



# Controlled Delivery of Agrochemicals

Ian Shirley



Chemspec europe Symposium 28 June 2007 RAI Amsterdam

# Scheme

Scope of this talk

Snapshot of the Ag industry

Range of CR technologies

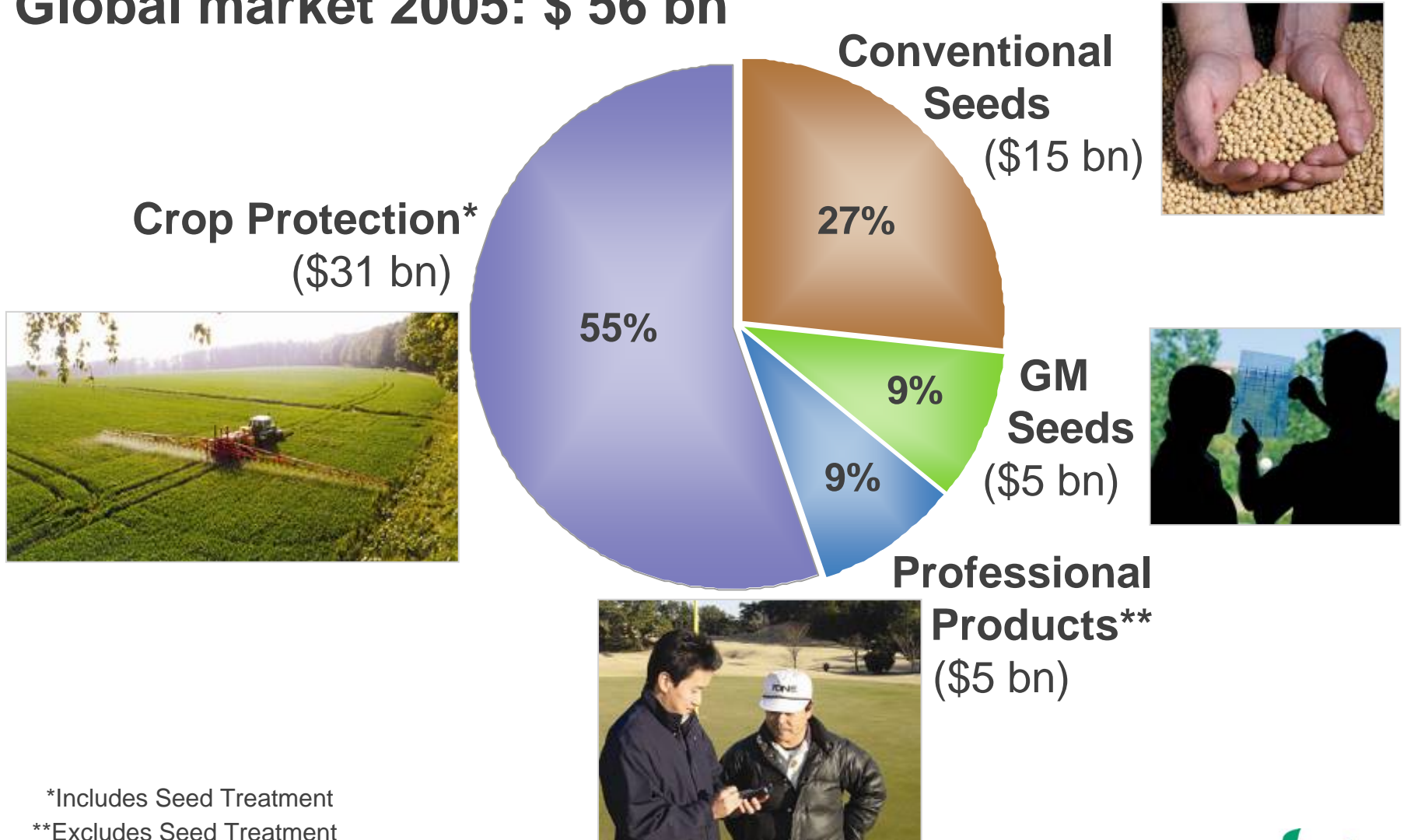
Examples of selected technologies

# Scope

- Controlled Delivery/Release technology is used in many industries – personal care, pharmaceuticals, food, agrochemicals
- “Agrochemicals” include pesticides (I/F), herbicides, fertilisers (adjuvants, attractants, biocides)
- Agrochemicals are used for crop protection, animal and public health, materials protection, home and garden etc
- This presentation
  - is restricted to “agrochemicals” where cost is an important factor of Pharma
  - provides a snapshot overview of selected topics over the last 15 years – **not comprehensive**
  - is presented from a formulators point of view
  - focus primarily on patents → reasonable reduction to practice
  - abbreviates **Active Ingredient** as “**AI**”

# Agribusiness: a large, global industry

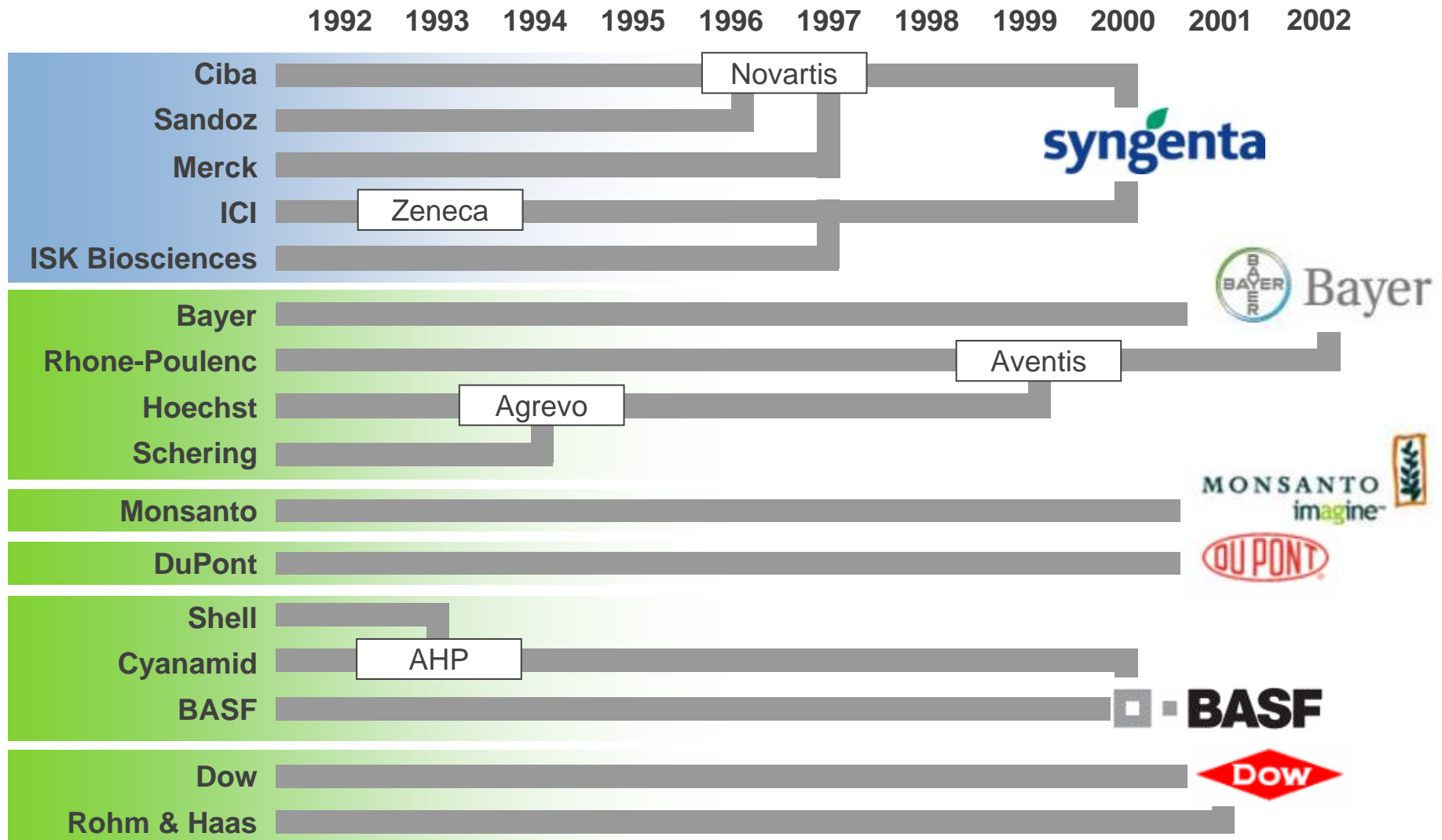
Global market 2005: \$ 56 bn



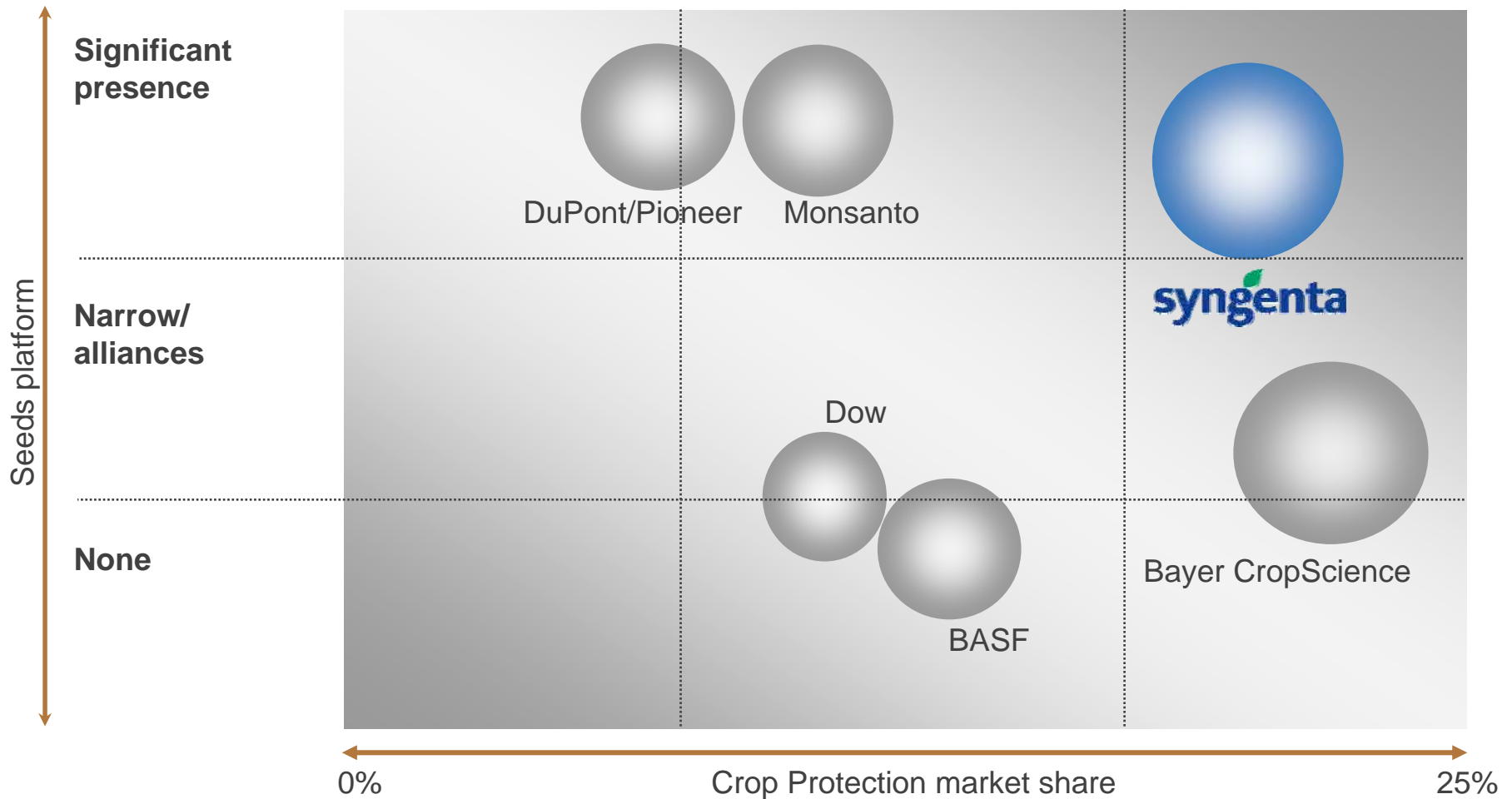
\*Includes Seed Treatment

\*\*Excludes Seed Treatment

# Our industry family tree

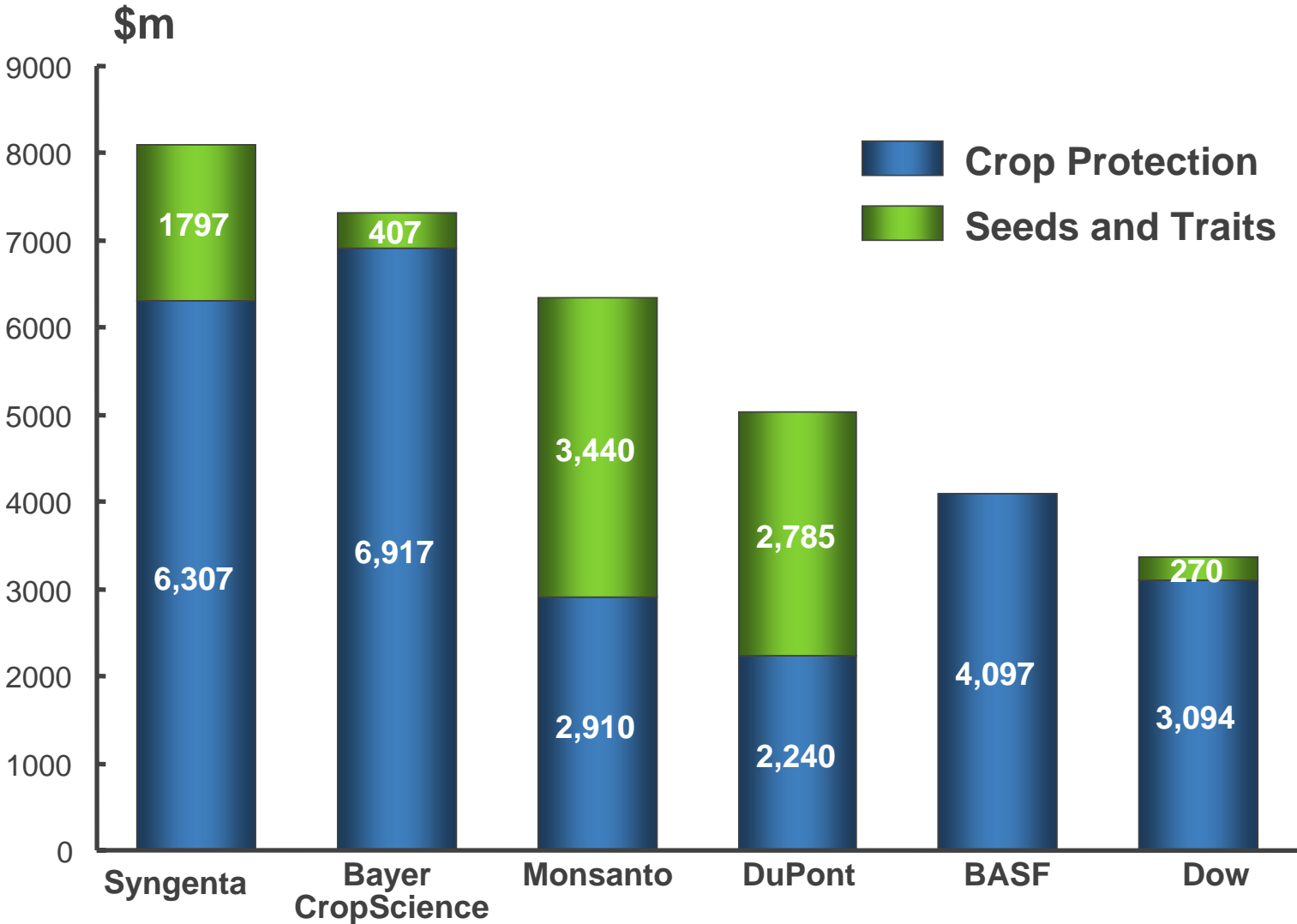


# Six global competitors

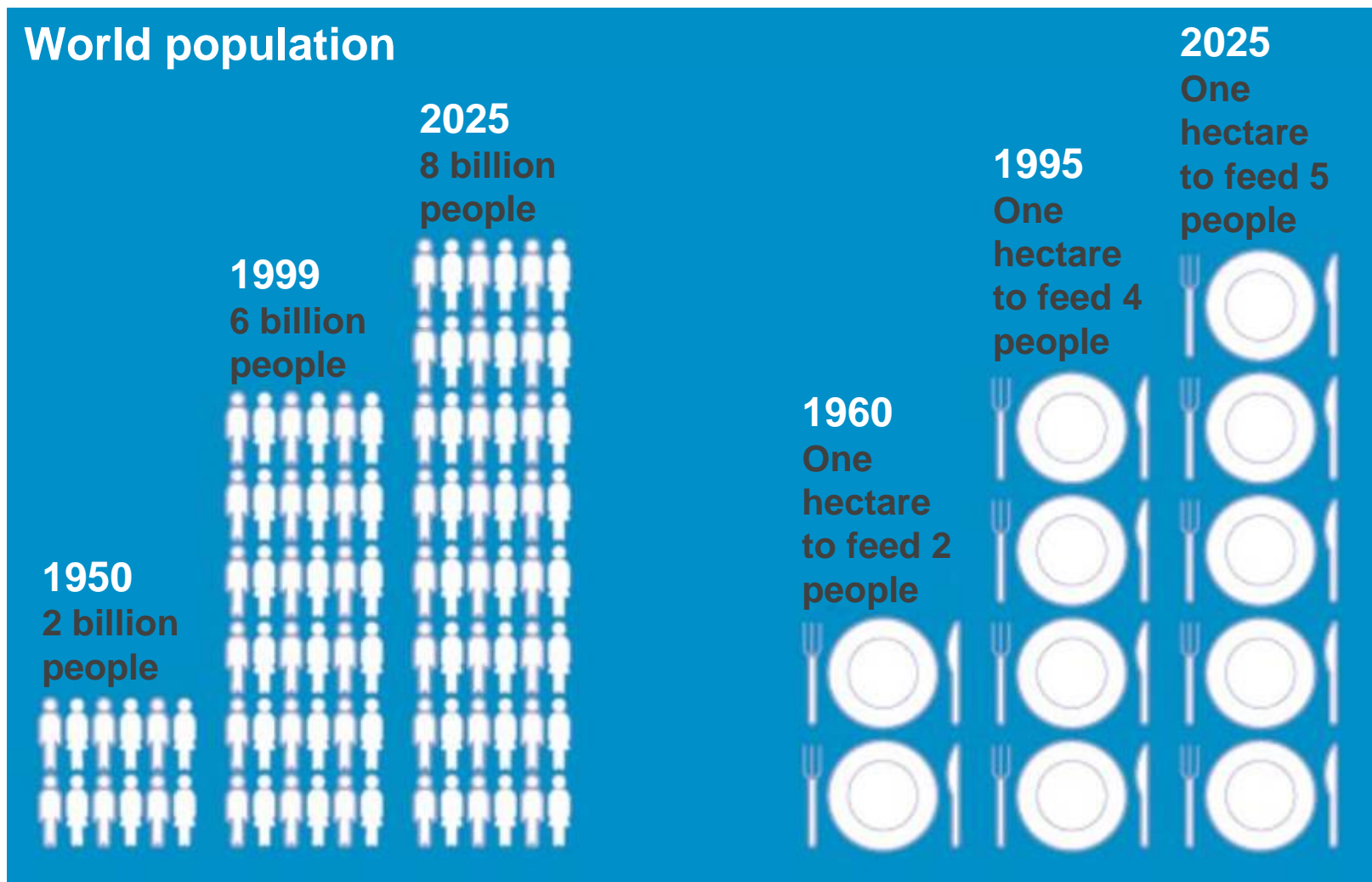


Source: Phillips McDougall, Syngenta

# 2005 Sales of Major Agribusiness Companies

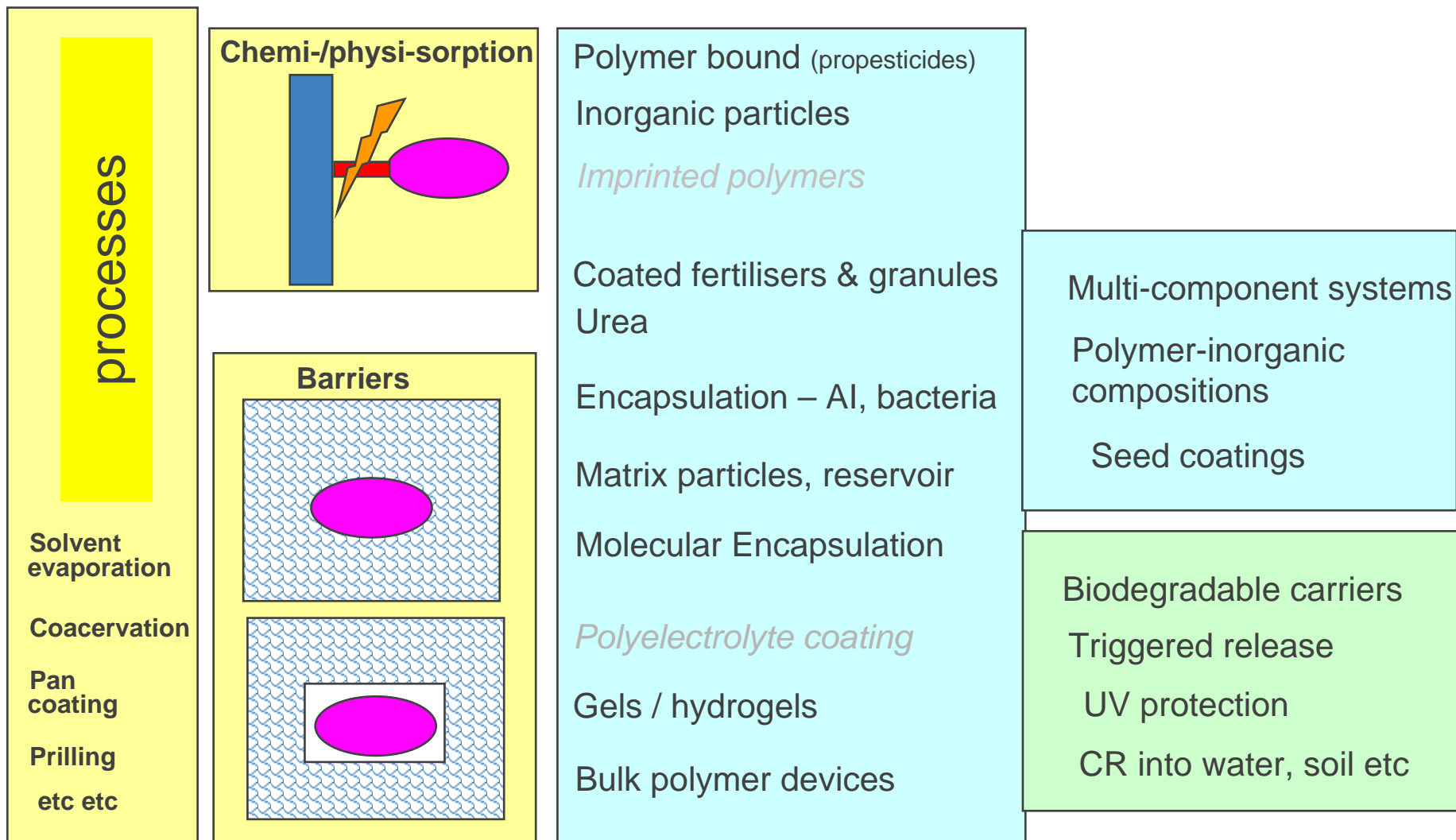


# Demand is driven by population growth and scarcity of land



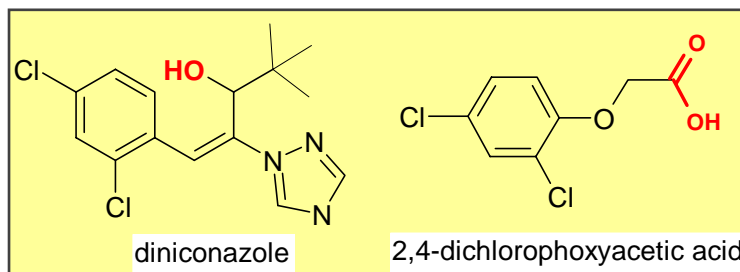
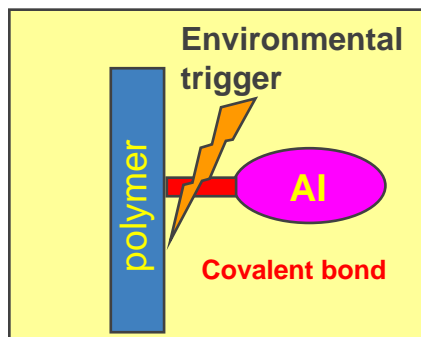


# Controlled delivery technologies in Ag - a simplified view

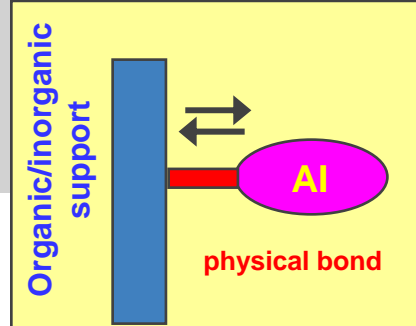


# Chemi-sorption – polymer bound AI's

- AI is covalently bonded to (polymeric) support
- After application bond cleaved by trigger (environmental eg pH, hydrolysis) to liberate AI
- Little recent patent activity (primarily papers) → limitations
  - AI specific (ie not generic)
  - AI must have appropriate functional group
  - Environmental triggers unpredictable

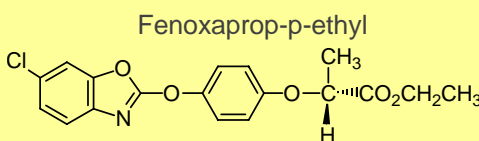
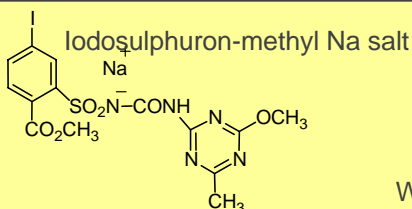


# Physi-sorption

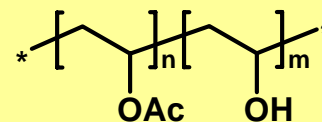


- Low cost, low tech
- Physical bonding to organic or inorganic supports

H-bonding between AI-polymer (PVOH) gives some control over rel rate (cf when no polymer is present)



WO 2001084927



Inorganic carrier	AI	Driver	
Activated carbon	S-methoprene	Mosquito larval control	US2006/0188572
Colloidal silica, alumina	Codlemone	<i>Lepidoptera</i> pheromone	US2003/0031694
Activated carbon	isothiazolone	Microbial control (coatings)	EP1142477

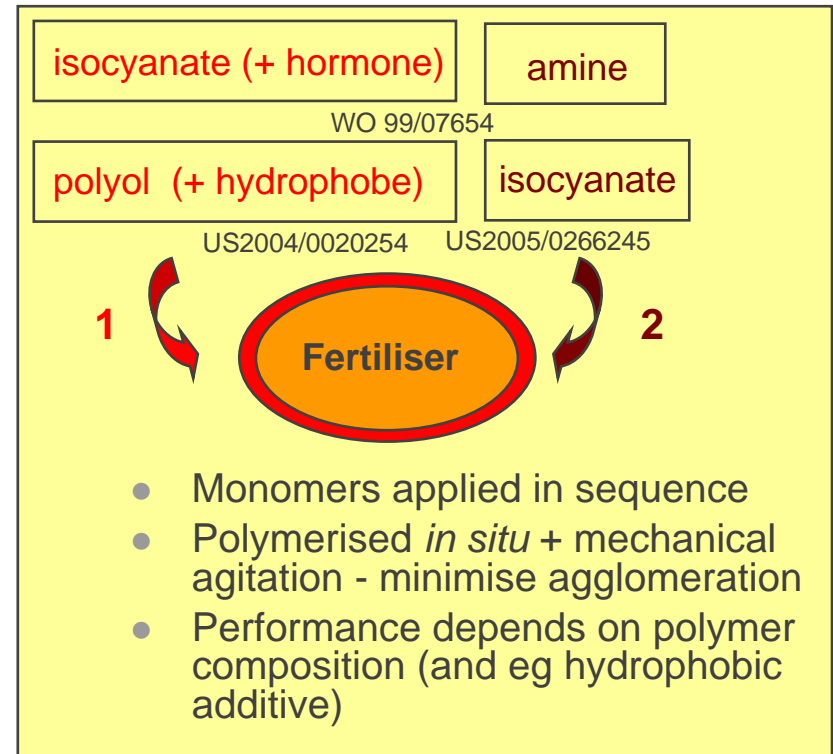
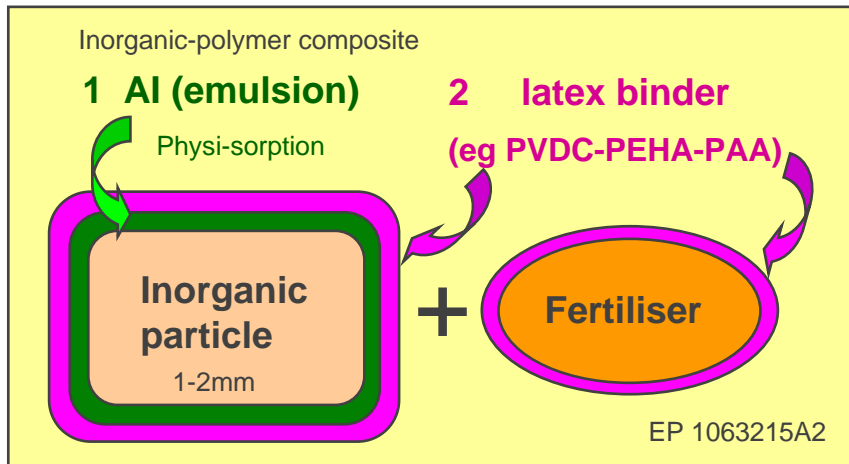
# Coated Fertilisers and Granules

Multi-component systems

Polymer-inorganic compositions

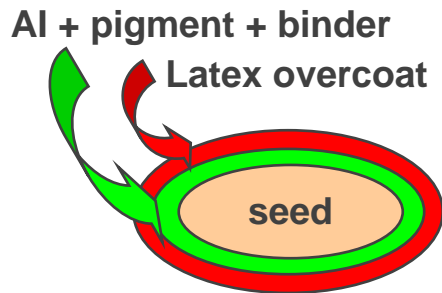
Seed coatings

- Twists on established generally low cost technology
- Significant patent activity in Japan
- Many processes; vacuum coatings <sup>US6080221</sup>, latex, *in situ* polymerisation



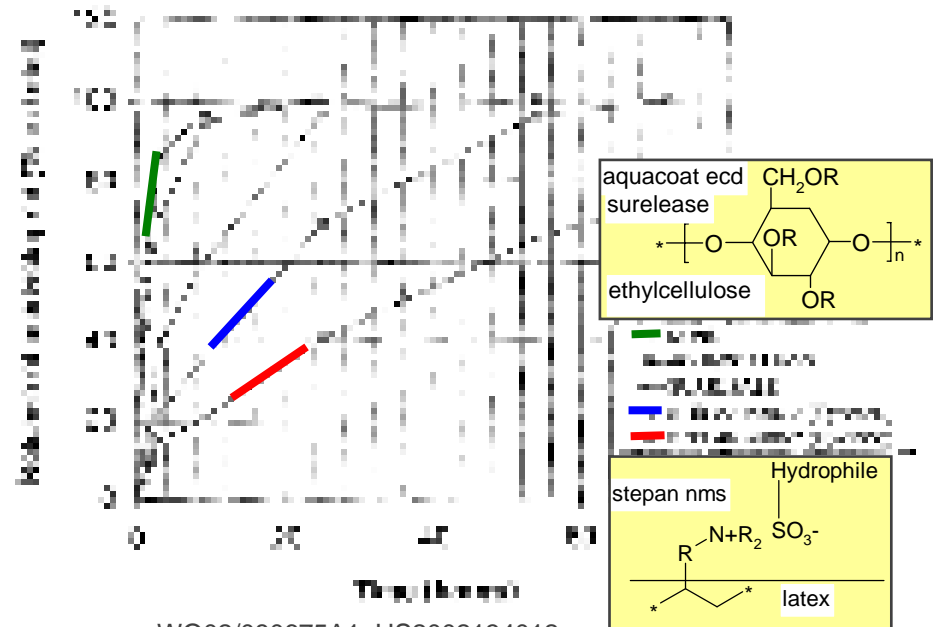
# CR – seed coatings

- One stop ST – convenience of spray or soil applied
- Must minimise AI exposure – no dust
- Must release AI at chosen rate
- Must not inhibit germination



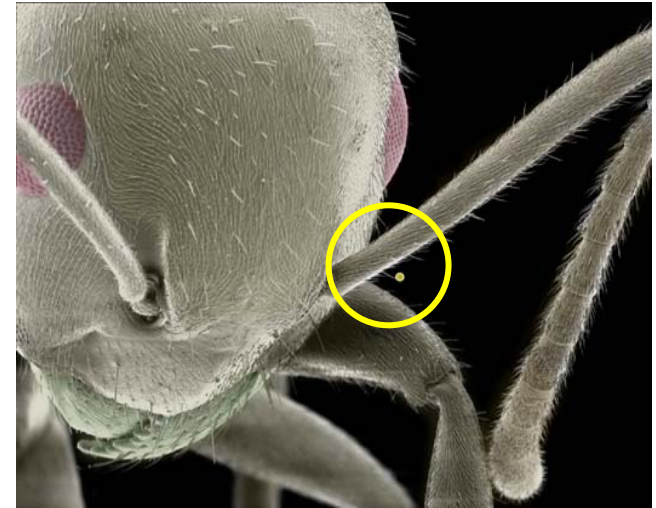
Latex overcoats control release rate (into water) of imidacloprid

Figure 1.



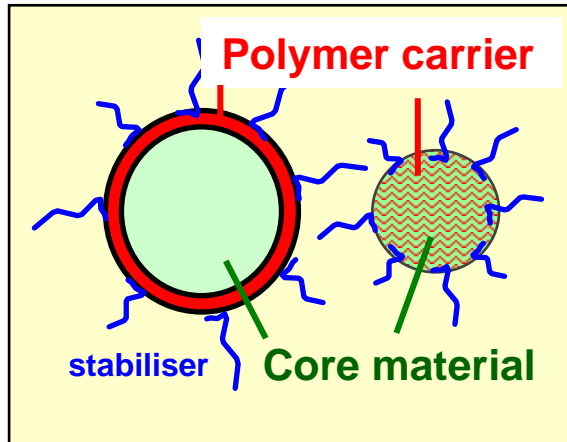
WO02/080675A1, US2002134012

# MICROCAPSULE TECHNOLOGIES FOR AG



- Basic concepts have been covered
  - Professor Dennis Poncelet, ENITIAA (Food Engineering School), France  
[Microencapsulation: Fundamentals, Applications and Technology](#)
  - Dr Ronald J Versic, Ronald T. Dodge Co., USA  
[Using Microencapsulation to Achieve Controlled Release](#)
- Focus here is on recent work, particularly from the Ag majors, where there is strong drive for commercialisation

# Microcapsules general

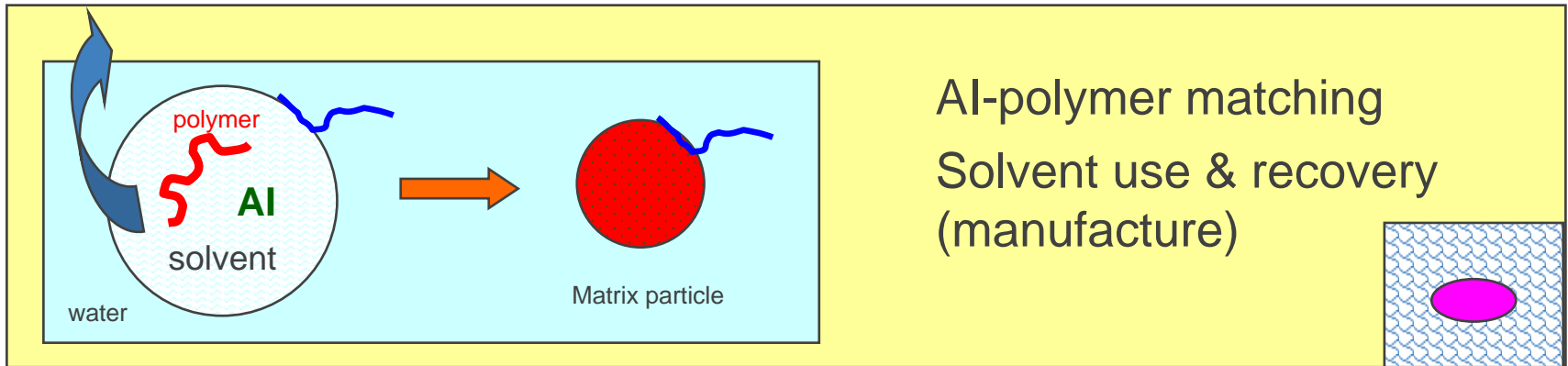


- Versatile technology – high payloads, safety
- FTO important → Majors carve territory
- Much work outside Ag – narrow picture here of some key players

- Options for varying parameters

- **Colloid stabilisers**
- **Polymer composition/quantity and surface modification**
- **Core materials – solvents; mixtures; eutectics, solid dispersion**
- Capsule sizes
- Mixtures – caps + other types
- Process
- Presentation

# Matrix microparticles – solvent evaporation process



Lignin acetate

Imidacloprid  
Silthiopham

UV photostabilisation

Monsanto US2003 0013612

Poly(lactic Acid)  
Cellulose acetate butyrate  
Poly(styrene)

Cyproconazole

Phytotox reduction

Monsanto US7070795

PMMA, PS-co-MAN, PVAc  
Phthalic anhydride,  
Dibutylphthalate

Tebuconazole

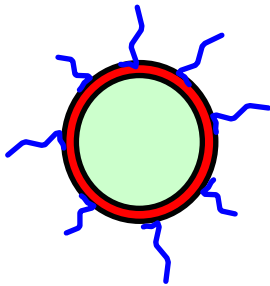
Plasticiser controls  
release rate

Monsanto WO02/21913



# Bayer capsule technology - 1

Ag applications illustrated here – does not include uses in perfumes, carbonless copy paper etc



**2001 protein hydrolysates** – EP1151789 US2002009495 – mainly carbonless paper copying

**2000 \*oxadiazinetrione (+TDI) + poly-ol/amine** DE19840583, US6566306 DE19840582, US6653256

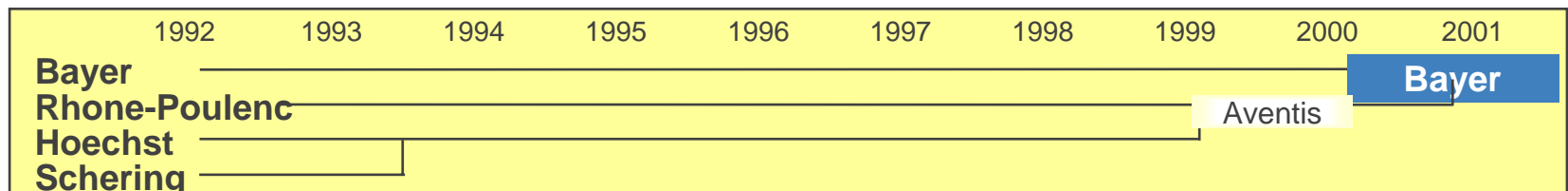
**2002 isocyanurate + guanidine** US6797670B2 EP1199100 – mainly carbonless paper copying

**2001 \* PU 2 phase wall + dispersed solid encapsulated in non-solvent + external SC** WO2001068234, US6730635

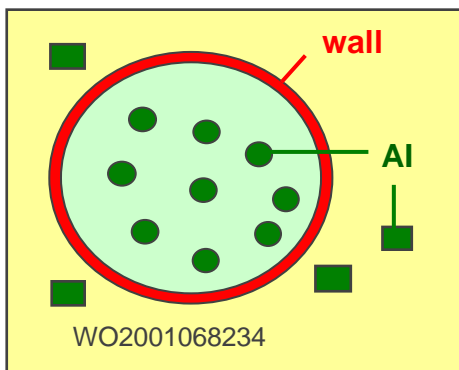
**2001 \*PU 2 phase + dispersed solid encapsulated in non-solvent strengthened by vinyl polymerisation** 2001 DE19947147, CA2385991 –ST CS strength

**2003 penetrant aid + non-encapsulated AI SC** WO2003099005, US2005221991

Aqueous endosulfan microcapsule dispersion DE19646880 **Hoechst**

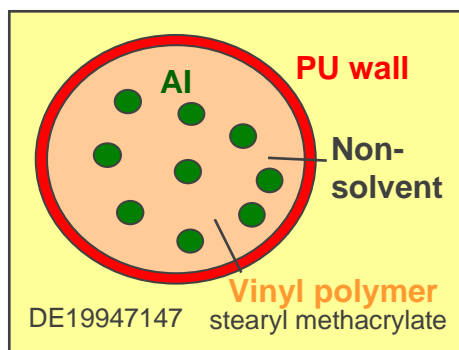


# Bayer capsule technology - 2



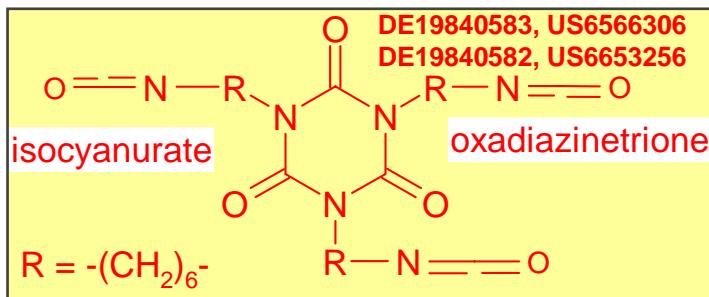
**PU 2 phase wall + dispersed solid encapsulated in non-solvent + external SC**

- Controlled release + formulation stability
- Multi-component system



**PU 2 phase wall + dispersed solid encapsulated in non-solvent strengthened by vinyl polymerisation**

- Enhancing capsule strength for seed treatment

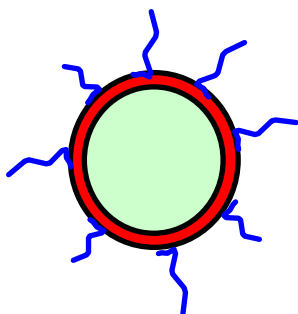


**oxadiazinetriene (+TDI) + poly-ol/amine**

- Release rate via wall composition

# BASF capsule technology - 1

Ag applications here do not include uses in leather, pressure sensitive recording materials, vitamin, printing, coatings, copying, laundry, detergents, dyes, adhesives (except latent heat storage)

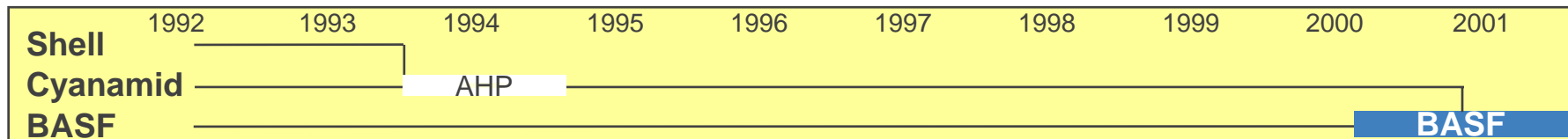


2007 \***polymer particle film formation** from **Pickering emulsion** WO07033931

1993 **Gelatin-glutaraldehyde coacervate on diazinon containing feeding deterrent** DE4309756 (Micro Flo Co)

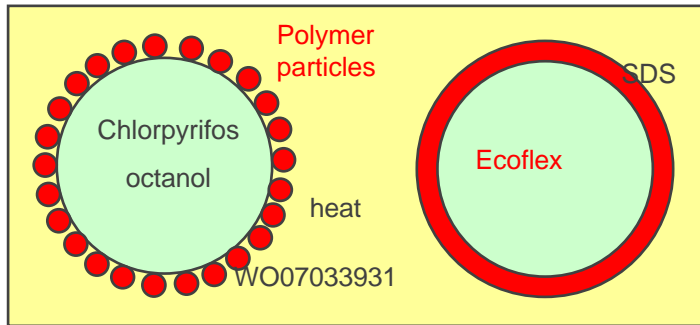
2006 \***WO2006/092409 H2O absorbing inclusion PU 2 phase wall** release

2004 **PU 2 phase wall Pendimethalin** – WO2004/008852



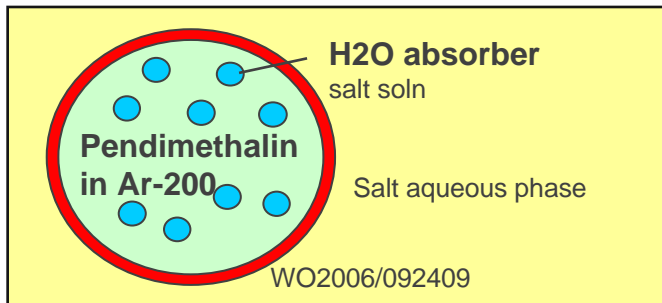
Shell & Cyanamid activity predates the present 15 year analysis.

# BASF Capsule Technology - 2



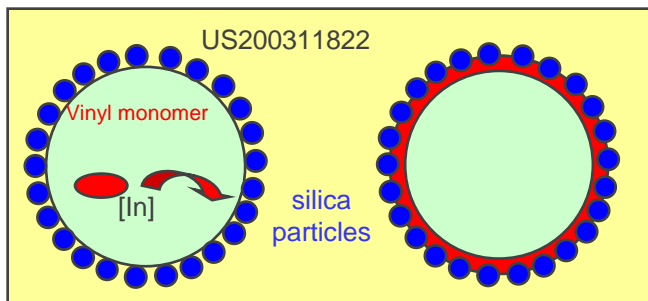
polymer particle film formation of pickering emulsion

- Potential for variation of polymer compositions



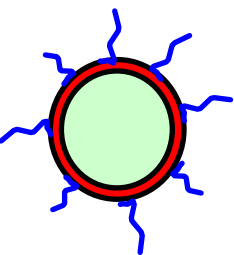
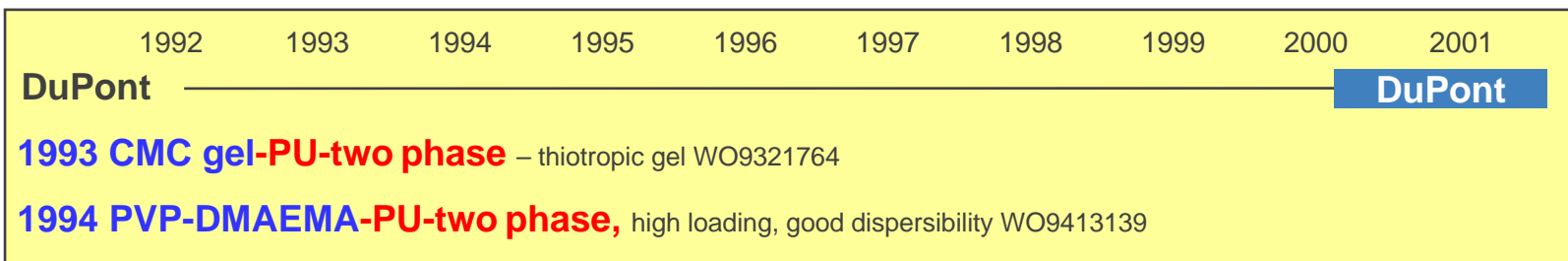
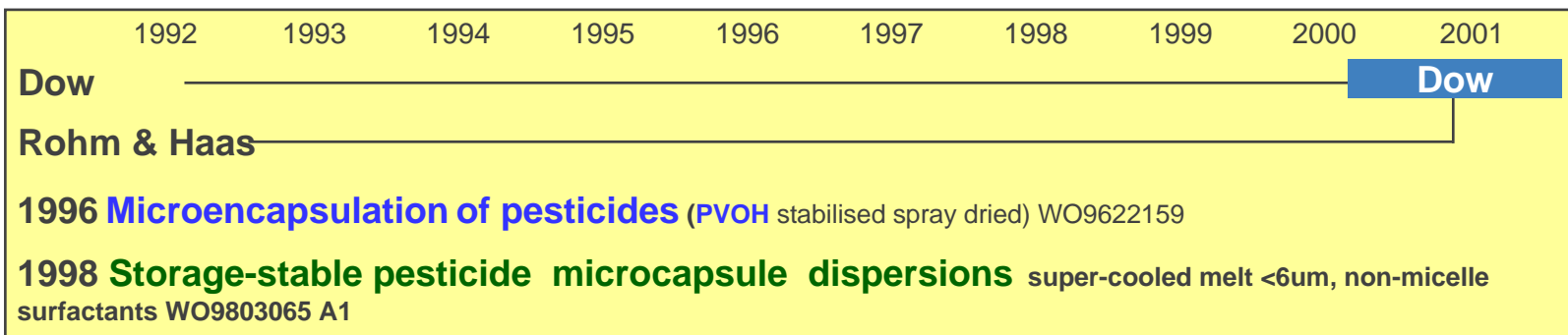
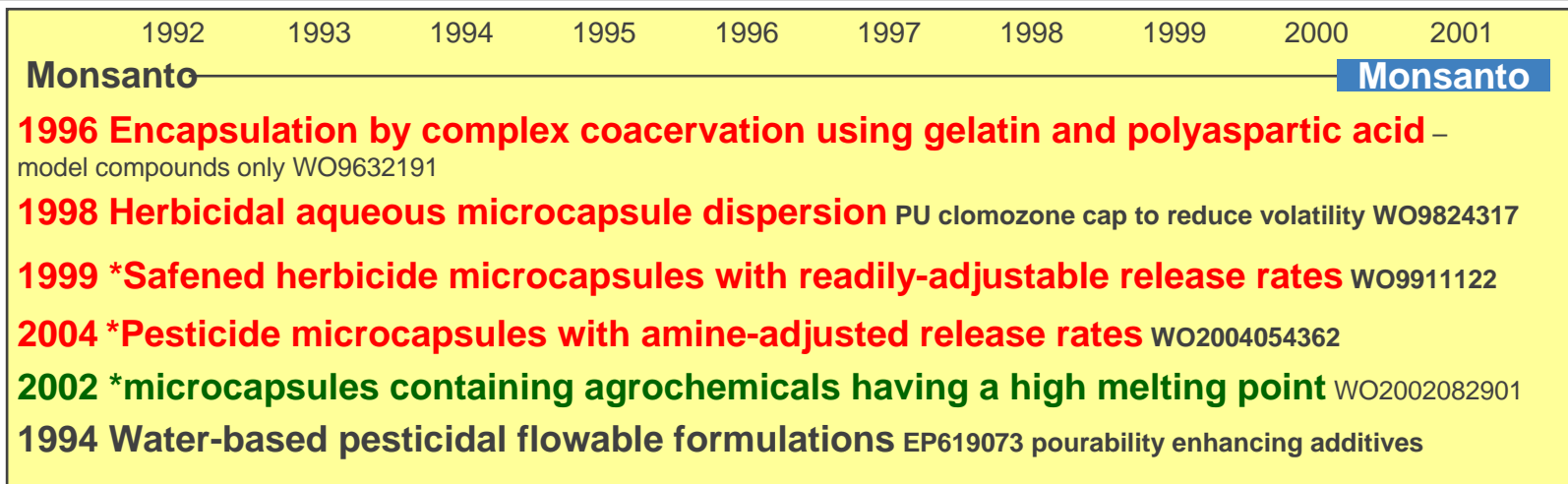
PU 2 phase wall encapsulating AI & H2O absorbing inclusion

- Objective – fast release, and seed treatment for fungicide or insecticide
- Technical - Osmotic balance? Dry vs wet? Release in spray tank?

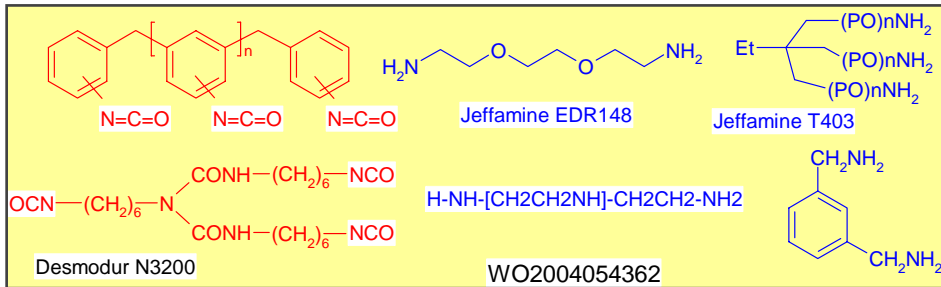


*in situ* vinyl monomer polymerisation via pickering emulsion  
(Not Ag but neat – heat storage)

# Ag Industries - capsule technology

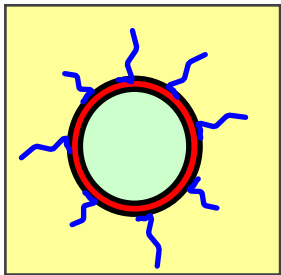


# Monsanto reservoir capsule technology



## capsules with amine-adjusted release rates

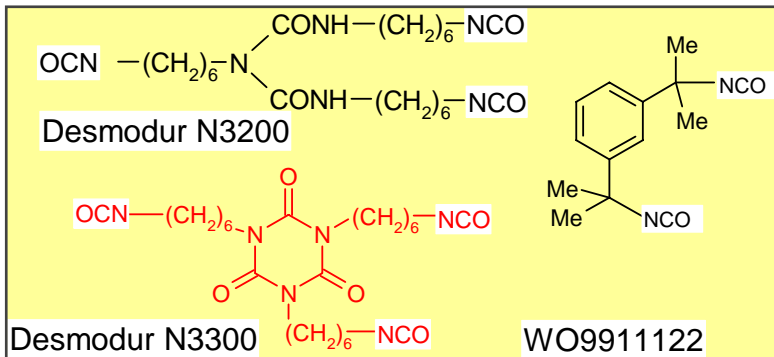
- Combination of amines gives good control over release rate



## AI-melting point depression

WO2002082901

- silthiopham (86°C) + tebuconazole (100°C) → 50°C eutectic or depressed by acetyl tri-n-butylcitrate
- Desmodur N3200+TMXDI ← TETA/Jeffamine T404
- Low odour; process at manageable temps for high mp AI; differential rel rate of diff AI's; different isocyanate feedstocks



## adjustable rel rate safened herbi caps

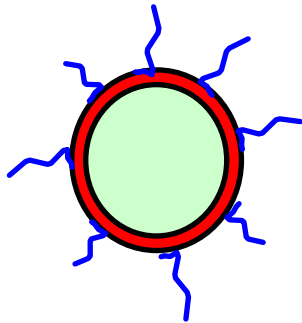
- Blends of di-/tri-NCO's cured (TETA or DETA) → release rates days to years.
- Differential rel of co-encapsulated AIs.
- Carves out wall composition IP

# Syngenta capsule technology

**S-MA surfactant-PU-two phase** US5310721, EP551796

**PVOH-PVEMA -polyester** EP517669

**non-ionic surfactant -PU-two phase** EP611253



\*microcaps in water dissolvable tapes WO9720627

Nano-capsules by phase inversion WO2002068111

Microcapsules bound to fabric WO2007036710

**melamine-formaldehyde coacervate** WO2000062612

**Urea-dialdehyde** EP532462

\***Fast release by monomer composition** WO97/44125

\***Acid triggered release** WO2000005952

\***Triggered release ester capsules** WO2000005951

\***Triggered release disulphide capsules** WO2001019509

\***Surface modified capsules** WO2001094001

\***Reactive polymeric surfactants** WO2002100525

**U-F coacervation** EP532463

\***Co-encapsulated organic photoprotectants** WO2006089747

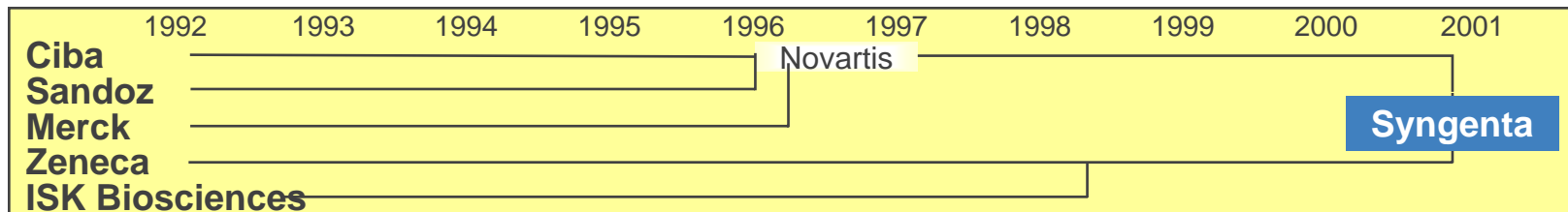
\***Particulate Ultraviolet protectant** US5846554

\***CS of Oil Dispersion** WO 95/13698

**Encapsulated adjuvants** WO 2004/017734

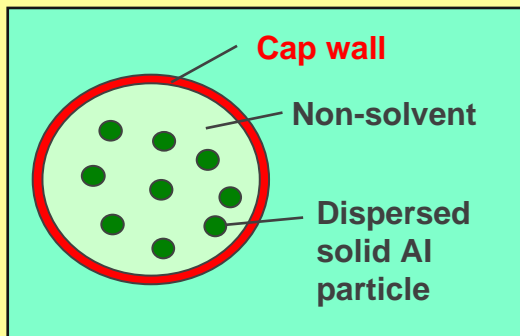
**Nucleation promoter for microcrystal formation** WO9603039

**UV protectant and dispersed AI** WO9633611



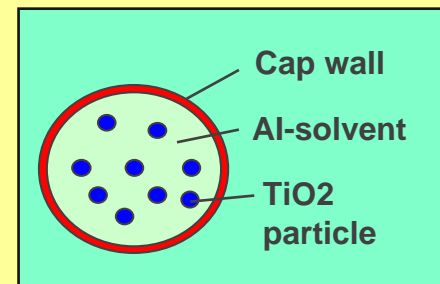
# Encapsulated dispersions

- High mp 'low solubility' AI is dispersed in non-solvent & dispersion is encapsulated.
- Formulation stability, benefits some AI's
- Requires careful selection of oil dispersant and capsule stabilisers
- Load capacity is a limitation



WO 95/13698

- Similar technology can be used to co-encapsulate particulate photoprotectants such as TiO<sub>2</sub>



US5846554



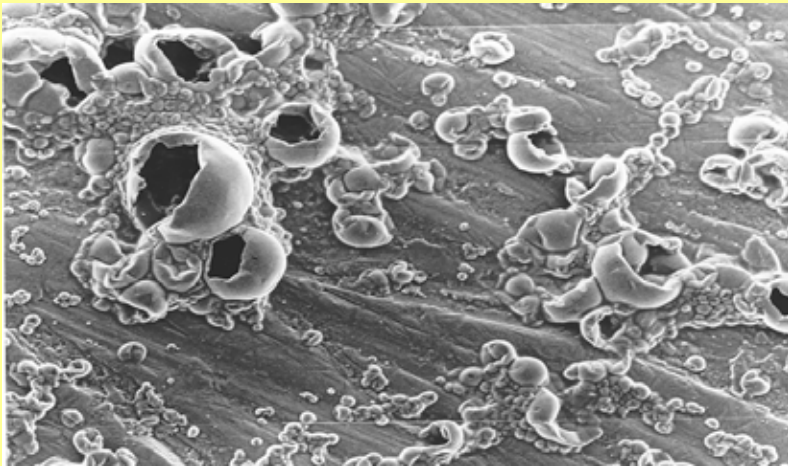
# Triggered release

## Physical

Wall composition / quantity robust for processing

Fast release by **burst** on drydown and/or high surface area of small capsules

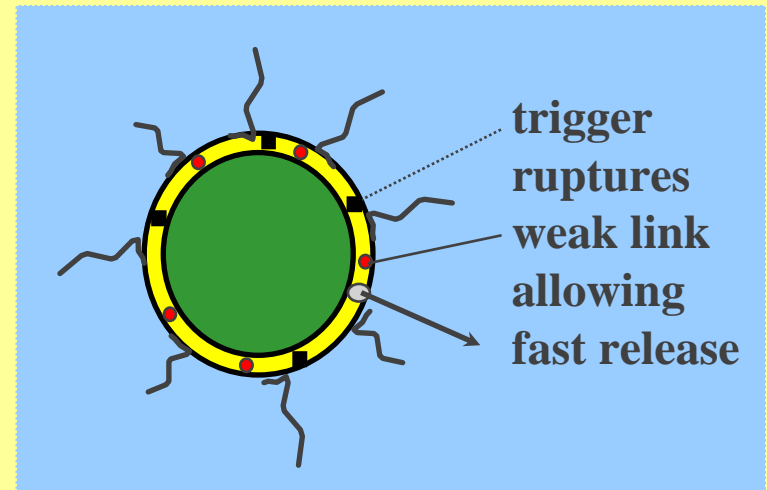
Operator safety



## Chemical

**Acid** or **base** sensitive groups are built into the capsule wall

pH trigger is activated on demand  
punctures reduce wall thickness to zero → fast release



WO2000005952

WO2000005951

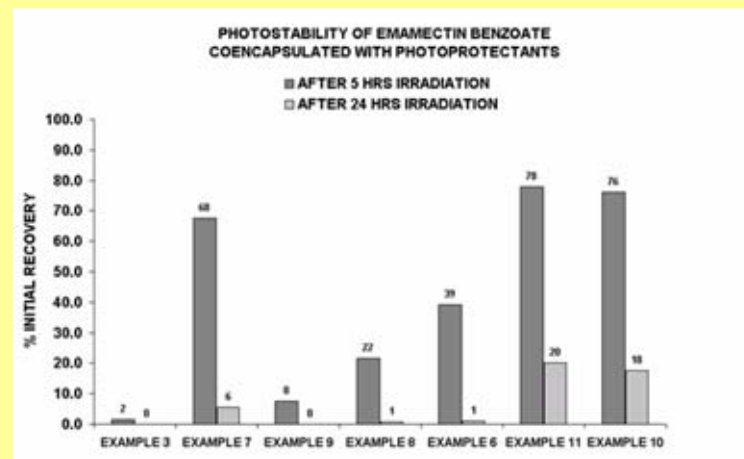
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# Triggered release – contact and feeding activity

Emamectin benzoate is a potent *lepidoptericide*

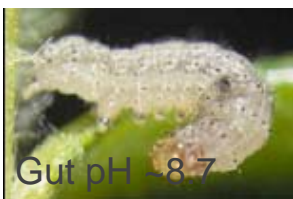
Triggered release targets specific pests - affords protection for beneficial insects (safened  $\geq$  x10) for

- *Typhlodromus pyri* (mite predator)
- *Apis mellifera*



Incorporation of photostabilisers in capsules affords UV protection to the mectin

WO2006089747



*Spodoptera littoralis*

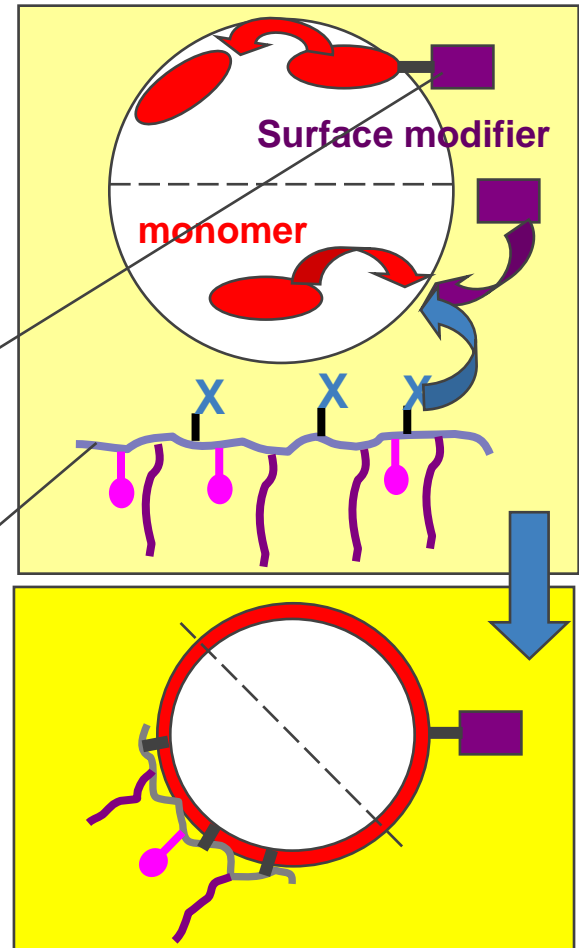
Formulation type	Feeding activity % mortality at <b>2ppm</b> AI	Contact activity % mortality at <b>33ppm</b> AI
SG	100	80
CS w/o photostabiliser	90	5
CS with photostabiliser	96	0

# Surface modified capsules

- Surface modification enables enhanced stability by non-detachable stabiliser
- **Modifiers** (reacted into the **polymer wall**) may be
  - small molecules or polymers
  - anionic, or cationic or neutral (steric)

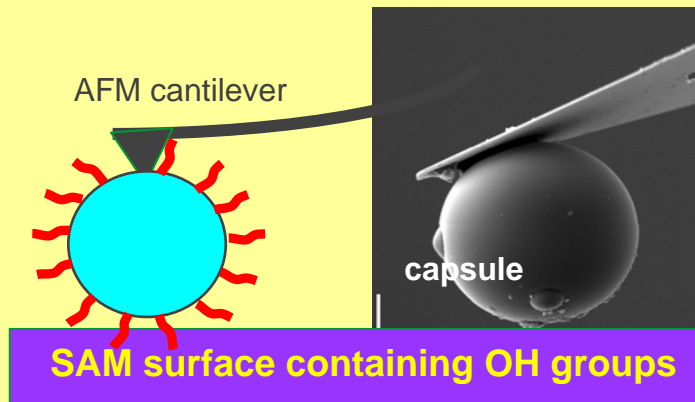
WO2001094001

WO2002100525

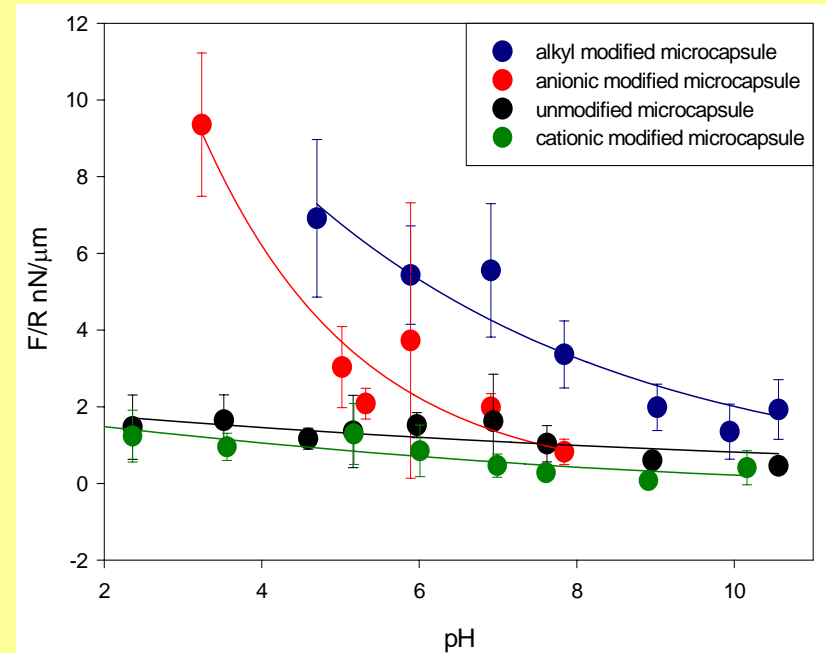


# Measuring adhesion

Characterise attraction between *individual* surface modified particles and substrates by AFM

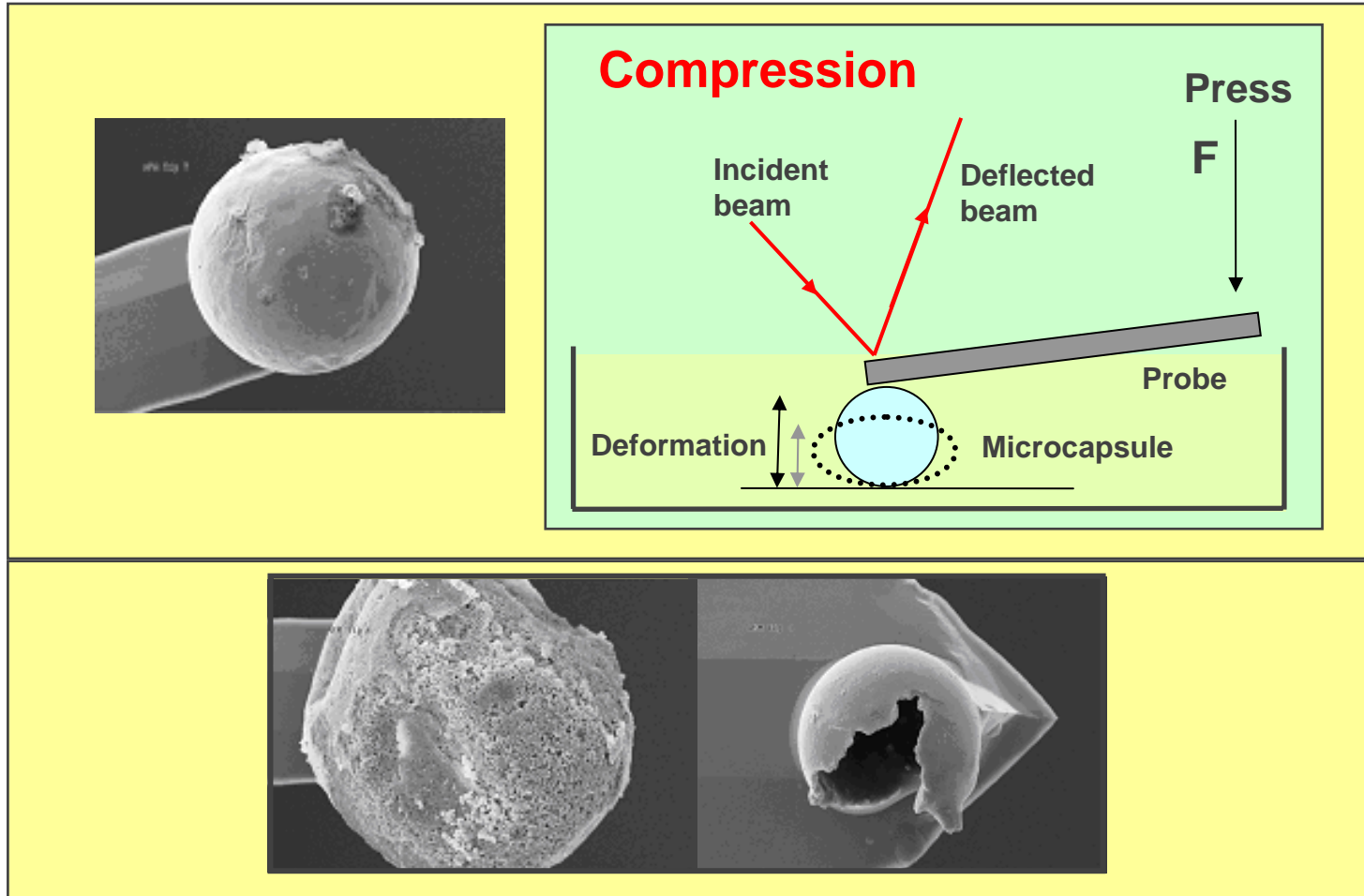


Adhesion **steric** > **anionic** >> **cationic** ~ non-modified capsules on SAM surface containing OH groups



# Measuring strength (1)

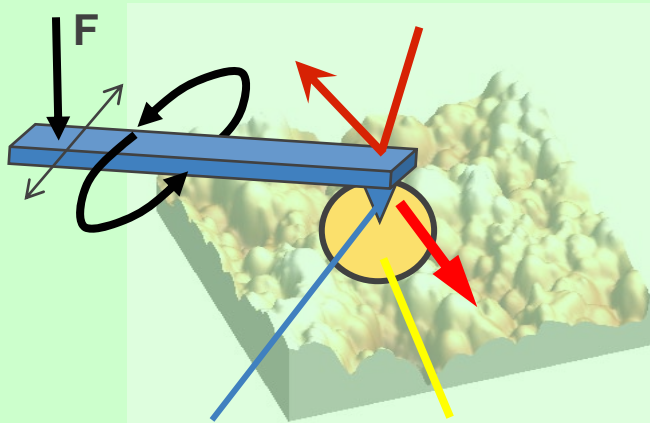
AFM-SEM is used to characterise the compressive strength of individual microcapsules



# Measuring strength (2)

As the probe is raster-scanned across the surface, torsional forces are realised in the AFM cantilever

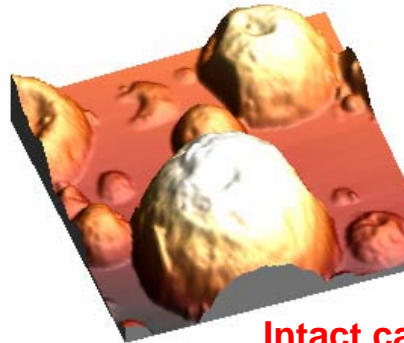
## Shear



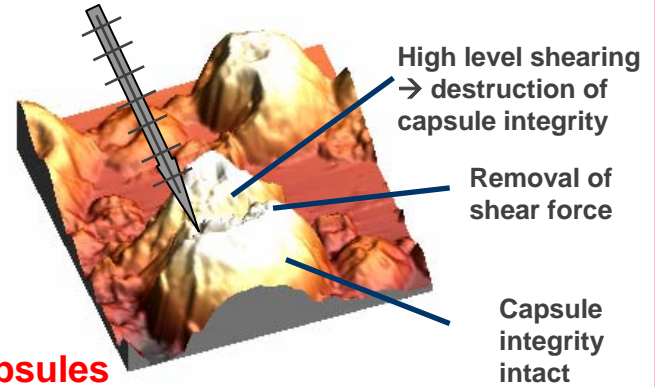
Scrape – bare probe or attached cap

The applied shear force is a function of the speed of raster and the normal force (N) applied

## Bare AFM Tip



Intact capsules

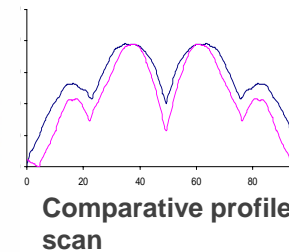


## Capsule attached to AFM Tip

Before application of capsule probe shear force

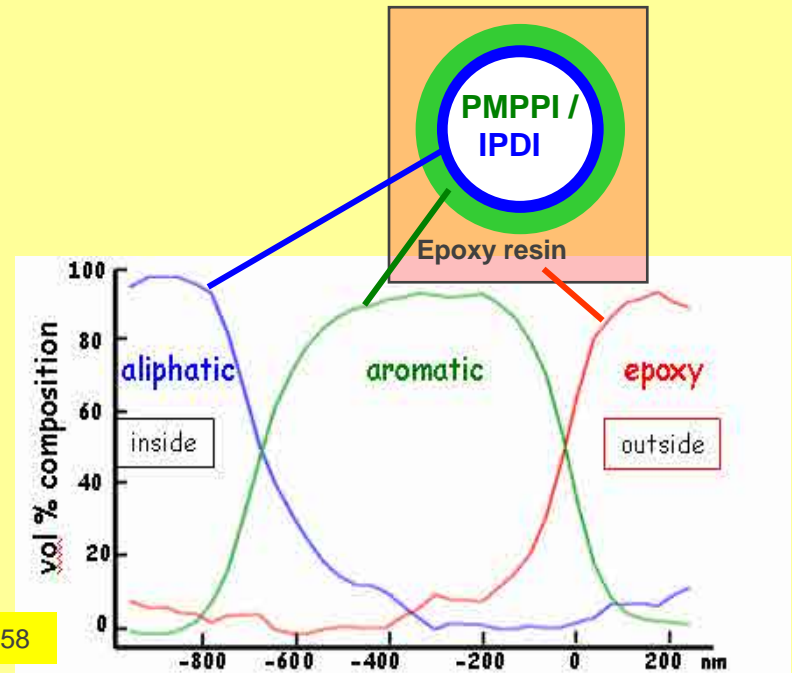
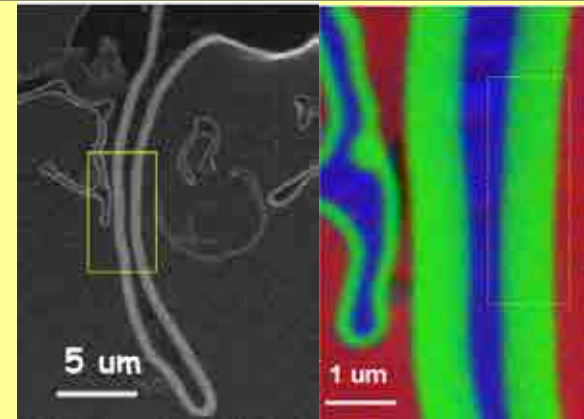


After application of capsule probe shear force

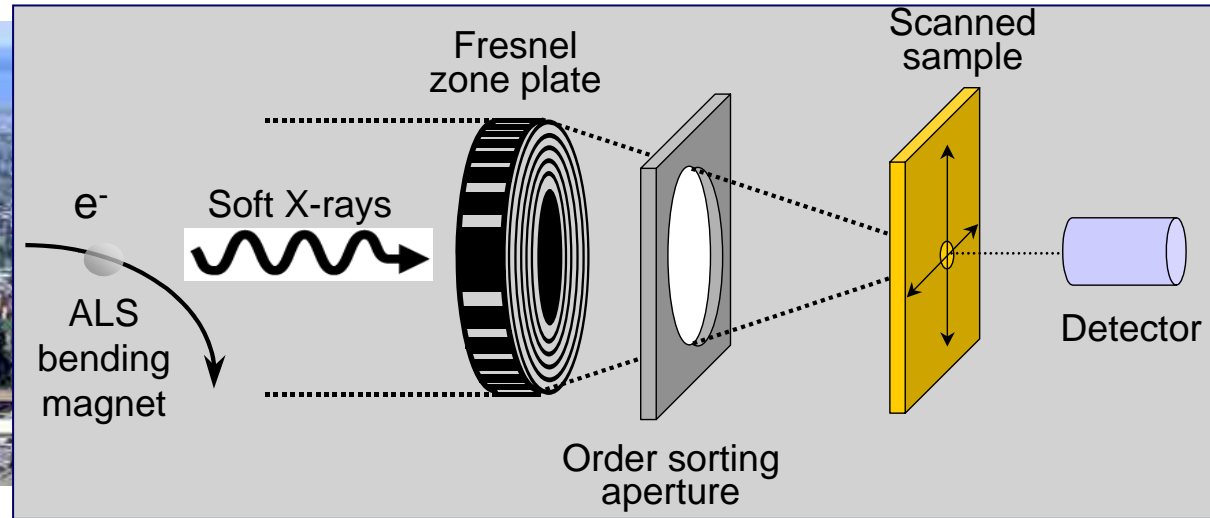


# Measuring composition

- An understanding of the morphology of mixed monomer wall compositions can help in product design.
- Model capsules made by differential reaction of IPDI and PMPPI (DETA)
- Scanning Transmission X-ray Microscopy profiles chemical gradients across microcapsule wall
- Can be much more complex!!



# Soft X-ray Spectromicroscopy with Scanning Transmission X-ray Microscopy



Chemical speciation through X-ray absorption spectra (NEXAFS)

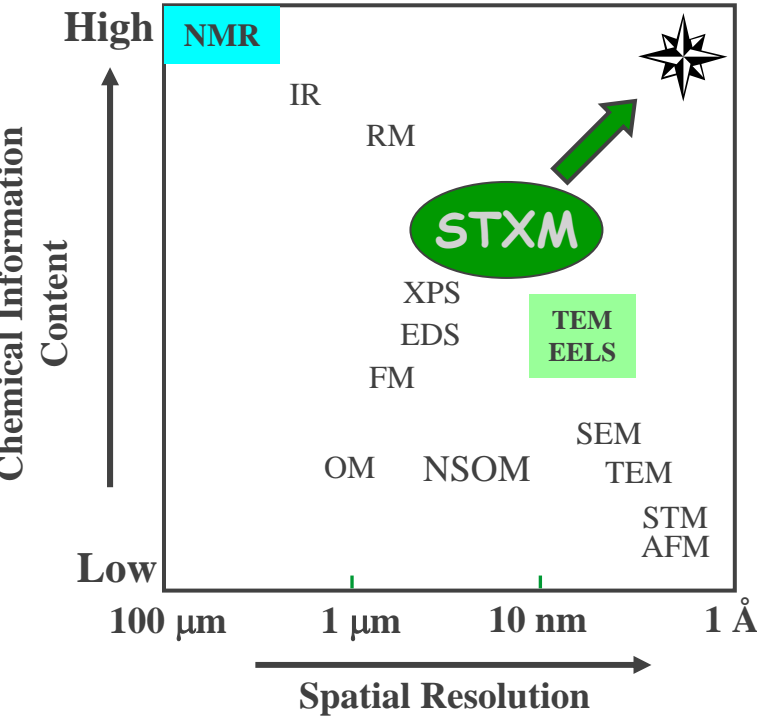
Spatial resolution  $\sim 30$  nm; Energy resolution  $< 0.1$  eV

- Beamline 5.3.2 at the Advanced Light Source, Berkeley, USA
  - Beamline 10ID1 at the Canadian Light Source, Saskatoon, Canada
  - Transmission requires thin samples  $\Rightarrow$  microtomed sections ( $\sim 100$  nm thick)
- 
- Quantitative chemical mapping in 2d and 3d
  - Quantitative molecular orientation mapping



# Comparison of spectro-microscopy techniques

GOAL: QUANTITATIVE CHEMICAL ANALYSIS at relevant spatial resolution



Technique	Spatial Resolution	Speciation Capability
nmr	> 1 μm	excellent
IR	> 1 μm	excellent
Raman	~0.3 μm	excellent
optical	~0.5 μm	needs chromophores
scanning probe	0.2-10 nm	variable
TOF-SIMS	~ 1 μm	excellent
EELS - (S)TEM	< 1 nm	good; BUT radiation damage !

**X-ray microscopy ~ 30 nm excellent**  
**STXM radiation damage 10<sup>3</sup> less than TEM-EELS**

# Hydrogels

- Micro-irrigation, mulching, plant tissue culture, seed coatings
- Cross-linked hydrophilic monomers → bulk polymer or microparticles loaded with AI

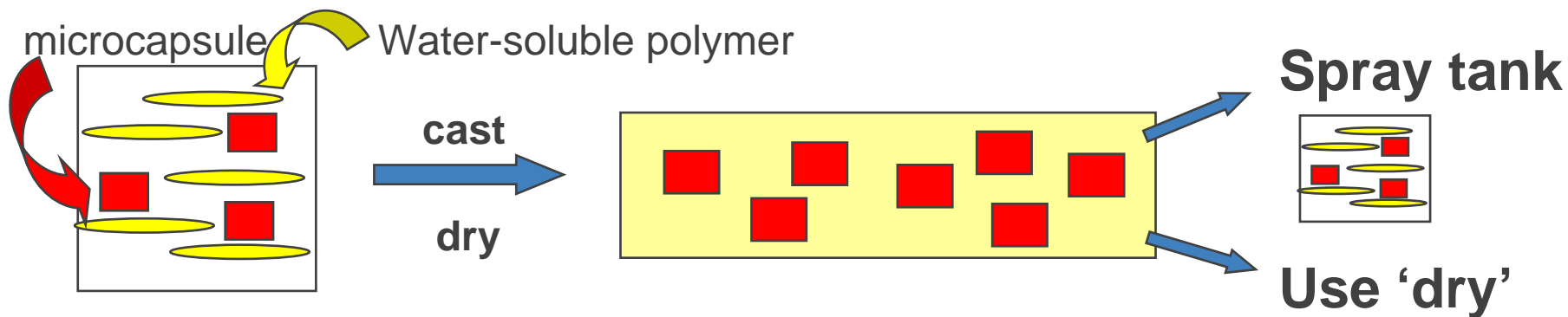
carrier	AI	Driver	
MBAm-AA; MBAm-AMPS AA-MAc	HCO <sub>2</sub> Na	Mite control in bee hives	WO 2006/017310A1
Aqualon aquasorb (CMC) Aridall superabsorber (acrylics)	Triticonazole Imidacloprid	Seed treatment - enhanced AI uptake (phyto?)	WO 02/21914 Monsanto
Carageenan; Na-alginate	CH <sub>2</sub> FCO <sub>2</sub> Na	Possums etc	WO 00/02447

## Biodegradable carriers

- Al + biodegradable polymer melt extruded with optional additives (synthetic polymer, plasticiser, fillers) to lace, rod, ribbon (→ chopped)
- Morphology depends on composition – homo-/hetero-geneous
- Aimed primarily at soil/water – release rate control by diffusion and biodegradation

Carrier	AI	Use	
Aliphatic polyester	Imidacloprid	aphid control; 16-100% biodeg 5 mths	EP0843963A1
PLA + p(butylene adipate terephthalate)	Clothianodin Strobilurin *Tetrafurantidine	Disease and insect control	US2004/0259736 BASF
(modified) starch (+synthetic EVA, PVC)	Chlorpyrifos Carbosulfan	Wireworm and bloodworm control	US5741521
Cellulose acetate; starch	Fipronil Chlorpyrifos	Termite control (implanted rods)	US 6337079 (2002)

# Water Dispersible Tapes

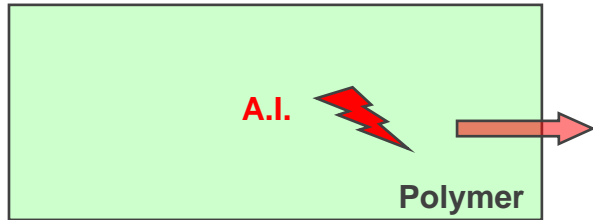


- Flat flexible water dispersible sheet that may be cut or shaped
- Dissolves in spray tank to release CS
- Advantages
  - reduced operator contact
  - measurable/unit doses
  - mixed product compatibility

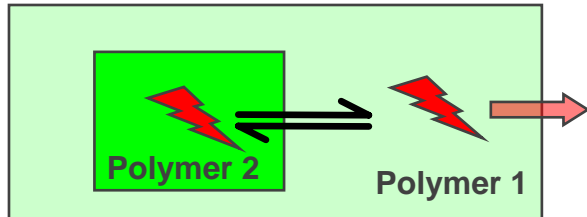


**WO 97/20627**

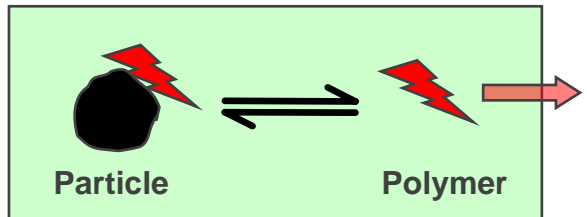
# Controlled release from bulk polymers by diffusion



Release rate depends on compatibility of AI with polymer



Release rate depends on compatibility of AI with polymers 1 and 2  
Polymer 2 matrix or reservoir



Release rate depends on adsorption of AI to particle and compatibility with polymer

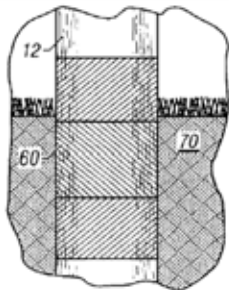
## Variables

- Polymer types (tp or ts, x-link density, water permeability, biodegradability; photostability; hydrolysable)
- Processes - melt extrusion and lamination, in situ polymerisation eg urethane coatings
- Adsorption equilibrium for particles

# Controlled delivery from bulk polymers

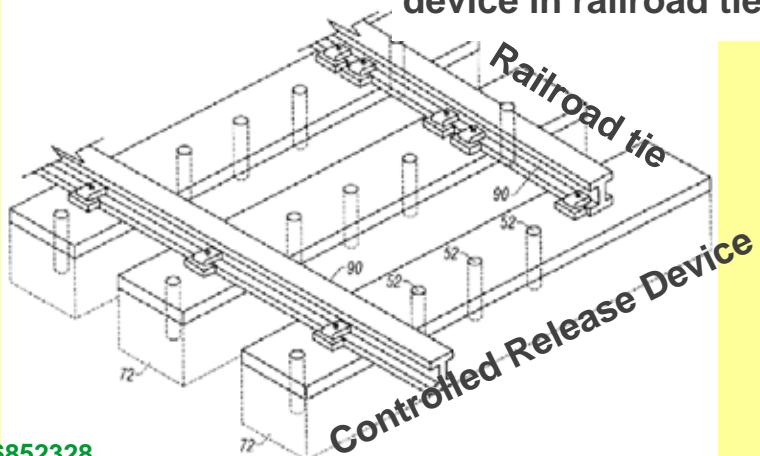


Polymer-Al strip  
melt bonded on  
support film

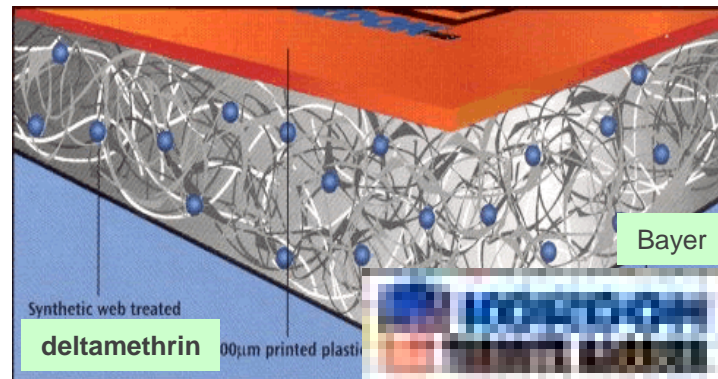


Polymer-Al coating  
on pole

Controlled release  
device in railroad tie

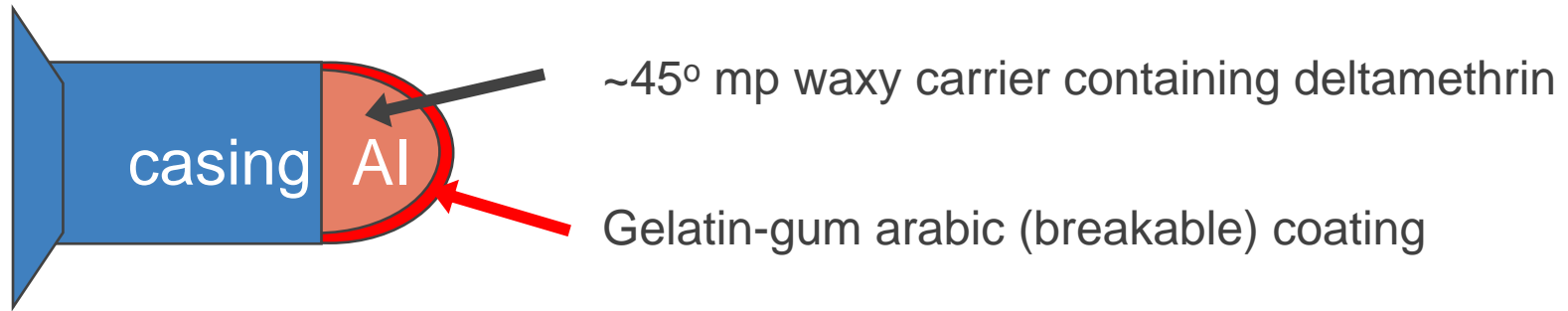


US6852328



Pyrethroid ear tags

And ...



EP 1163846 (2001)

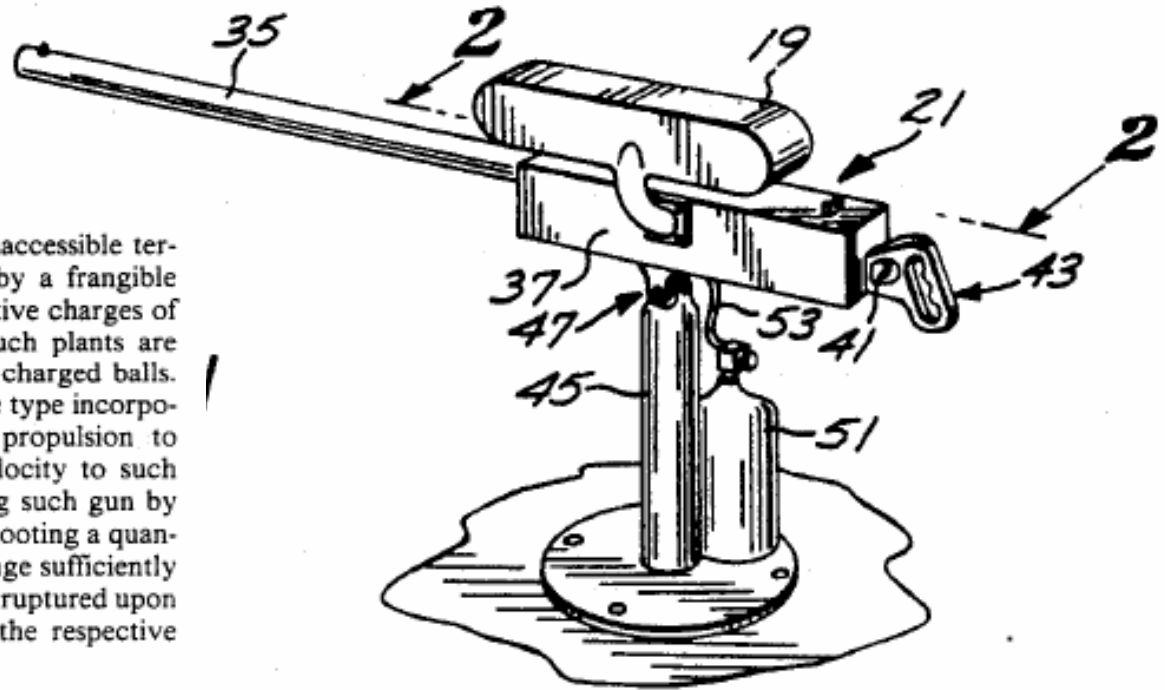
- Al macro-capsule attached to flat head of pellet
- Fired from air-rifle at processionary pine moth nests
- Two shots for large nests

# Targeted delivery in action

[57]

## ABSTRACT

A method of eradicating plants on an inaccessible terrain by selecting hollow balls formed by a frangible membrane, filling such balls with respective charges of herbicide fluid of the type to which such plants are susceptible to provide a supply of such charged balls. Selecting a repeater ball firing gun of the type incorporating a mechanism having sufficient propulsion to transmit a certain minimum muzzle velocity to such balls in a repetitive manner, transporting such gun by helicopter to hover over such terrain. Shooting a quantity of such balls at each plant from a range sufficiently close to cause the skins of such balls to be ruptured upon impact to thereby splash herbicide on the respective plants.



**Marijuana is eradicated on inaccessible terrain by targeted delivery of an herbicide, preferably glyphosate, from a helicopter. The herbicide is packed into balls made of frangible skins and shot from the helicopter, using a gun.**

US5174807



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- To the organisers for the invitation to speak at this meeting
- To the audience for your attention