



Asia leads the way

Dr Rob Bryant reviews the development, commercialisation and maturation of agchems in a year when the weather, escalating costs and changes in global planting patterns have created interesting challenges for the industry

Information gathered by Agrow and Agranova suggests that 2007 was a slightly more productive year for the entry of novel agrochemical actives (ais) into active development (see Table 1). Over 100 new compounds had been identified between the start of 2007 and January 2008. Unsurprisingly, given the increased emphasis on biotechnology in the US and Europe, the percentage of new leads coming from Asia reached an all-time high of 76%. Over the past few years, China and Korea have emerged to join Japan as important centres for agrochemical research. Admittedly, there has been some “catch-up” in identifying new leads and many Chinese development compounds are not particularly innovative, but this is likely to be the situation in the early days of any new endeavour.

Table 1: New agrochemical developments in Asia, 2007/2008

US/Europe	20
Japan	21
China	54
Korea	6
Total	101

Source: Ag Chem Base (Agranova)

The early days of Japan’s agrochemical discovery effort was also not taken particularly seriously by Westerners. However, the significance of Japanese agrochemical research today is demonstrated by the importance major multinationals place in agreeing joint development programmes with leading Japanese companies.

India remains stubbornly resistant to the challenges of innovative discovery in the life sciences, both in agrochemical research and in pharmaceutical discovery. The comparative weakness of the Indian public sector probably is the major reason for this paradox. Certainly, India lacks neither the scientific nor the technological base for this important activity.

Gathering information and drawing conclusions about innovation is difficult. R&D spend is much quoted in the US and Europe, but this has proved to be a very poor guide. Experience teaches that such figures tend to be more about commercial posturing than any real measure of inspired discovery effort. Comparing numbers of patents, citations or any other similar measures, such as numbers of development compounds being

introduced, is also often misleading. Nevertheless, if a long enough period of time is taken, useful insights might be obtained. A comparison of the leading organisations that have come up with the most new developmental leads (agrochemical and biological) from 1998 to 2008 is presented in Table 2. The big three European companies are at the top of the list, as could be expected, given the fact that all have made substantial acquisitions to become what they are today. However, the growing significance of Asian organisations during the last ten years is again clearly confirmed, with nearly 40% of the leads generated by the top 18 organisations.

Table 2: Innovation by leading R&D companies and institutes by number of new leads *, 1998-2008

Bayer Cropscience	58
BASF	36
Syngenta	34
Sumitomo Chemical	20
USDA	18
Dow Agrosience	17
DuPont Agro	17
Nihon Nohyaku	14
Shenyang Research Institute (SYRICI)	12
FMC	12
Sankyo Agro	11
Otsuka Chemicals	10
Zhejiang Research Institute (ZRICI)	11
Isagro-Ricerca	9
Kumiai	9
Arysta Lifescience	8
Nissan Chemical	6
Korean Research Institute (KRICT)	6

Sub-total for leading companies 309

Total agrochemical leads identified 610

Source: Ag Chem Base (Agranova)

*Note: around 150 biologicals also entered development

Insecticides to the fore

In spite of all the agchem leads entering development, the annual crop of new approvals and launches remains disappointingly low. However, 2007 was marked by the first launch of an insecticide with a novel mode of action (MOA) since 1993 (when imidacloprid was first commercialised by Nihon Bayer). In the Philippines, DuPont has started to sell its new ryanodine receptor insecticide, chlorantranilprole (Rynaxypyr), as a treatment for rice and vegetables, under the brand name Prevathon. The mode of action is complex, but

basically it acts on the calcium channel receptors that control nervous impulses in insects. It works in a similar way to a natural product, ryania, which was marketed as an insecticide by Merck in the 1940s. The problem with ryania was that it was as effective against mammals as it was against insects. This new class of active ingredient has the major advantage that it has far greater selectivity towards insects. DuPont's follow-up compound, cyazypyr, is not expected to reach market much before 2010.

Another ryanodine receptor insecticide, Bayer-Nihon Nohyaku's flubendiamide, which won its first approvals in 2007, is generally considered to be of more limited spectrum, offering more restricted modes of application. Other new insecticides that won their first approvals in 2007 included Bayer's third tetrone acid derivative (spirotriamet), Otsuka's first new product since 1994, cyflumetofen (brand name Danisaraba) and Dow's second spinosyn insecticide, spinetoram (brand name Delegate, Radiant).

Approvals for three herbicide variants on established themes were awarded to Dow and Bayer. Isagro launched another herbicide of an established MOA, orthosulfamuron (Strada), in the US. Two fungicides also saw their first approvals, Dow's variant on an old theme, meptyldinocap, and Isagro, with valiphenal, another variant on an established theme.

Replacing methyl bromide as a soil fumigant, which is its main use, has proved far harder than the legislators originally expected, when they agreed to ban it as part of the Montreal Protocol in 1997. According to the US EPA, 65,000 tonnes of methyl bromide is still used annually, of which North America uses about 40%. Arysta Lifesciences' newly introduced Midas contains the well-established chloropicrin (ineffective against nematodes) with the newly approved iodomethane. The US EPA granted a one-year registration for Midas in October 2007, which probably reflects the concerns expressed about its safety by a number of scientists and pressure groups in the US. Arysta also obtained approval for the use of iodomethane as a timber treatment in Japan in November 2007.

Application of metam salts as soil fumigants, which have the advantage that they lack proprietary protection, is also on the increase. Dow's Telopic (dichloropropene mixed with chloropicrin) and BASF's Basamid (contains dazomet, which decomposes to methyl isothiocyanate in the soil) are two other alternatives that are co-marketed by ICL, the world's biggest producer of bromomethane.

Frustration of registration

The European Union continued to frustrate the efforts of the generics agchems industry in 2007, with continued failure to complete the re-registration process. And by granting a 10-year data exclusivity for an old product like ethofumesate in 2007, the whole exercise seems one designed to pander to Europe's big three companies. This former Fisons active ingredient was originally discovered in 1969 – see British Patent 1271659 (for younger readers: look this company up in your history books!). Napropamide is another product that is expected soon to receive a new lease of proprietary life through an Annex I listing.

However, the multinational groups have not been getting it all their own way. The registration for Dow Agro's trifluralin has been withdrawn by the EU, which cites the compound's persistence as the reason for the ban. Many EU formulations, including rapeseed herbicides, will be discontinued by this decision, which Dow is currently challenging.

In China, the government has also helped the multinational agchem groups by banning the use of all agrochemical brand names from 8 January 2008. Re-registering brands is far less of a burden relatively speaking to a multinational than to a local company. At the end of 2007, 23,000 brands (a conservative estimate) had been registered (700 alone for imidacloprid formulations). This tactic was used in 2006 to simplify the huge number of pharmaceutical brands, but the measure also assisted the multinational companies to establish a stronger foothold in that country. While one can sympathise with the Chinese authorities, who have been playing a cat-and-mouse game with the endless cunning of Chinese producers of formulations, this action is also likely to allow the multinational giants to secure a firmer presence in this expanding market.

Big price increases have been imposed by the brand leaders in 2007. These have been only partly justified by increased costs, generated by energy and feedstock price inflation. It is hoped that a good percentage of the higher profits being generated by the multinational discovery companies will be used to invigorate their R&D rather than continue to make their shareholders richer. Without their leadership in discovery, and a continued flow of new agrochemical products, the industry is unlikely to meet the challenges of a rapidly changing world. 

Dr Rob Bryant runs a specialist consultancy, Brychem, which undertakes confidential studies on the fine chemical industry and its major customers (www.brychem.com). See also Agranova (www.agranova.com).

NEW ACTIVE INGREDIENTS REGISTERED OR LAUNCHED IN 2007

Company & Product	Use	Status
HERBICIDES/PLANT GROWTH REGULATORS		
BASF		
profoxydim (Aura)	rice herbicide	approved in Australia
tepraloxymid (Equinox)	herbicide for peas, linseed & lentils	launched in Canada
topramezone (Convey)	maize herbicide	launched in Argentina & Mexico
Bayer CropScience		
pyrasulfotole (Huskie ¹ /Infinity ¹ /Precept ²)	cereal herbicide	first global approval in US; approved in Canada & Australia
tembotrione (Equinox)	maize herbicide	first global approval in Austria; approved in US
Degussa/Agricola		
forchlorfenuron (Sitofex)	plant growth regulator for kiwi fruit	launched in Italy
Dow AgroSciences		
aminopyralid (Simplex ³)	herbicide for use on grassland	approved in Germany
florasulam (Torpedo ⁴)	cereal herbicide	approved in Australia & US
pyroxsulam (Admitt)	cereal graminicide	first global approval in Chile
Isagro/RiceCo		
orthosulfamuron (Strada)	rice herbicide	first global approval & launch in US
Ishihara Sangyo Kaisha		
flazasulfuron	herbicide for non-residential turf	approved in US
Stähler		
beflubutamid (Herbaflex)	cereal herbicide	listed in EU Annex I
Sumitomo Chemical/Interfarm		
flumioxazin (SumiMax)	wheat herbicide	approved & launched in UK & Ireland
FUNGICIDES		
BASF		
metrafenone (Vivando)	fungicide for grapevines	approved & launched in Italy
orysastrobin (Arashi)	rice fungicide	launched in Japan & South Korea
Bayer CropScience		
fluopicolide (Infinito ⁵)	fungicide for potatoes & other vegetables	approved in Germany and Poland
fluoxastrobin (Vigold)	fungicide for potatoes & tomatoes	approved in Mexico
prothioconazole (Proline/Provost ⁶)	fungicide for cereals, canola, lentils, pulses, peanuts & brassicas	approved in US & Canada
Dow AgroSciences		
meptyldinocap (Karatane Star)	fungicide for grapevines	first global approval in Romania, approved in Italy, UK & Chile
DuPont		
proquinazid (Talendo)	fungicide for grapevines	approved in Italy
Isagro		
valiphenal (Yaba M)	fungicide for grapevines, potatoes & vegetables	first global approval in Cuba

INSECTICIDES/ACARICIDES

Bayer CropScience

ethiprole (Curbix)	insecticide for sugar cane & rice	approved in Brazil
spirodiclofen (Envidor)	acaricide for pome fruit, citrus fruit & grapevines	approved & launched in Italy
spirotetramat (Movento)	insecticide for pome, stone & citrus fruit, grapevines, nuts, vegetables & potatoes	first global approval in Tunisia
thiacloprid (Calypso)	insecticide for pome fruit	approved in Canada

Certis Europe

Spodoptera exigua nuclear polyhedrosis virus (Spod-X)	bio-insecticide for peppers & ornamentals	listed in EU Annex I; approved in Spain
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Dow AgroSciences

spinetoram (Delegate/Radiant)	insecticide for fruit, vegetables & field crops	first global approval in New Zealand; approved in US & Canada
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DuPont

chlorantraniliprole (Prevathon)	insecticide for cabbages, aubergines, long beans & rice	first global approval & launch in Philippines; & launched in Indonesia & Romania
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Isihara Sangyo Kaisha/Belchim

flonicamid (Teppeki)	insecticide for tomatoes, curcubits, peaches & melons	approved in Italy
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Makhteshim-Agan Industries

novaluron (Rimon)	insecticide for potatoes & apples	approved in Canada
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Nihon Nohyaku/BASF

metaflumizone (Verismo/Alverde)	insecticide for tomatoes, potatoes, peppers & chillies	first global launch in Colombia; launched in Austria & Indonesia; approved in Germany; approved in US as fire-ant bait
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Nihon Nohayku/Bayer CropScience

flubendiamide (Phoenix/Fenos/Fame/Belt)	insecticide for fruit, vegetables, soybeans & tea	first global approvals in Japan & Philippines; approved in India & Pakistan
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Otsuka

cyflumetofen (Danisraba)	acaricide for fruit trees, vegetables, tea & ornamentals	first global approval & launch in Japan
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Sankyo Agro/Comercial Química Massó

milbemectin (Milbeknock)	acaricide for apples & strawberries	approved in Italy
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Sumitomo Chemical

pyridalyl (Pleo)	insecticide for cabbages	approved in China
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FUMIGANTS

Arysta LifeScience

iodomethane (Midas ¹)	soil fumigant for strawberries, tomatoes, peppers, stone fruit, nuts, grapevines, turf & ornamentals	first global approval in US
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Dow AgroSciences

sulfuryl fluoride (ProFume)	fumigant to control insects in buildings & storage, pests in silos & warehouses	approved in Australia
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¹ in combination with bromoxynil; ² in combination with MCPA; ³ in combination with fluroxypyr; ⁴ in combination with clopyralid; ⁵ in combination with propamocarb; ⁶ in combination with tebuconazole; ⁷ in combination with chloropicrin.