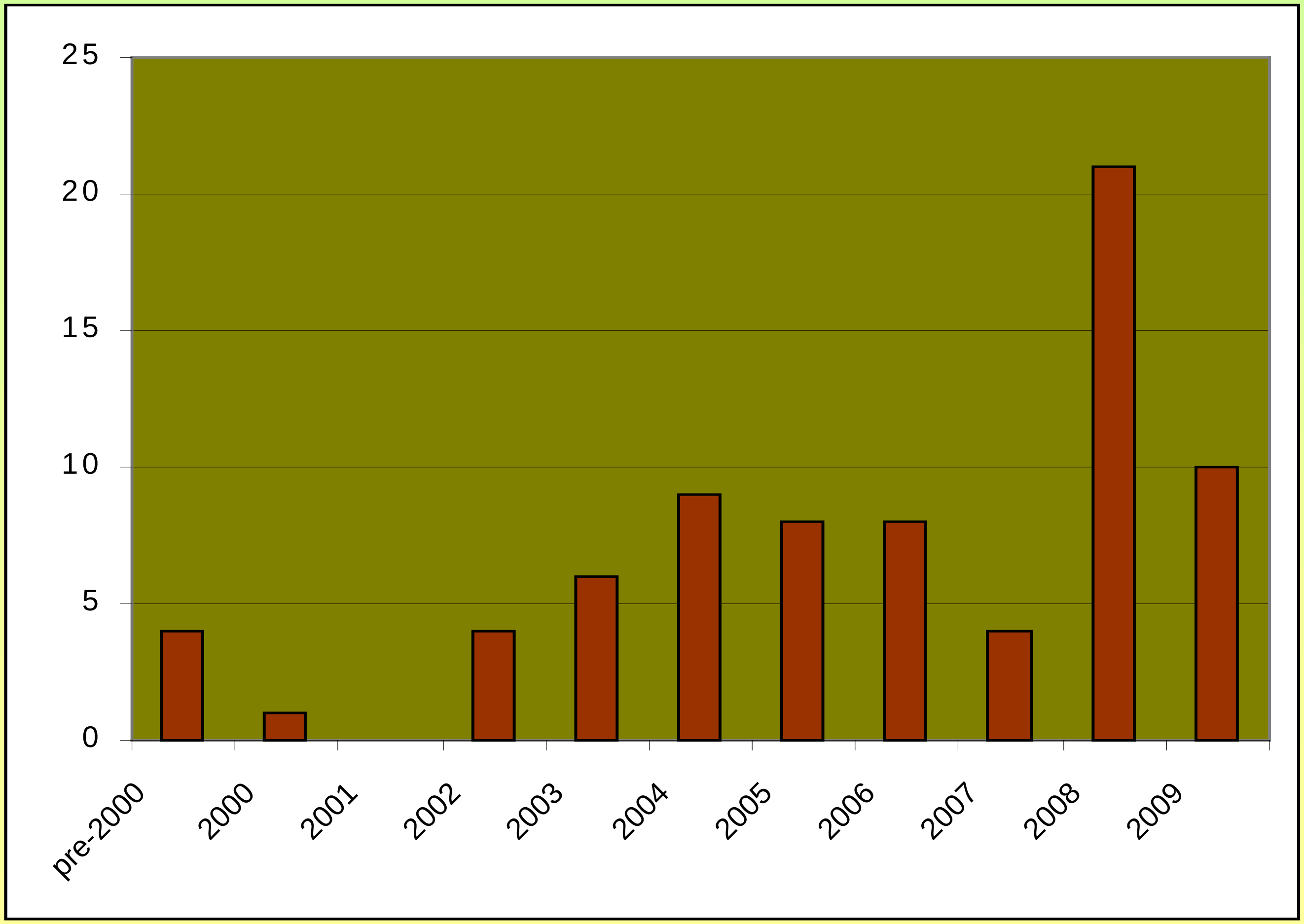
- Although it is still early days and targets have a tendency to be "me-toos", it is likely that China will soon become a major source of new technologies in the near future

The next two slides summarise some of this activity

Centres of agrochemical research in China

- China Agricultural University, Beijing
- East China Normal University, Shanghai
- Guizhou University
- Hunan Research Institute of Chemical Industry (HRICI)
- Jiangxi Agricultural University
- Kunming Institute of Botany
- Nankai University
- Jiangsu Pesticide Research Institute, Nanjing
- Sichuan Academy of Chemical Industry Research & Design
- Shanghai Institute of Organic Chemistry (SIOC)
- Shanghai Pesticide Research Institute
- Shenyang Resaerch Institute of Chemical Industry (SYRICI)
- Zhejiang Chemical Industry Research Institute (ZCIRI)

Fruits of agrochemical research in China – new leads 2000-2009



Graph shows the numbers of new leads originating in China by year

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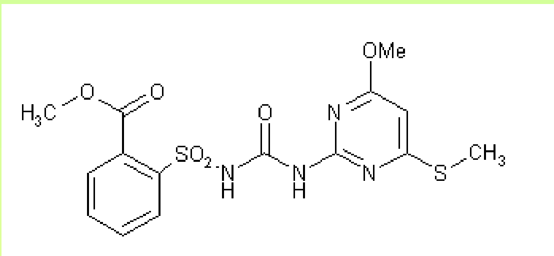
Newer Chinese compounds

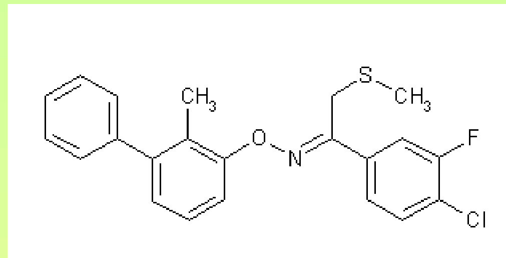
HERBICIDES

INSECTICIDES

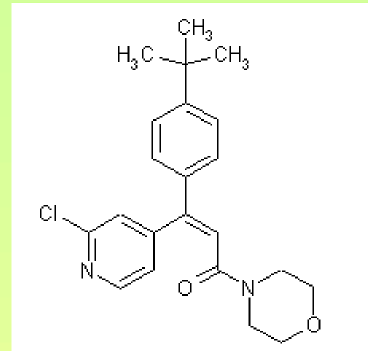
FUNGICIDES



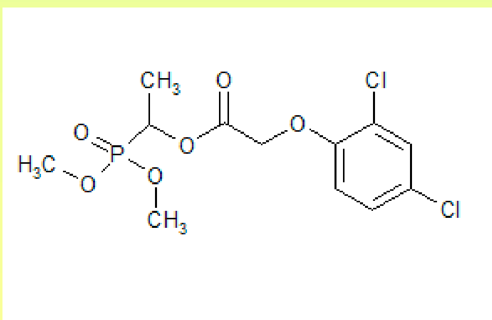
Methiopyrsulfuron
(HRICI)



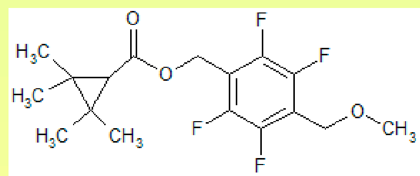
HNPC-A2005
(Hunan RICI)



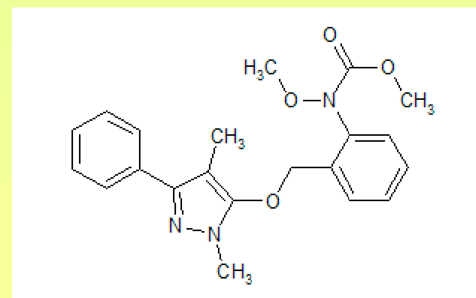
Pyrimorph
(China Agricultural University)



HW-02
(Huazhong University)



Tetramethylfluthrin
(Jiangsu Yangnong Chemical)



Pyrametostrobin
(SYRICI)

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For more information, see Ag Chem New Compound Review (Vol 28) 2010

Summary

- Advances in the discovery and development of new agrochemicals has slowed in the West,following a productive twentieth century.

- Although GM technology will deliver benefits, the need for new chemical solutions will continue.

- Research on combatting pests and diseases using novel chemical solutions is likely to more successful in countries that understand the need to foster scientific innovation and in companies that learn to manage individuals with the necessary talent

- If Europe and the USA cannot solve their current supply shortage of young scientists, discovery will become concentrated in Asia.

It matters less where new research occurs, more that its fruits are not lost.

Thank you

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Dr Tom Sparks - advice and valuable corrections on the content of this talk

Useful references

A short history of Fungicides: Vince Morton and Theodor Staub
Callisto - a very successful maize herbicide inspired by alleochemistry: Derek Cornes
Ryanodine receptor agonists: Ag Chem New Compound Review (Vol 24) 2006
Golden Age of Insecticide Research: Past, Present,or Future:Casida & Quistad
History of crop protection; Crop Life International (2002)

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