Agrochemical pest control: new active ingredients are still needed

The Agrochemical Conference 2012

Newmarket, England

November 2012

AGRANOVA

Agenda

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

Introduction - part I

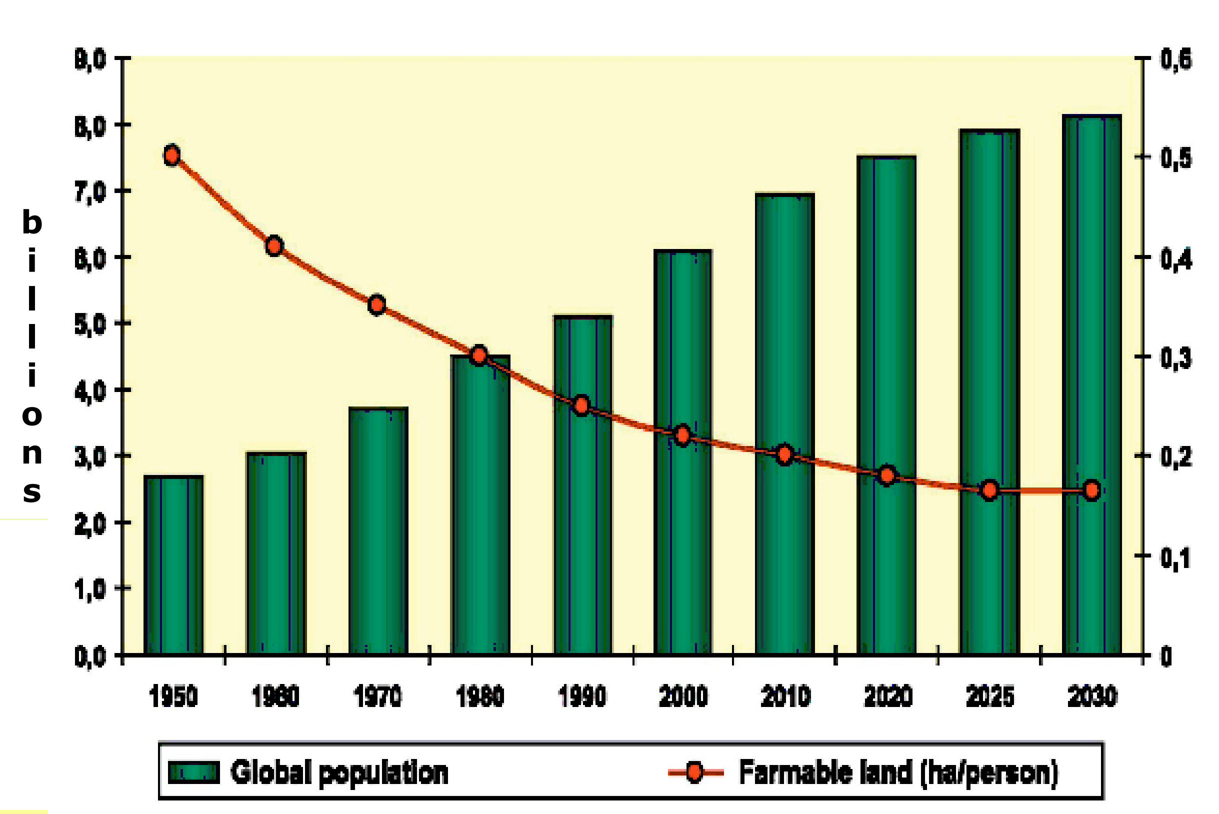
- Bringing new agrochemical solutions to market has become much more expensive as *public distrust* of the industry has increased.
- The fact that some of this mistrust is irrational can neither be ignored, nor easily overcome. The case of *GMOs* in Europe illustrate this issue.
- In Europe and the USA, many older registrations have been withdrawn because registration maintenance makes them too expensive to maintain. This is creating treatment gaps, especially for minor crops, but also significant applications such as *nematode* control.
- New pest outbreaks emerge regularly and these can be hard to control with existing pesticides. An additional complication is that *resistance* to existing diseases, insects and weeds continues to develop.
- Not all such challenges can be met by reformulation and combinations of active ingredients.

AGRANOVA

Sustained or improved crop yields are needed as never before, as the world population continues to grow.

Introduction - part II

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



(source: AgraQuest presentation)

AGRANOVA

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

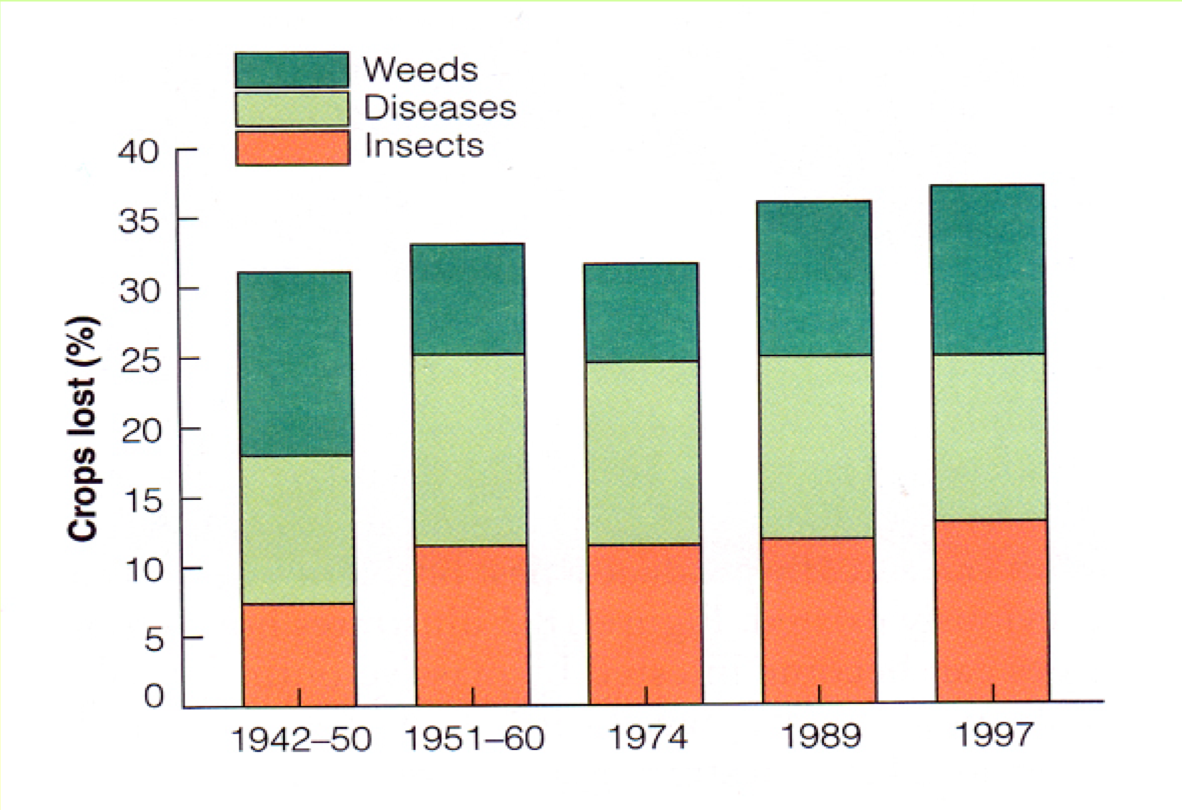
Introduction - part III

- It is widely reported that as much as 40% of agricultural crops are *destroyed* by pests before 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 the need continues for *new technologies* to help farmers contain or perhaps reduce losses.
- Novel technologies and farming systems, such as IPM (integrated pest management) biopesticides, and GM seeds have made useful contributions to reducing this waste in some, but not all, markets.
- Agrochemicals offer a quick, flexible solution to pest problems that is complementary to other technologies
- This is why the development of novel agrochemical *active ingredients* remains the cornerstone of the war on pests.

Conclusion: efforts to discover, develop and introduce new pesticides remain a vital activity, if food shortages, famine and civil disturbance are to be avoided in the future.

US Crop losses 1942-1997

(as % of total crop)



Crop losses in USA (Pimentel 1991, 1997)

Some factors that drive this surprising fact:

- Nature abhors a vacuum - kill one pest and another pops up to replace it
- 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

(unfortunately, no newer data is available)

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

AGRANOVA

Innovation in crop protection

AGRANOVA

Discovery of agrochemicals (illustrations)

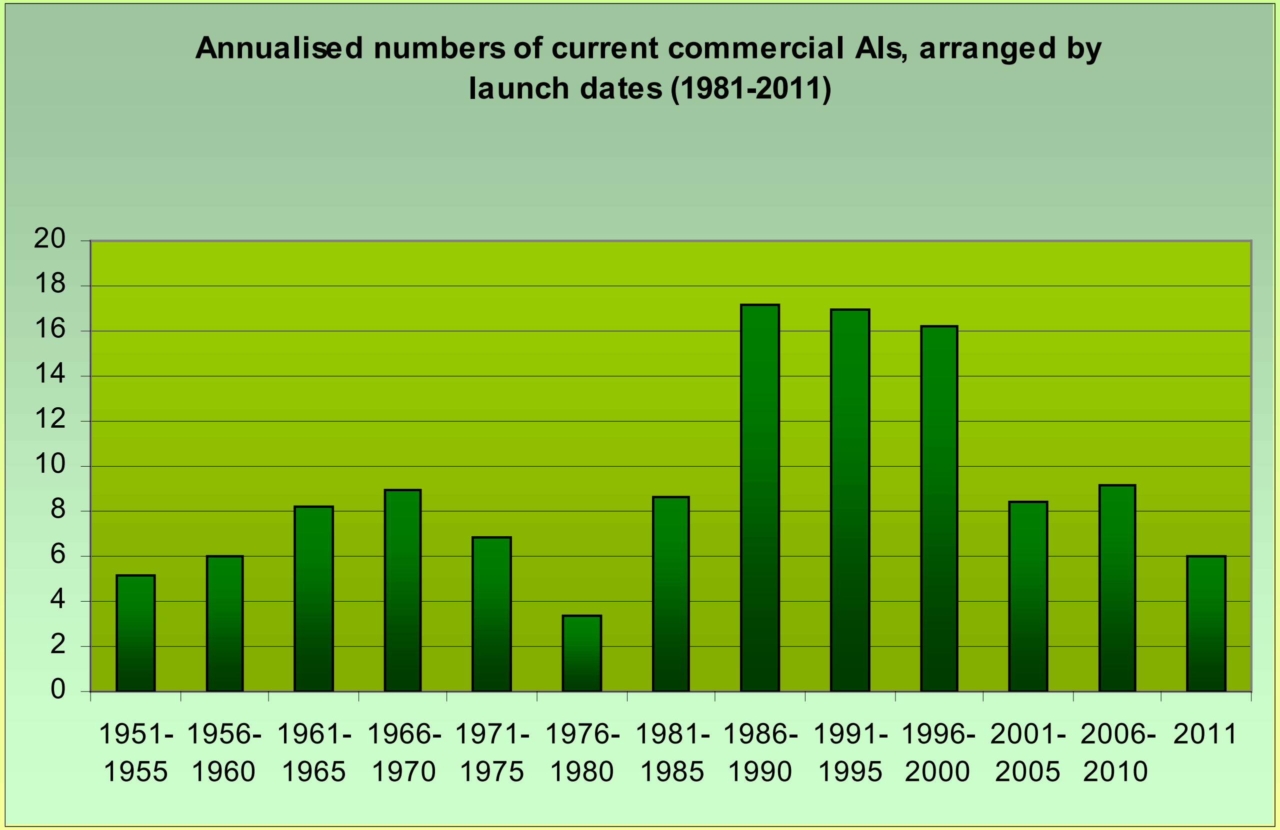
Class	*Discovery*	*First launches*
Callistemones	**1977** leptospermone. Biologist at Stauffer noticed weed suppression under bottle-brush shrubs (leptospermone was originally described in 1921 by Penfold)	**2001** mesotrione (Syngenta)
Phenoxy herbicides	**1940-1942** Independently developed by Templeman (ICI, UK) and Jones (American Chemical Paint Company, USA)	**1942-1948** 2,4-D, MCPA and 2,4,5-T
Ryanodine receptor agonists *	**1942** Ryania A crude extract from Brazilian shrub was marketed as a non-specific insecticide by Penick, using Ryanex brand-name (owned by Merck & Co.)	**2007** flubendiamide (Bayer-Nihon Nohyaku) **2008** chlorantraniloprole (DuPont) Rynaxypyr
Strobilurins	**1969** mucidin Musilek et al (fungal antibiotic) **1977** strobilurin A isolated from the mushroom by Anke & Steglich	**1996** kresoxim-methyl (BASF) **1997** azoxystrobin (Zeneca)

** important technical point: the diamides do not, in fact, interact with the ryanodine receptor, but operate through an allosteric effect (interacting with a distant part of the receptor protein, creating a conformational change)*

In spite of a great deal of effort to develop new compounds using knowledge derived from theoretical models of targets, the initial leads to the many important classes of AIs were discovered by accident or by the study of natural products.

AGRANOVA

Invention of today's agrochemicals

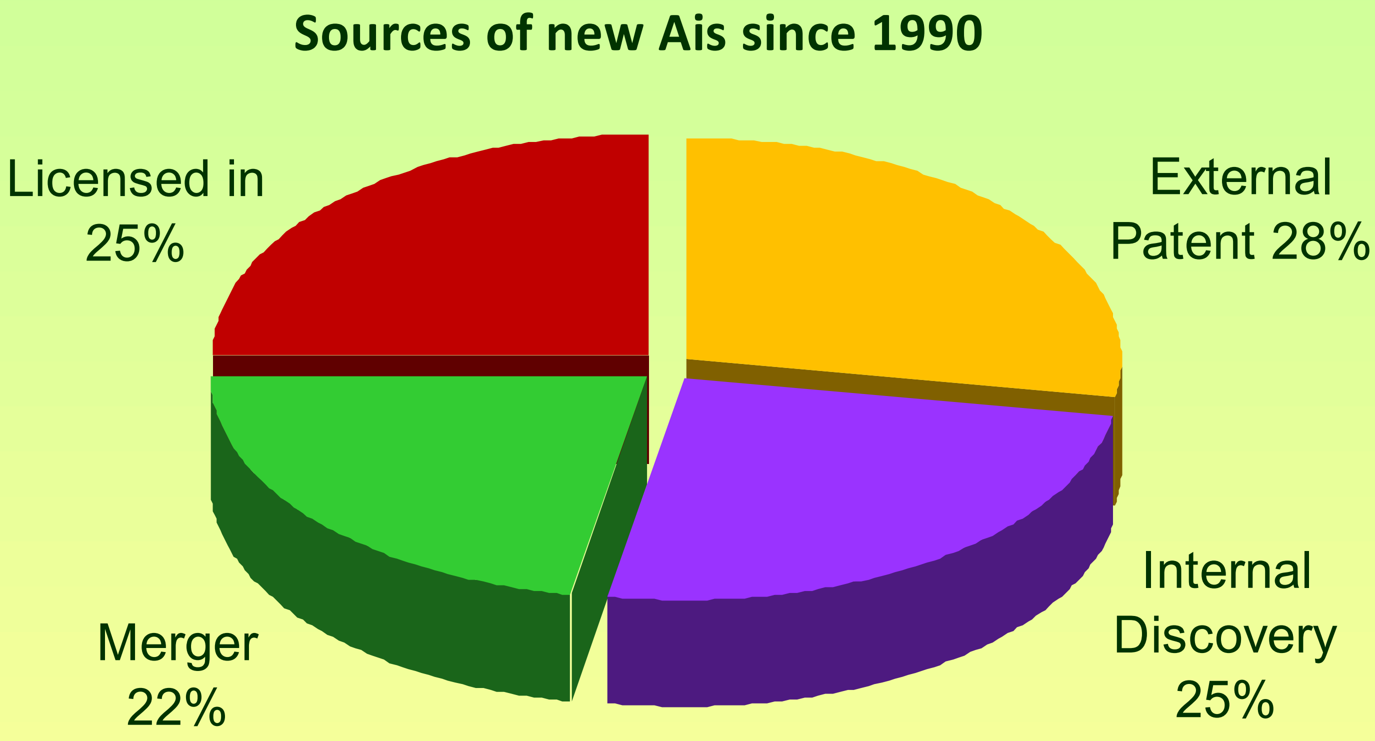


Source: Crop Protection Actives 2012 (Agranova)

*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)*

AGRANOVA

Innovation in major company R&D



Source: Dow AgroSciences / Agranova (total number of AIs: 36)

The reasons for this reduction in new agrochemical discovery within the leading Western companies are explored in the next slide

AGRANOVA

Reduced agrochemical discovery in the West

- Impact of biotechnology, especially GM crop science, on research planning. Subsequent investment in seeds and biotechnology
- Original thinking not being sufficiently supported
- Unsuccessful digression into automated discovery, *in vitro* and *in silicio methods*
- Industry consolidation leading to bureaucratic management within ever bigger companies
- Escalating development costs driven by increasing environmental and pointless regulatory legislation

Pre-discovery research partnerships (pioneered by Eli Lilly) and outsourcing research to third parties are two ways by which R&D success has been improved in the pharma sector.

AGRANOVA

The problem of resistance demands continuing innovation

- Development of resistance to agrochemical treatments is hard to avoid, especially in the faster evolving pests such as insects and micro-organisms such as fungi and bacteria

- Combining 1,2 or 3 active ingredients with different modes of action (MoAs) has become an increasingly popular means to broaden the spectrum of activity and, to a lesser extent, reduce the development of resistance

- However, this trend is driven as much by commercial reasons as by scientific need

- Ultimately, applying a better understanding of the pest's life-cycle and physiology to defeating its depredations is vital for continuing support of agriculture

The challenges of both nature and an evolving approach to what is acceptable by the general public emphasises the need to innovate at the AI level

AGRANOVA

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.

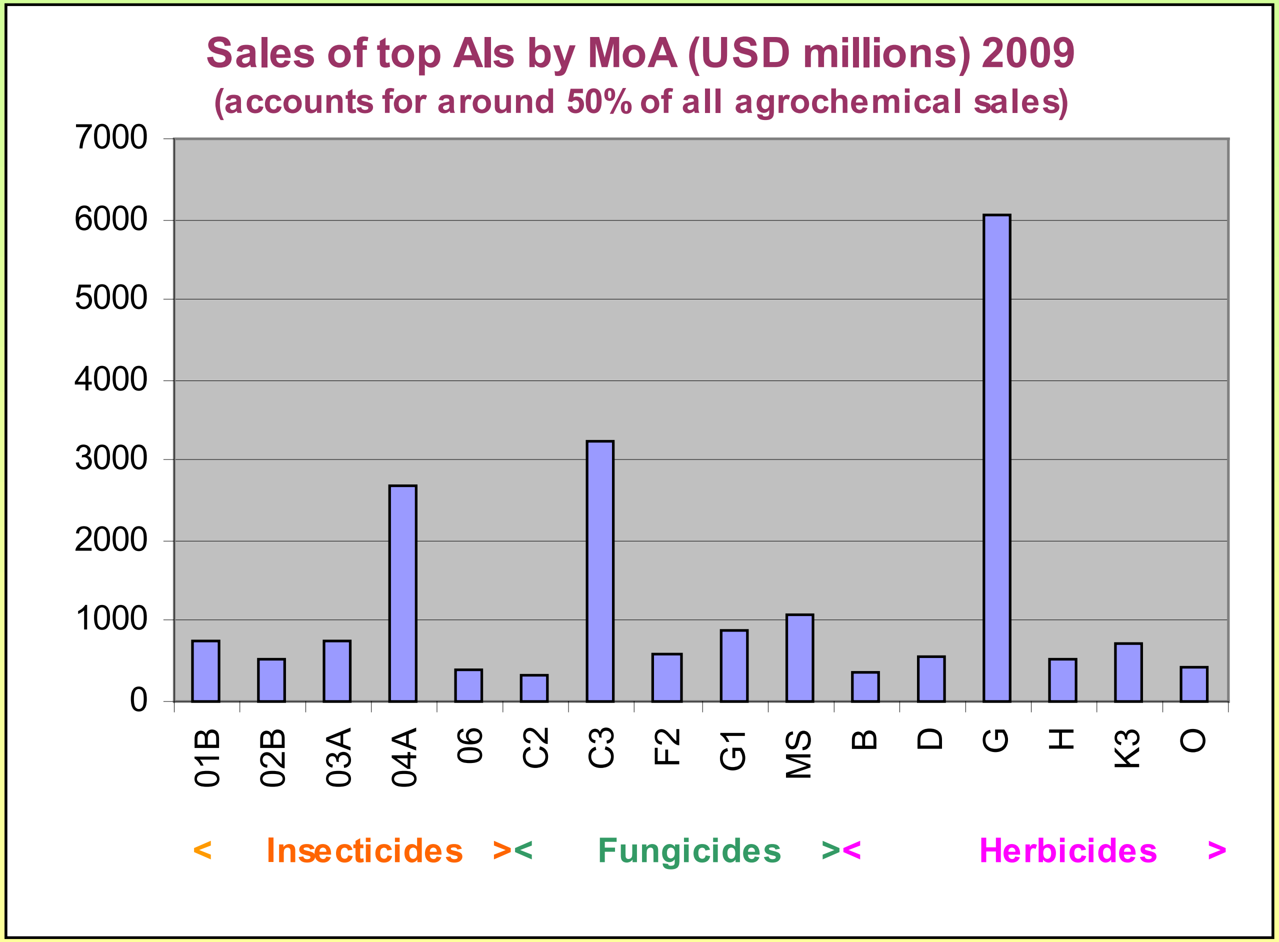
- This paucity of effective modes of action is shown in the following slides

- 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.

AGRANOVA

Major pesticide groups and their modes of action



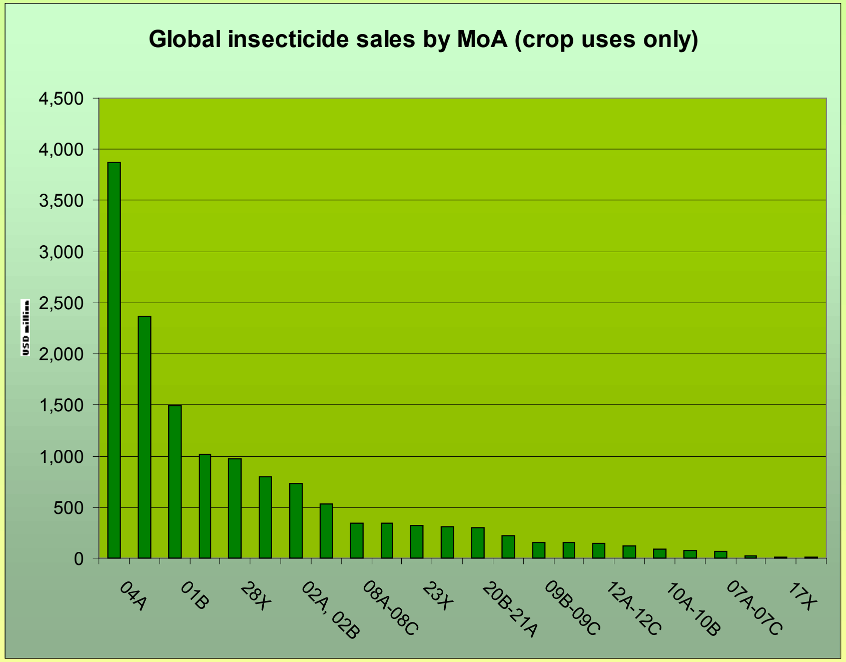
01B	acetylcholineesterase inhibitor
02B	GABA-gated chloride channel antagonist
03A	sodium channel modulator
04A	nicotinic acetylchloline receptor agonist
06	chloride channel activator
C2	Respiration
C3	Respiration
F2	Bleaching: Inhibition of 4-hydroxyphenyl-pyruvate-dioxygenase
G1	Sterol synthesis in 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)

AGRANOVA

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

Global insecticide sales by modes of action 2011

Total global insecticide sales were USD 14.5 billion in 2011 (at end-user level)



Description	IRAC code	2011 sales
nicotinic AC receptor agonist	04A	3,868
Na+ channel activator	03A	2,363
ACE inhibitor (OP)	01B	1,498
Cl- channel activator (CCA)	06	1,021
ryanodine receptor modulator	28X	975
ACE inhibitor (carbamate)	01A	798
GABA-gated CCA	02A, 02B	726
chitin synthesis inhibitors	15X-16X	529
non-specific (multisite)	08A-08C	344
allosteric nicotinic AC activator	05	340
ACCase inhibitor	23X	316
voltage-dependent Na+ channel blockers	22A-22B	306
mitochondrial electron transport inhibitor	20B-21A	294
unknown	3-UNKN	224
homopteran antifeedant	09B-09C	158
moulting disruptor	18X	155
mitochondrial ATP synthase inhibitor	12A-12C	140
nicotinic AC channel blocker receptor blocker	14X	118
mite growth inhibitor	10A-10B	91
phosphorylation uncoupler	13X	73
juv. hormone mimic	07A-07C	66
mitochondrial electron transport inhibitor	25X	18
dipteran moulting disruptor	17X	14
octopaminergic receptor agonist	19X	9

Sources: Insecticide Resistance Action Committee (classification of MoAs)
Crop Protection Actives 2012 (sales data for 2011)

*This picture tends to remain static, as new MoAs replace older ones. Without this **constant replacement**, loss of pest control becomes a real possibility. Treatments for sap-sucking insects and for nematodes are two such examples.*

AGRANOVA

Dwindling numbers of nematode treatments

- Nematodes cause huge crop losses, valued at anything between USD 80-120 billion in 2000
- A survey in 1986 showed that nematode crop losses in the developed world were around 3-4%, but 21% in the developing world
- This difference was largely due to the use of fumigants (to pre-treat the soil) and nematocides for pest control in the growing crop.
- By 2016, use of nearly all important nematocides will have been phased out in the West, with very little in the way of effective treatments being available

Bionematocides may or may not prove to be effective. The likelihood is that the losses will continue increase at a time when demand continues to increase

AGRANOVA

Commercial nematode treatments

Treatment class	Brands	Active Ingredient	Global sales* 2011 (USD mn)
Fumigant	Dowfume	methyl bromide	53
	Telone	1,3-dichloropropene	265
	Busan, Vapam	metam-sodium	51
	Basamid	dazomet	151
	Larvacide	chloropicrin	247
	Midas	Methyl iodide	-
	Trapex	methyl isothiocyanate	-
	Enzone	sod. tetrathiocarbonate	-
	Nemamort	DCIP	16
Organophosphate	Counter	terbufos	16
	Nemacur	fenamiphos	6
	Apache	cadusafos	-
	Thimet	phorate	41
	Hostathion	triazophos	-
	Nemakick	imicyafos	14
	Miral	isazofos	-
	Prophos	ethoprophos	-
Carbamate	Temik	aldicarb	116
	Standak	aldoxicarb	-
	Vydate	oxamyl	71
	Furadan	carbofuran	133
	Lance	cleothocarb	-
	Eclahra	fosthiazate	61

Source: Agranova

* At end-use level; includes all uses, not just for nematode treatments

AGRANOVA

The sales value of commercial nematocides and fumigants is estimated at USD 1.4 billion

Biotech nematode treatments*

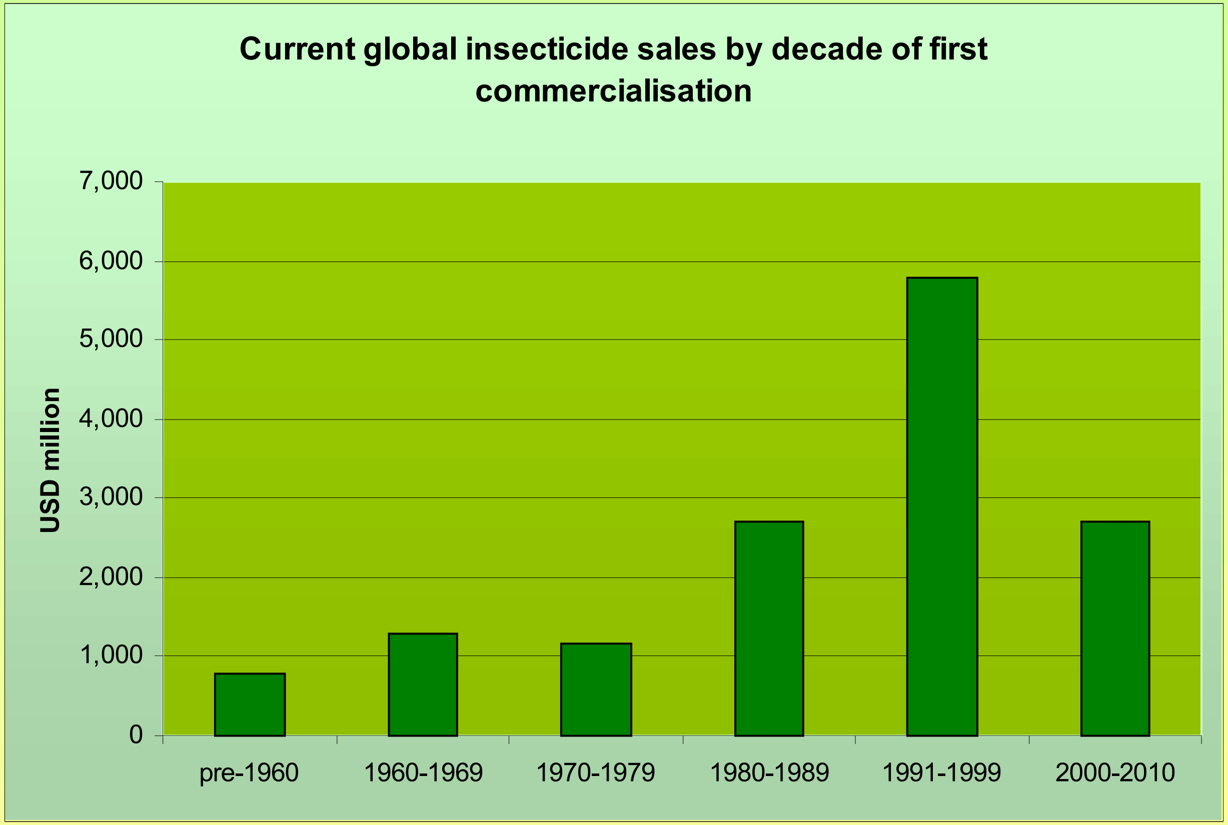
** microbial bionematocides only; plant extracts such as garlic not included*

Brands	Active Ingredient	Status
Bionem	Bacillus firmus	commercial
Prophyta, Nema	Paecilomyces lilacinus	commercial
Nemacheck	P. lilacinus strain 251	commercial
Ditera	Myrothecium verrocarria	commercial
Econem	Pasteuria usgae	commercial
Chancellor	B. firmus strain I-1582	experimental
-	Pasteuria nishizawae	Experimental
Houbao Lun Zhijun	Verticillium chlamydosporium ZK7	experimental

The sales value of commercial bionematocides, including plant extracts, probably lies within the range of USD 30-40 million

AGRANOVA

Global insecticide sales



The commercial value of insecticides introduced in the sixties and seventies is fast declining; new MoAs will be needed to replace those launched in the nineties during the next decades

AGRANOVA

Cross resistance: the problem with “me-too”s

This is why new MoAs need to be developed!

It is analogous to the problem with Ford Escorts in the UK during the 1980s. The same key fitted 1 in 9 cars!

This is also why farmer education remains a major challenge to the agrochemical industry.

Flubendiamide (Takumi) was registered in May 2007 and within 15 months it had begun to lose its value (following the same fate as spinosad, chlorfenpyr, abamectin and indoxacarb before). Overuse is a major issue in this rapid loss of efficacy. By the time chlorantraniliprole Rynaxypyr) was launched (in 2010, cross-resistance meant that it too was ineffective against DBM.

AGRANOVA

AI launches since 2000 - MoAs

Launch	Common Name	Chemistry	IRAC code	Group (IRAC)	MoA
2008	spirotetramat	spirotetronic acid	23X	tetronic and tetramates	AcetylCoA carboxylase (ACCase) inhibitor (lipid synthesis)
2003	spiromesifen	spirotetronic acid	23X	tetronic and tetramates	AcetylCoA carboxylase (ACCase) inhibitor (lipid synthesis)
2002	spirodiclofen	tetronic acid	23X	tetronic and tetramates	AcetylCoA carboxylase (ACCase) inhibitor (lipid synthesis)
2011	lepimectin	semisynthetic milbemectin derivative	06	avermectin/milbamectin	Chloride channel activator
2000	chromafenozide	hydrazide	18X	diacylhydrazines	Ecdysone agonists / moulting disruptors
2010	pyriprole	phenylpyrazole	02B	phenylpyrazole (fiprole)	GABA-gated chloride channel antagonist
2005	ethiprole	arylpyrazole	02B	phenylpyrazole (fiprole)	GABA-gated chloride channel antagonist
2006	bistrifluron	benzoylphenylurea	15X	benzoylureas	Inhibitors of chitin biosynthesis, type 0
2003	noviflumuron	benzoylurea	15X	Benzoylureas	Inhibitors of chitin biosynthesis, type 0
2002	tolfenpyrad	carboxamide	21A	METI acaricides	Mitochondrial complex I electron transport inhibitors
2008	cyenopyrafen	pyrazole	25X	cyenopyrafen	Mitochondrial complex II electron transport inhibitors
2007	cyflumetofen	bridged diphenyl	25X	cyflumetofen	Mitochondrial complex II electron transport inhibitors
2002	fluacrypyrim	strobilurin (but with miticidal activity)	20C	fluacrypyrim	Mitochondrial complex III electron transport inhibitors
2002	dinotefuran	nitroguanidine (neonicotinoid)	04A	neonicotinoid	Nicotinic acetylchloline receptor agonist
2002	clothianidin	neonicotinoid	04A	neonicotinoid	Nicotinic acetylchloline receptor agonist
2000	thiacloprid	chloronicotinyl (neonicotinoid)	04A	neonicotinoid	Nicotinic acetylchloline receptor agonist
2008	spinetoram	mixture of spinosyn derivatives	05	spinosyn	Nicotinic acetylchloline receptor allosteric activator
2007	chlorantraniliprole	anthranilamide	28X	diamides	Ryanodine receptor modulator
2007	flubendiamide	phthalic acid diamide	28X	diamides	Ryanodine receptor modulator
2003	flonicamid	pyridinecarboxamide	09C	flonicamid	Selective homopteran feeding blocker
2002	gamma-cyhalothrin	synthetic pyrethroid	03A	pyrethroids/pyrethrins	Sodium channel modulator
2002	metofluthrin	synthetic pyrethroid	03A	pyrethroids/pyrethrins	Sodium channel modulator
2010	pyrifluquinazon	quinazolinone	3-UNKN	pyrifluquinazon	Unknown
2004	pyridalyl	dichlophenyl diether	3-UNKN	pyridalyl	Unknown
2007	metaflumizone	semicarbazone	22B	metaflumizone	Voltage-dependent sodium channel blockers

Sources: Pesticide Resistance Action Committees (classification of MoAs) and Crop Protection Actives 2010 (Agranova)

Four new MoAs and two unknown MoAs, plus ten known MoAs.
Conclusion: still too many "me-too"s

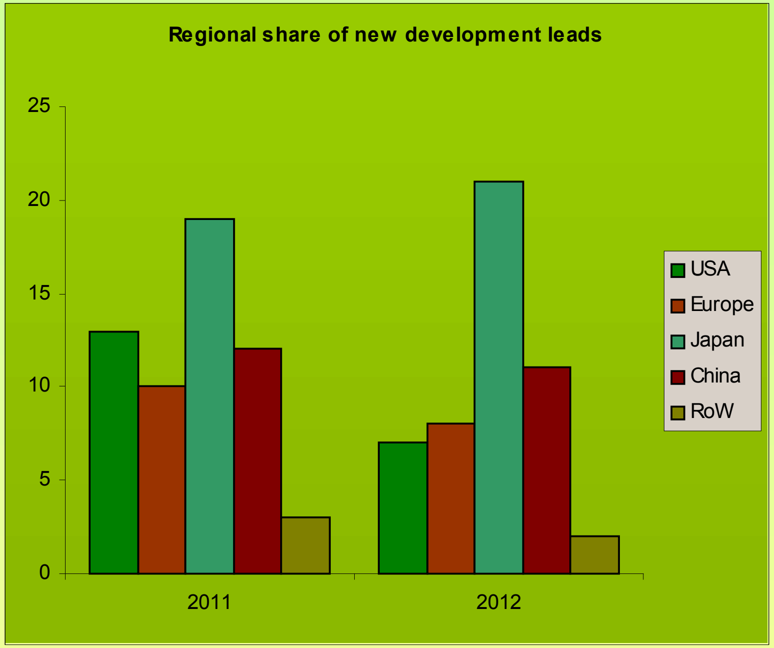
AGRANOVA

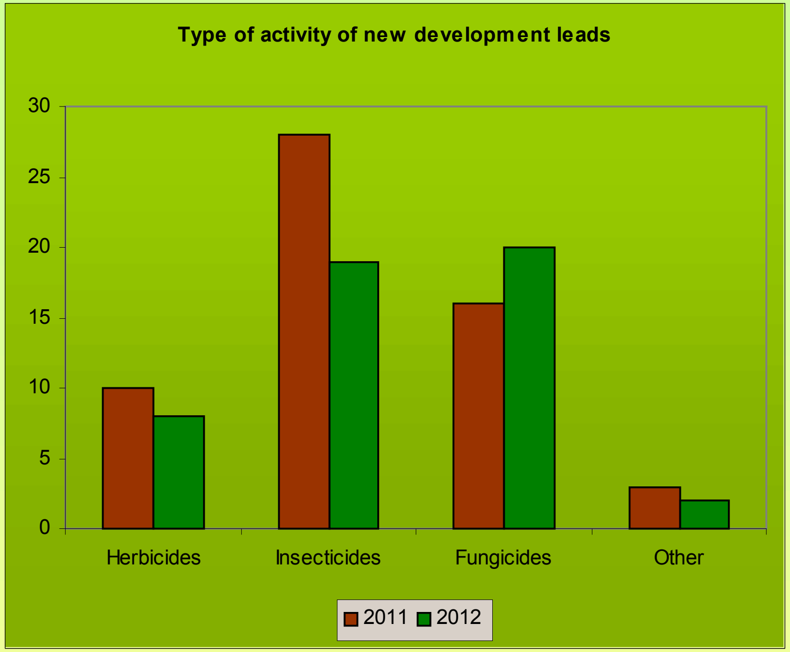
Developing new AIs with novel modes of action

- 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.
- “Intermediate derivatisation discovery” approach is one new idea that has been developed by SYRICI with success in China
- Re-examination of useful leads discarded in the 1970-1990s might also 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.

Current R&D pipeline

Taking up the burden of discovery





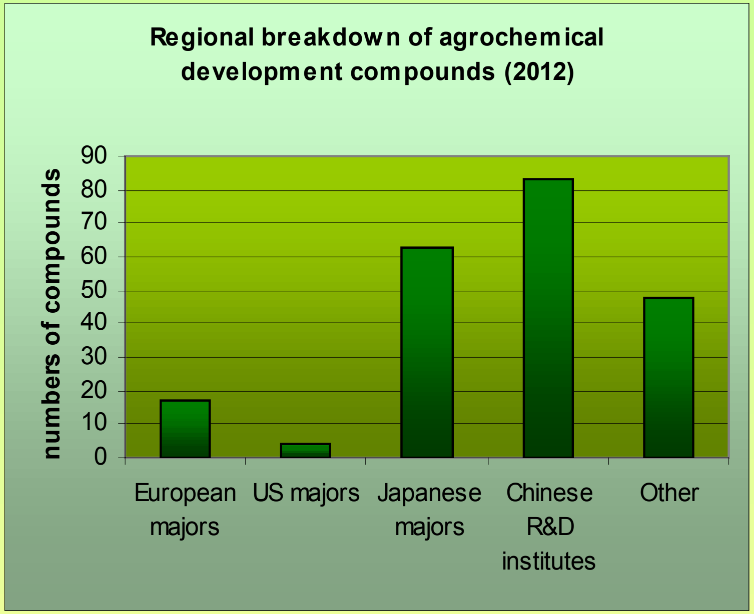
Source: Ag Chem New Compound Review (Vol 29-30) 2011-2

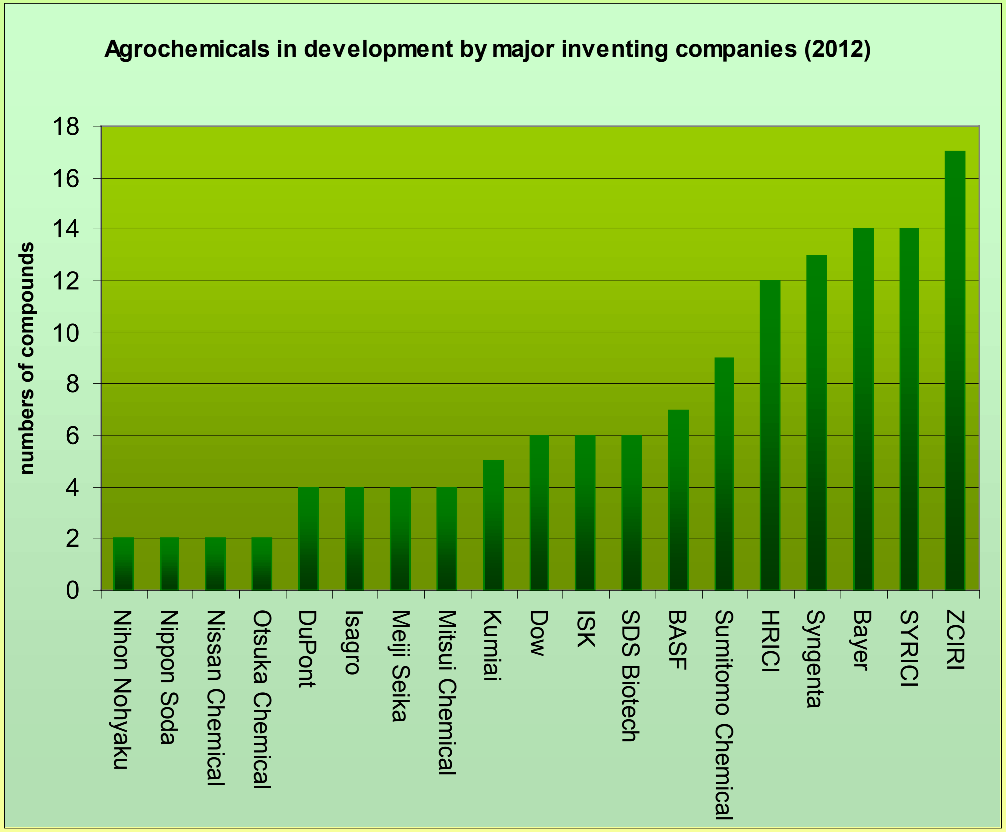
- In the late 1990s-early 2000s Japan took over from the USA and Europe as a major source of new agrochemical discovery
- China's R&D effort emerged in the mid-2000s as a new centre for discovery

AGRANOVA

*Research into new herbicides has reduced, as a result of the changing centres of R&D efforts. Around **two thirds** of new developments were novel agro**chemicals***

Current R&D pipeline - discovery groups





The striking decline in US & European agrochemical research is, in part, the result of the emphasis on GM crop research.

Source: Ag Chem Base 2012 (Agranova)

- Current pipeline contains around 220 development products
- R&D is no longer dominated by the major agrochemical companies*

AGRANOVA

*** NOTE: this is a quantitative analysis and the quality of new developments**

Outlook

AGRANOVA

Outlook

- Advances in the discovery and development of new agrochemicals has slowed in the West, following a productive twentieth century.
- Although new biotech solutions are delivering benefits, the need for new chemistries will continue to be vital to combat many pest problems.
- 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 sustain their leadership role, discovery will become concentrated in Asia.

It matters less where new research occurs,
more that its fruits are brought to market.

AGRANOVA

If you have been, thank you for listening

Acknowledgements

Dr Tom Sparks (Dow AgroSciences) for useful comments and information.

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

Dr Rob Bryant

Agranova

34 The Drive

Orpington, Kent BR6 9AP

United Kingdom

Tel: +44 1689 600 501, Fax: +44 1689 897 786

Email: rob@agranova.co.uk

Website: www.agranova.com

AGRANOVA