Innovative pesticides are what the world needs

CCM China

Crop Protection Summit

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Agenda

- Introduction
- Innovation in crop protection
- Pesticide modes of action
- Current R&D pipeline
- Outlook

Introduction - part I

- 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- In Europe and the USA, many older registrations have been withdrawn because they are too expensive to maintain.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 creating treatment gaps, especially for minor crops.
- As well as new pest outbreaks that emerge, resistance to existing diseases, insects and weeds continues to emerge.
- Not all such challenges can be met by reformulation and combinations of active ingredients.

Improved crop yields are needed as never before, with an ever increasing world population.

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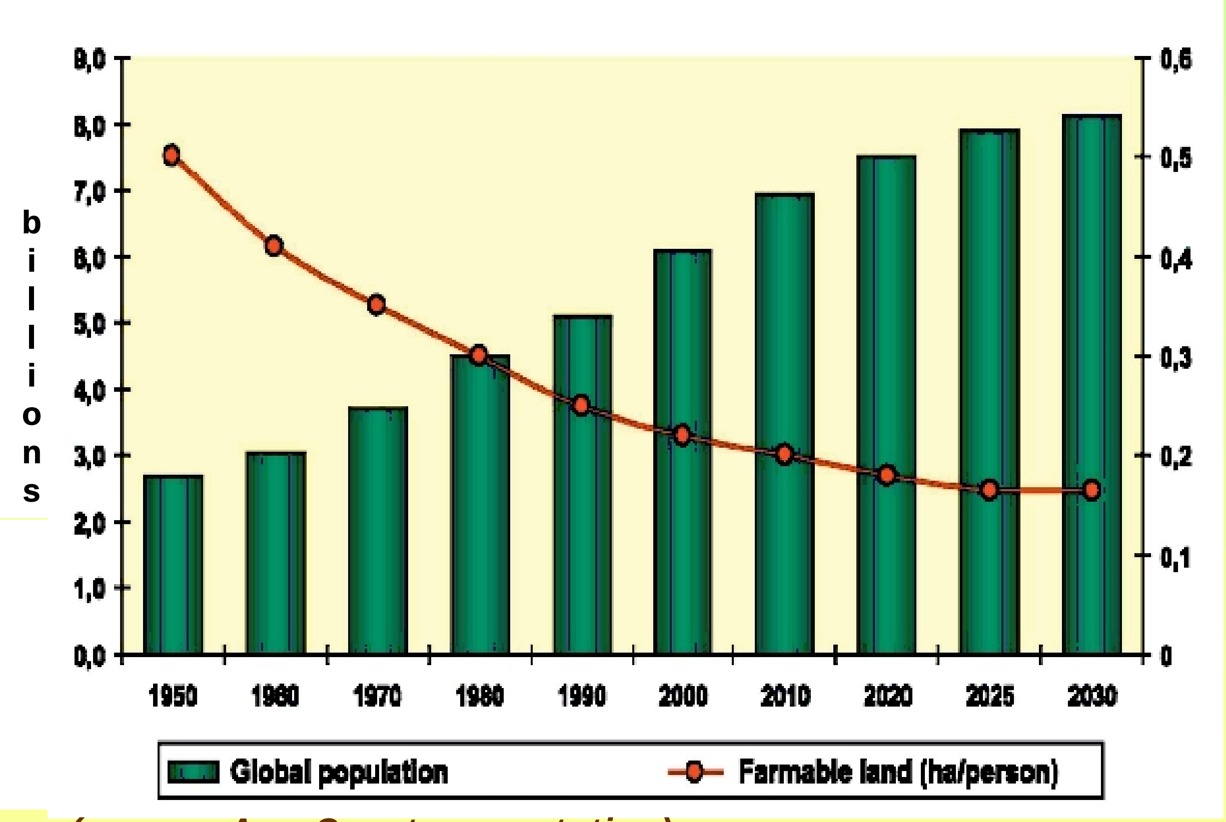
Introduction - part II

Decreasing area of agricultural land as the world's population increases, means productivity must improve



(source: AgraQuest presentation)

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Keeping up with the constantly evolving challenges from agricultural pests is a vital part of this effort

Introduction - part III

- It is widely reported that as much as 40% of agricultural crops are destroyed by pests before harvest and as much as 10% after harvest.

- Studies on the losses sustained in the USA carried out by more than one group in the 1990s and again in the mid-2000s actually showed an increase in percentage losses over this time (figure overleaf).

- Whatever, the precise number is, there is no doubt that it would be hugely beneficial if agronomists could find ways to help farmers reduce losses.

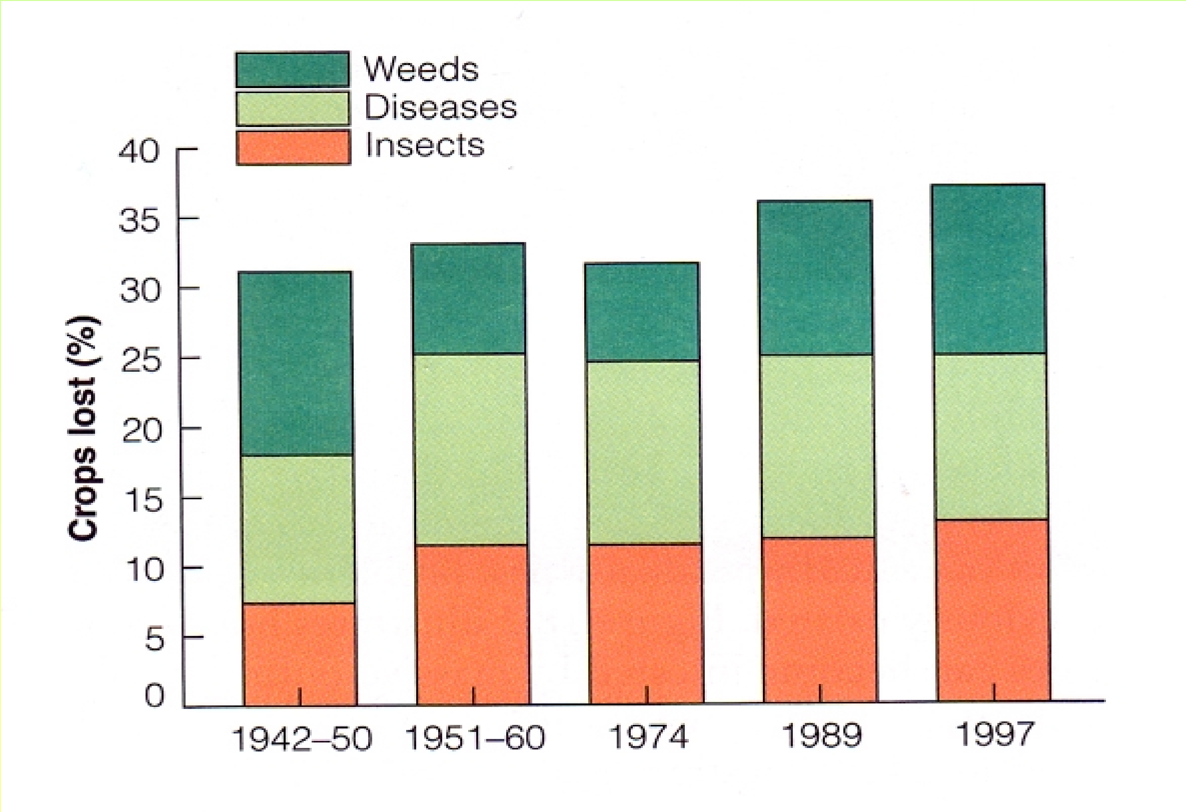
- Novel technologies and farming systems have made useful contributions to reducing this waste, but the development of novel agrochemical active ingredients remains the cornerstone of IPM (integrated pest management) systems.

- Although GM seeds, biopesticides, controlled applications using pesticide sampling/traps will make a substantial contribution, agrochemicals will continue to be needed to control a wide range of pests into the foreseeable future.

Conclusion: the discovery and introduction of new pesticides is essential, otherwise food shortages, famine and civil disturbance will surely follow.

US Crop losses 1942-1997

(as % of total crop)



Crop losses in USA (Pimentel 1991, 1997)

Some factors that drive this surprising fact:

- Farm subsidies prop up inefficient farmers
- Loss of useful AIs considered to be unsafe or too specialised to support registrations
- Concentration of costly R&D on major crops and pests

This slide was produced to justify banning chemical pesticides.
It is just as persuasive at showing the need for redoubling efforts to expand the use of all effective crop protection technologies

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Innovation in crop protection

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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*”.

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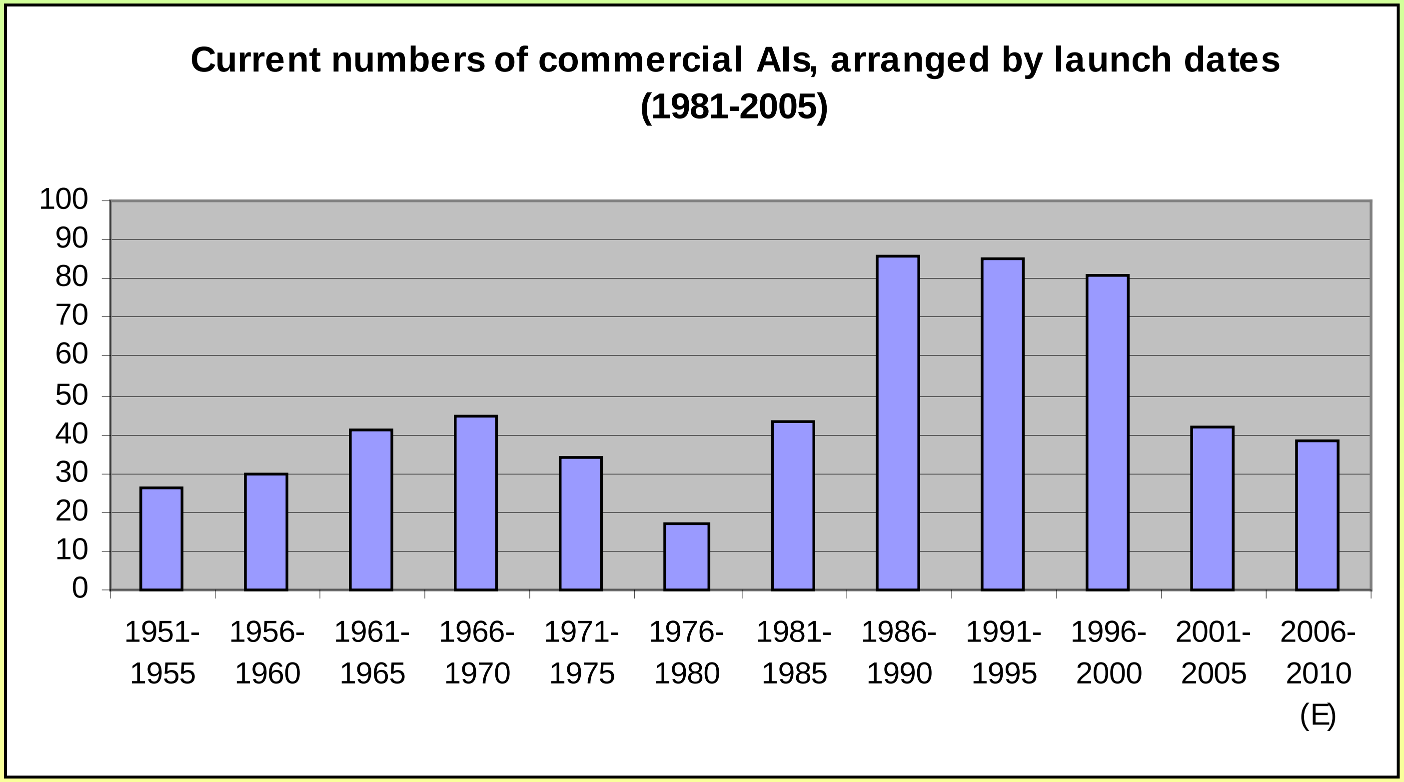
** Using models of how fundamental processes work as templates for the design of foreign molecules that can disrupt normal processes, allowing a desired result (plant or insect death, for example)to be obtained*

Invention of today's agrochemicals



*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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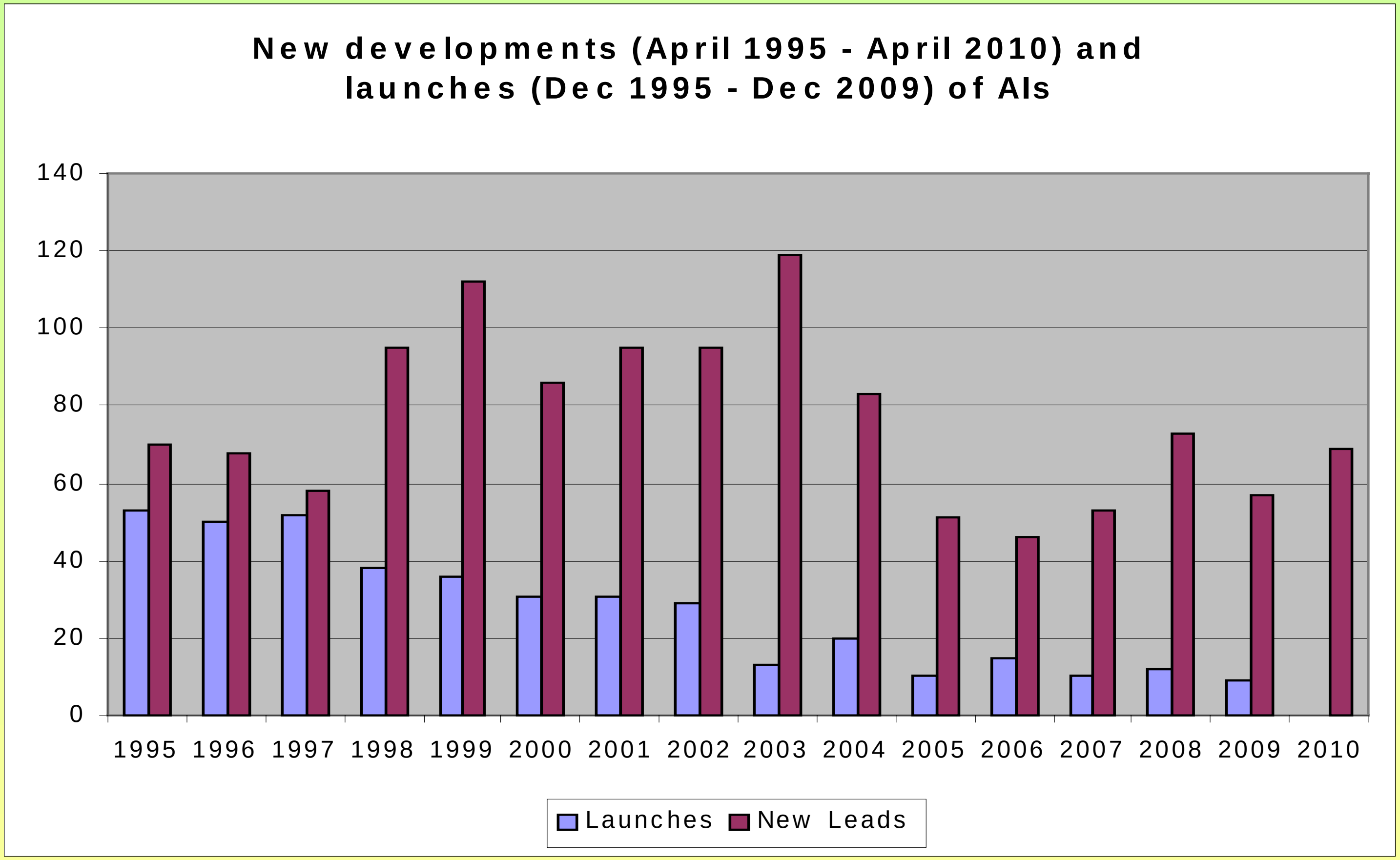
Recent history of new AIs and launches



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

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Since 1995, it has become increasingly difficult to convert a new lead to a successful new product.

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 new insecticides has become dominant, as a result of the changing centres of R&D

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Pesticide modes of action

Pesticide modes of action

- Traditionally, agrochemicals have been classified by their chemical structures. This system has certain merits, but it does obscure one essential truth:

There are relatively few mechanisms by which current agrochemicals usefully interact with target pests.

- This paucity of effective modes of action is shown in the following slides

- The importance of this lack of breadth is particularly acute in the case of rapidly evolving pests such as viruses, bacteria, fungae and, to a lesser extent, insects.

The following slides highlight this over-dependence on a limited number of weapons available to farmers.

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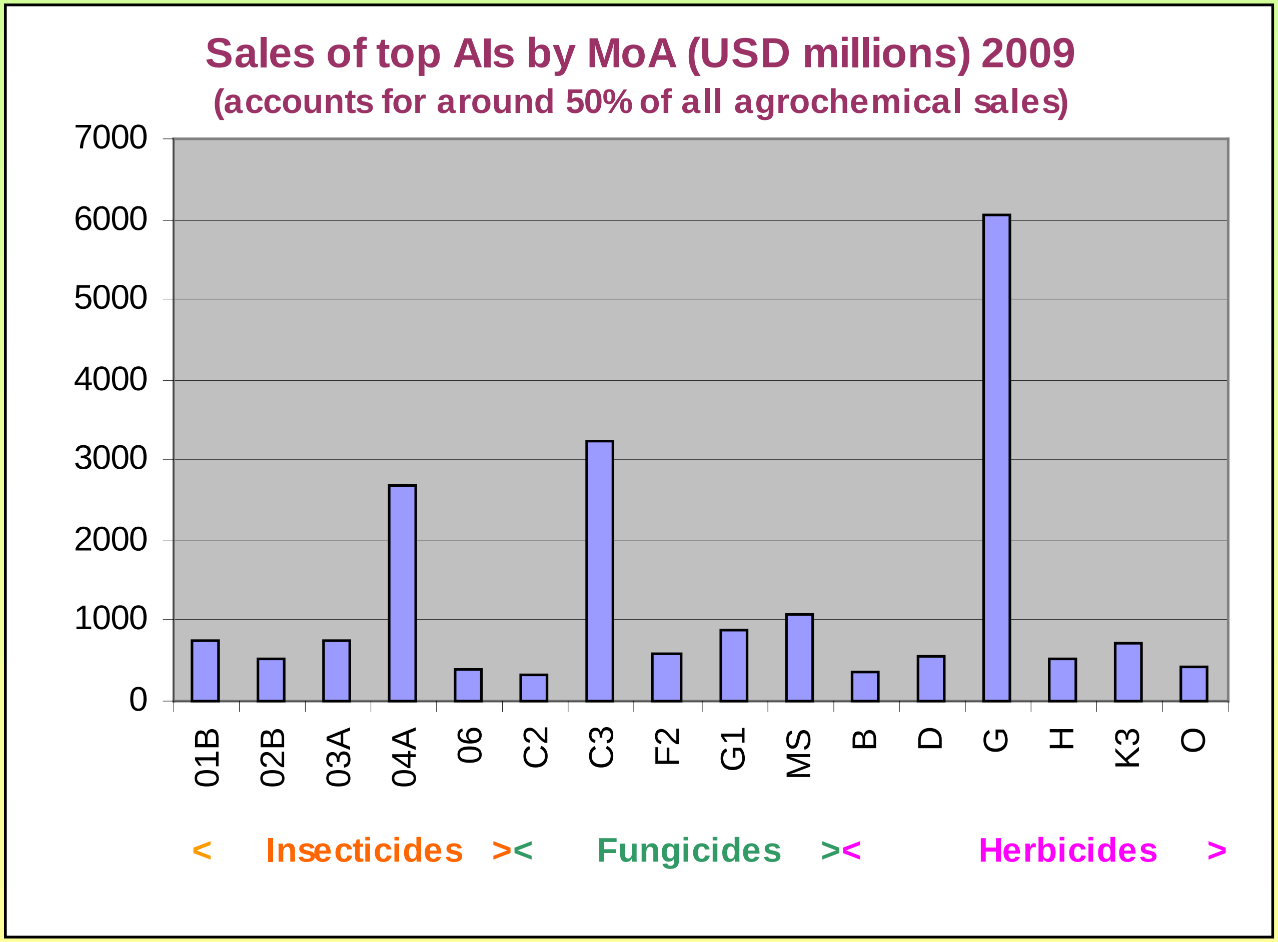
Major pesticide groups and their modes of action



01B	acetylcholineesterase inhibitor
02B	GABA-gated chloride channel antagonist
03A	sodium channel modulator
04A	nicotinic acetylchloline receptor agonist
06	chloride channel activator
C2	Respiration
C3	Respiration
F2	Bleaching: Inhibition of 4-hydroxyphenyl-pyruvate-dioxygenase
G1	Sterol synthesis in membranes
MS	Multi-site contact activity
B	Inhibition of acetolactate synthase ALS (acetohydroxyacid sy
D	Photosystem-I-electron diversion
G	Inhibition of EPSP synthase
H	Inhibition of glutamine synthetase
K3	Inhibition of VLCFAs (Inhibition of cell division)
O	Action like indole acetic acid (synthetic auxins)

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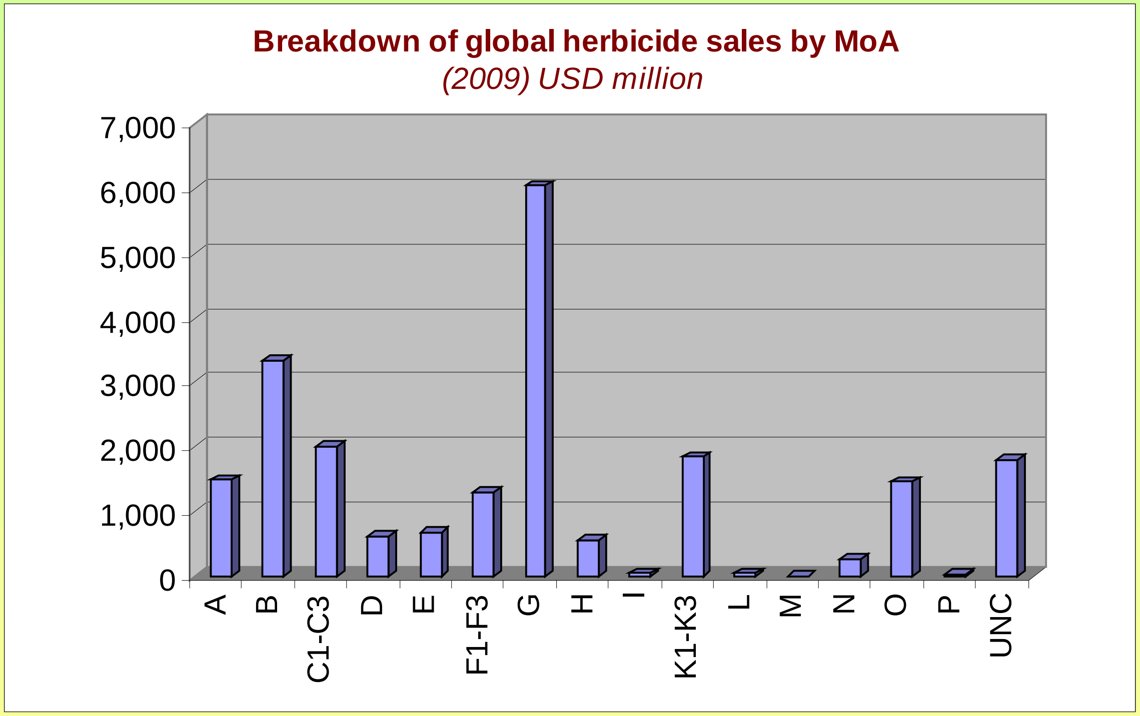
Sources: Pesticide Resistance Action Committees (classification of MoAs)
Crop Protection Actives 2010 (sales data)

Global herbicide sales by modes of action



Seven important MoAs

Modes of Action	***Site code***
Inhibition of acetylCoA carboxylase (ACCase)	A
Inhibition of acetolactate synthase (ALS)	B
Inhibition of photosynthesis at photosystem II	C1-C3
Photosystem-I-electron diversion	D
Inhibition of protoporphyrinogen oxidase (PPO)	E
Bleaching: Inhibition of carotenoid biosynthesis (other)	F1-F3
Inhibition of EPSP synthase	G
Inhibition of glutamine synthetase	H
Inhibition of DHP (dihydropteroate) synthase	I
Inhibition of VLCFAs (Inhibition of cell division)	K1-K3
Inhibition of cell wall (cellulose) synthesis	L
Uncoupling (Membrane disruption)	M
Inhibition of lipid synthesis - not ACCase inhibition	N
Action like indole acetic acid (synthetic auxins)	O
Inhibition of auxin transport	P
Unknown or uncertain mode of action	UNC

Sources: Herbicide Resistance Action Committee (classification of MoAs)
Crop Protection Actives 2010 (sales data)

Total global herbicide sales were USD 21.5 billion in 2009

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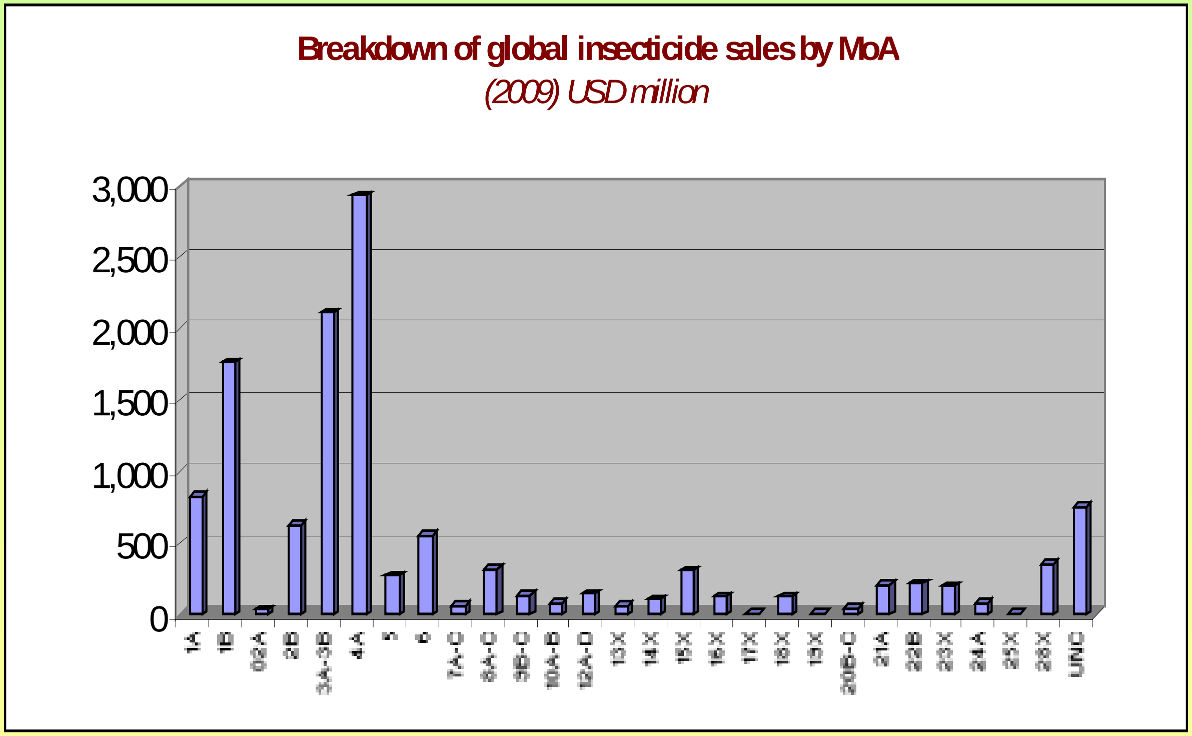
Global insecticide sales by modes of action



Sources: Insecticide Resistance Action Committee (classification of MoAs)
Crop Protection Actives 2010 (sales data)

Six important MoAs

Modes of Action	Site code
acetylcholineesterase inhibitor	1A
Acetylcholine esterase inhibitor	1B
GABA-gated chloride channel antagonist	02A
GABA-gated chloride channel antagonist	2B
sodium channel modulator	3A-3B
nicotinic acetylchloline receptor agonist	4A
nicotinic acetylchloline receptor allosteric activator	5
chloride channel activator	6
juvenile hormone mimic	7A-C
non-specific (multisite) inhibitors	8A-C
selective homopteran feeding blocker	9B-C
mite growth inhibitor	10A-B
Inhibitors of mitochondrial ATP synthase	12A-D
Uncouplers of oxidative phosphorylation	13X
Nicotinic acetylcholine receptor channel blockers	14X
Inhibitors of chitin biosynthesis, type 0	15X
Inhibitors of chitin biosynthesis, type 1	16X
Moulting disruptor, Dipteran	17X
Ecdysone agonists / moulting disruptors	18X
Octopaminergic receptor agonists	19X
Mitochondrial complex III electron transport inhibitors	20B-C
Mitochondrial complex I electron transport inhibitors	21A
Voltage-dependent sodium channel blockers	22B
Inhibitors of acetyl CoA carboxylase - Lipid synthesis	23X
Mitochondrial complex IV electron transport inhibitors	24A
Mitochondrial complex II electron transport inhibitors	25X
Ryanodine receptor modulators	28X
Compounds of unknown or uncertain mode of action	UNC

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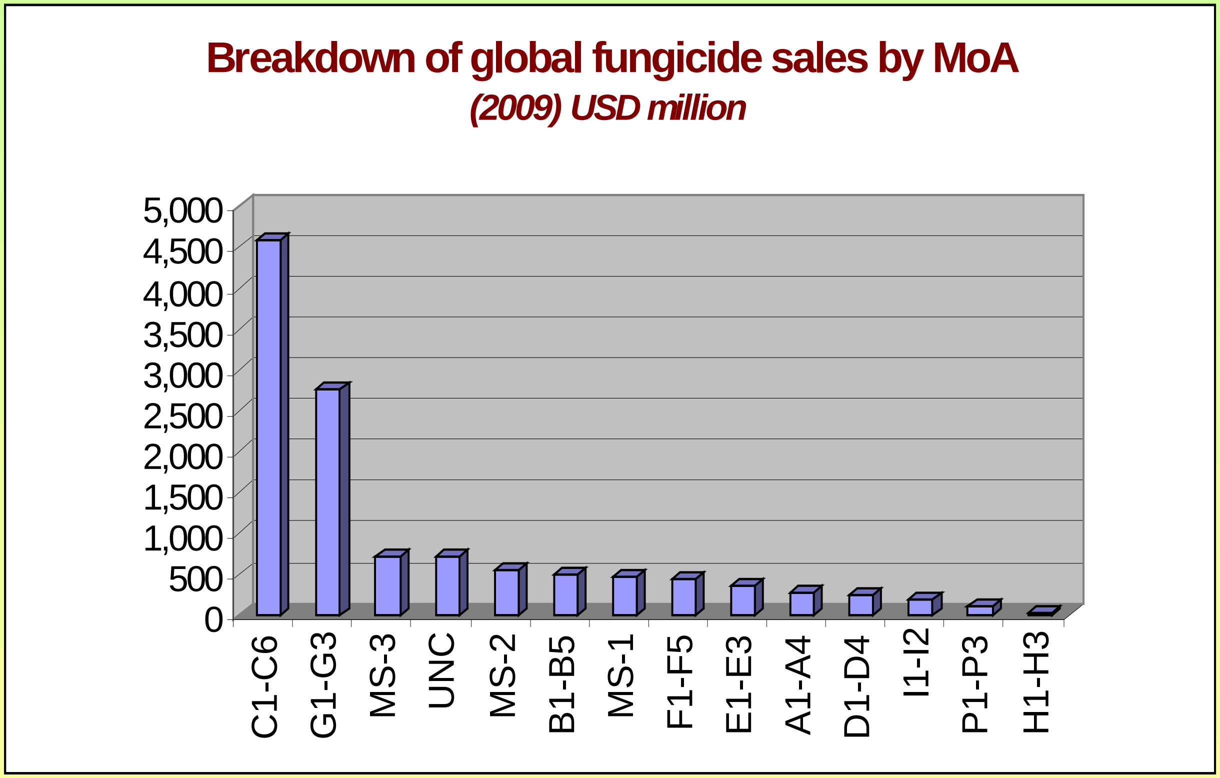
Total global insecticide sales were USD 12.5 billion in 2009

Global fungicide sales by modes of action



Sources: Fungicide Resistance Action Committee (classification of MoAs)
Crop Protection Actives 2010 (sales data)

Two important MoAs

Modes of action	***Site code***
Respiration	C1-C6
Sterol synthesis in membranes	G1-G3
Multi-site contact activity	MS-3
Unknown MoA	UNC
Multi-site contact activity	MS-2
Mitosis & cell division	B1-B5
Multi-site contact activity	MS-1
Lipids and membrane synthesis	F1-F5
Signal transduction	E1-E3
Nucleic acid synthesis	A1-A4
Amino acid and protein synthesis	D1-D4
Melanin synthesis in cell walls	I1-I2
Host plant defence induction	P1-P3
Glucan synthesis	H1-H3

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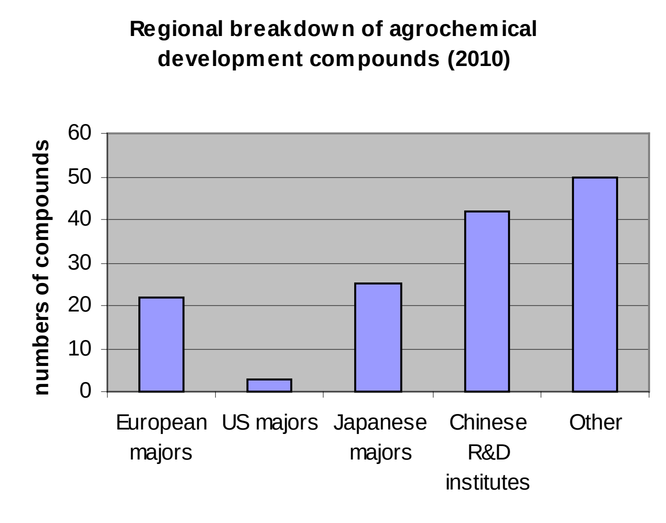
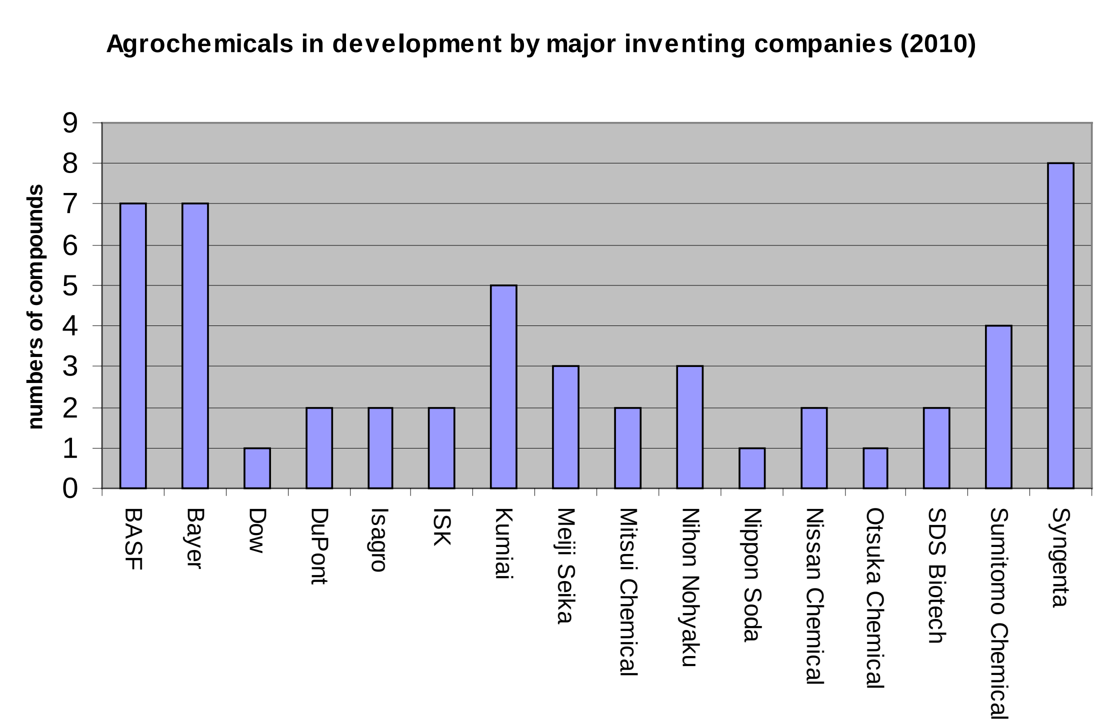
Total global fungicide sales were USD 12 billion in 2009

Current R&D pipeline

Current R&D pipeline - discovery groups





Source: Ag Chem Base 2010 (Agranova)

The striking decline in US agrochemical research is the result of the emphasis on GM crop research. However, over-dependence on a limited range of tolerant herbicides has its dangers, as illustrated by the emergence of glyphosate resistance, particularly in the USA.

- Current pipeline contains around 325 development products
- R&D is no longer dominated by the major agrochemical companies*
- 142 chemical compounds have been identified (see graphs above)
- 44 have known modes of action (see next slide)

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* However, this analysis neglects quality of AIs

Current R&D pipeline - MoAs

Entry year	Mode of action
2009	ABA pathway agonist
2009	Acetylcholine receptor agonist/antagonist
2009	Acetylcholine receptor agonist/antagonist
2009	mitochondrial transport chain at complex II - succinic acid inhibitor
2009	mitochondrial transport chain at complex III
2009	mitochondrial transport chain at complex III
2009	Sodium channel modulator
2008	ALS inhibitor
2008	Auxin-type activity
2008	Cell wall biosynthesis inhibitor
2008	Cell wall biosynthesis inhibitor
2008	Insect confuser / repellent
2008	Novel
2008	PPDK inhibitor
2008	PPO inhibitor
2008	PPO inhibitor
2008	PPO inhibitor
2007	Ecdysone agonist
2007	Enhances plants' abilities to produce antioxidants
2007	mitochondrial transport chain at complex II - succinic acid inhibitor
2007	mitochondrial transport chain at complex II - succinic acid inhibitor
2007	mitochondrial transport chain at complex II - succinic acid inhibitor
2007	mitochondrial transport chain at complex II - succinic acid inhibitor

2007	p-Hydroxyphenyl pyruvate dioxygenase (4-HPPD) inhibitor.
2007	Repellent
2007	Sterol synthesis inhibitor.
2007	Sterol synthesis inhibitor.
2006	ALS inhibitor
2006	Novel
2006	RyR calcium channel disruptor.
2004	Insect confuser / repellent
2004	Mitochondrial disruption of insect K channels
2004	Mycelium growth inhibitor
2004	Pheromone
2004	PPO inhibitor
2004	Ryanodine (RyR) receptor calcium channel disruptor
2003	A cellulose synthesis inhibitor.
2003	ALS inhibitor
2003	Melanin biosynthesis inhibition.
2002	ALS inhibitor.
2002	mitochondrial transport chain at complex III
2002	Mycelium growth inhibitor
2002	Novel
2002	p-Hydroxyphenyl pyruvate dioxygenase (4-HPPD) inhibitor.
1999	PPO inhibitor
1998	mitochondrial transport chain at complex II - succinic acid inhibitor
1988	Inhibition of cell wall (cellulose) synthesis

Sources: Pesticide Resistance Action Committees (classification of MoAs)
Ag Chem Base 2010 (Agranova)

Out of this substantial list, only three of the developmental chemical actives are known to have novel modes of action

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Current R&D pipeline

- There continues to be too much emphasis on major crops, which is driven by the need to recoup the costs of ever increasing regulatory burdens and decreasing success in innovation.

- Commercial thinking is also hampered by lack of innovation. The far better returns in non-crop markets demonstrate this potential.

  Example: Treatments for forestry and wood preservation have remained largely unchanged for many years.

- Only recently have governments woken up to the increasing problem of food security. Tackling this will demand the best brains on the planet, not the most hide-bound.

- A long-term view that is hard for commercial organisations to justify is needed to support the development of a whole range of technologies.

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Food security is too important to to leave to single issue pressure groups or to commercially funded R&D.

Developing new modes of action

- Crucially, discovery groups need to be able to explore novel ideas much more freely.
- Too much "research" is carried out using "me-too" concepts and funding decisions are too often made by conservative criteria.
- Re-examination of useful leads discarded in the 1970-1990s might reveal new activity, especially if guided by the search for new MoAs.
- Sharing results and ideas from other disciplines will always prove to be productive. The secretive approach adopted by "big ag" has proved to be detrimental to new discovery.

Outlook

Outlook

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

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Thank you

Coco Yang, for inviting me to make this presentation to CCM's China Crop Protection Summit 2011

Acknowledgements

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Useful references

Classification of pesticide MoAs published by the Resistance Action Committees for herbicides (HRAC), insecticides (IRAC) and fungicides (FRAC). See http://www.plantprotection.org/hrac/, http://www.irac-online.org/ and http://www.frac.org

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