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“Formulation Approaches to Manipulation of Leaf Uptake””

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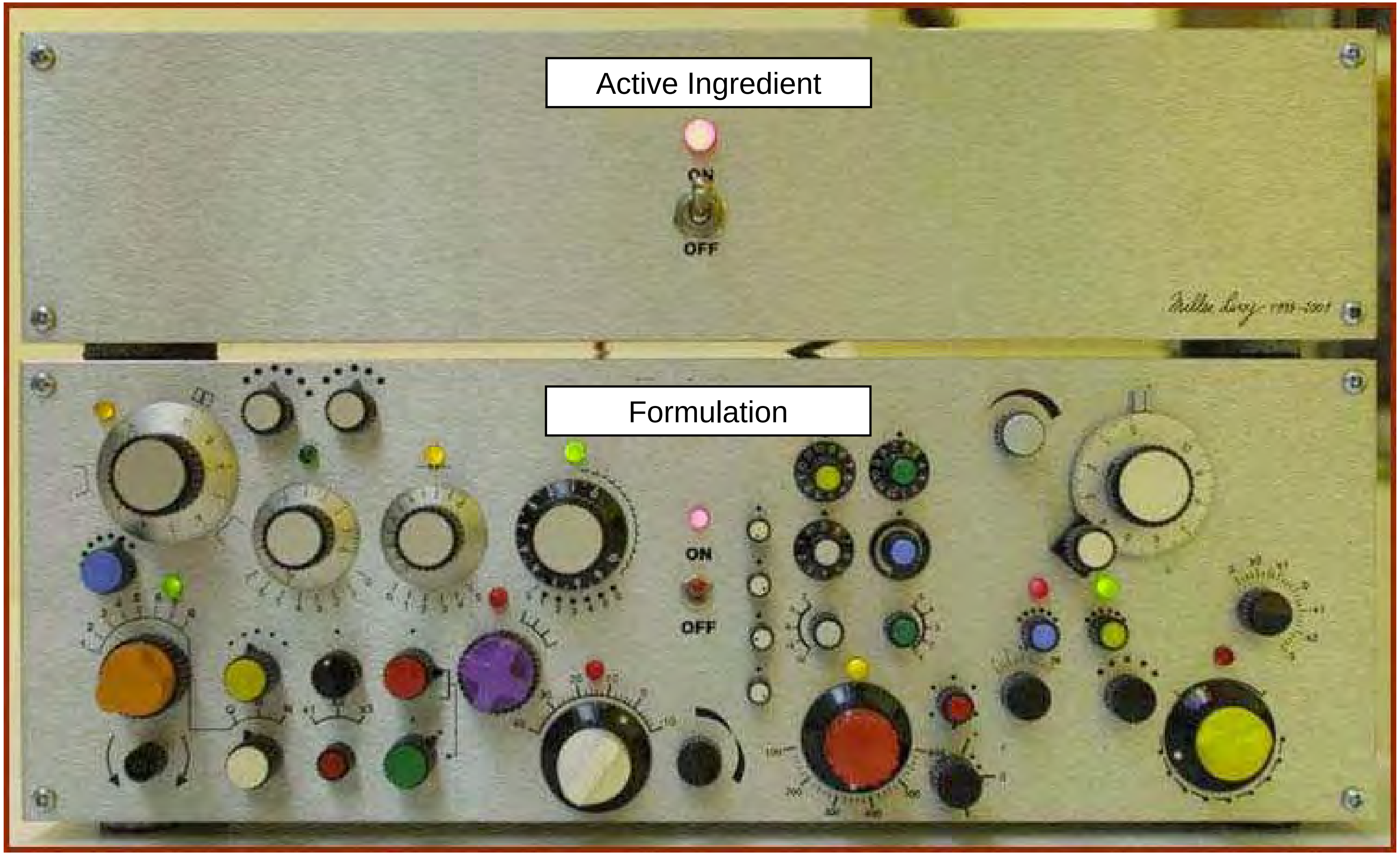
Contents

- Biodelivery – what do we understand?
- Adjuvants for enhanced delivery.
- Uptake routes – manipulation approaches.
- Chemical behaviour of adjuvants – fate processes.
- Factors influencing Formulation approaches.
- Search for “greener” inerts.

The complexity of Bio-delivery



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Formulation design for activity – What do we know?

Plant uptake Lipo.

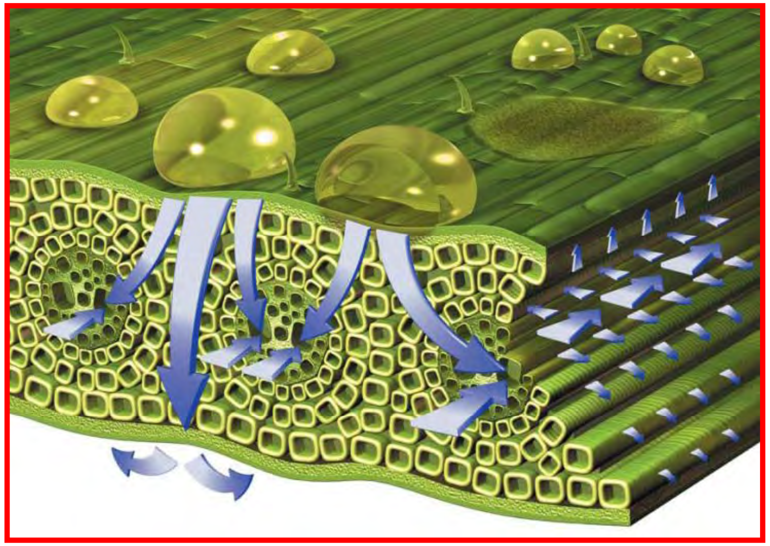
Plant uptake Hydro

Fungal uptake

Insect uptake

Spray modification

Retention aids



Rainfastness / stickers

UV Protection

Spreaders

Challenges of Crop Protection delivery

- **Right amount of compound**
- **Right place.**
- **Right time**
- Optrimised system;-
  - Effective “biodelivery”
- Non optimised system;-
  - Pollution
  - Chemical wastage.

Use of adjuvant technology

- Old view ("conventional wisdom")
  - Act as "wetters". Early uses relate to soap solutions with copper salt fungicides
- Current reality
  - To overcome biodelivery issues inherent in the active ingredient.
  - Active ingredients must ultimately reach the target and dissolve in the organism to reach the site.
  - Most active ingredients have physicochemical issues which require formulation/adjuvancy techniques to maximise potential.
    - Issues include melting point & solubility, vapour loss.

Adjuvant terminology

- Terminology around tank-mix adjuvants can be very confusing, especially as many adjuvants have dual functionality.

- Definitions can vary between countries. For example in the UK the following definition is used by CRD (Chemical Regulations Directorate), according to EU legislation;-

  Definition of an 'Adjuvant'

  Under Article 2 Scope (3d) of 1107/2009 an adjuvant is defined as:

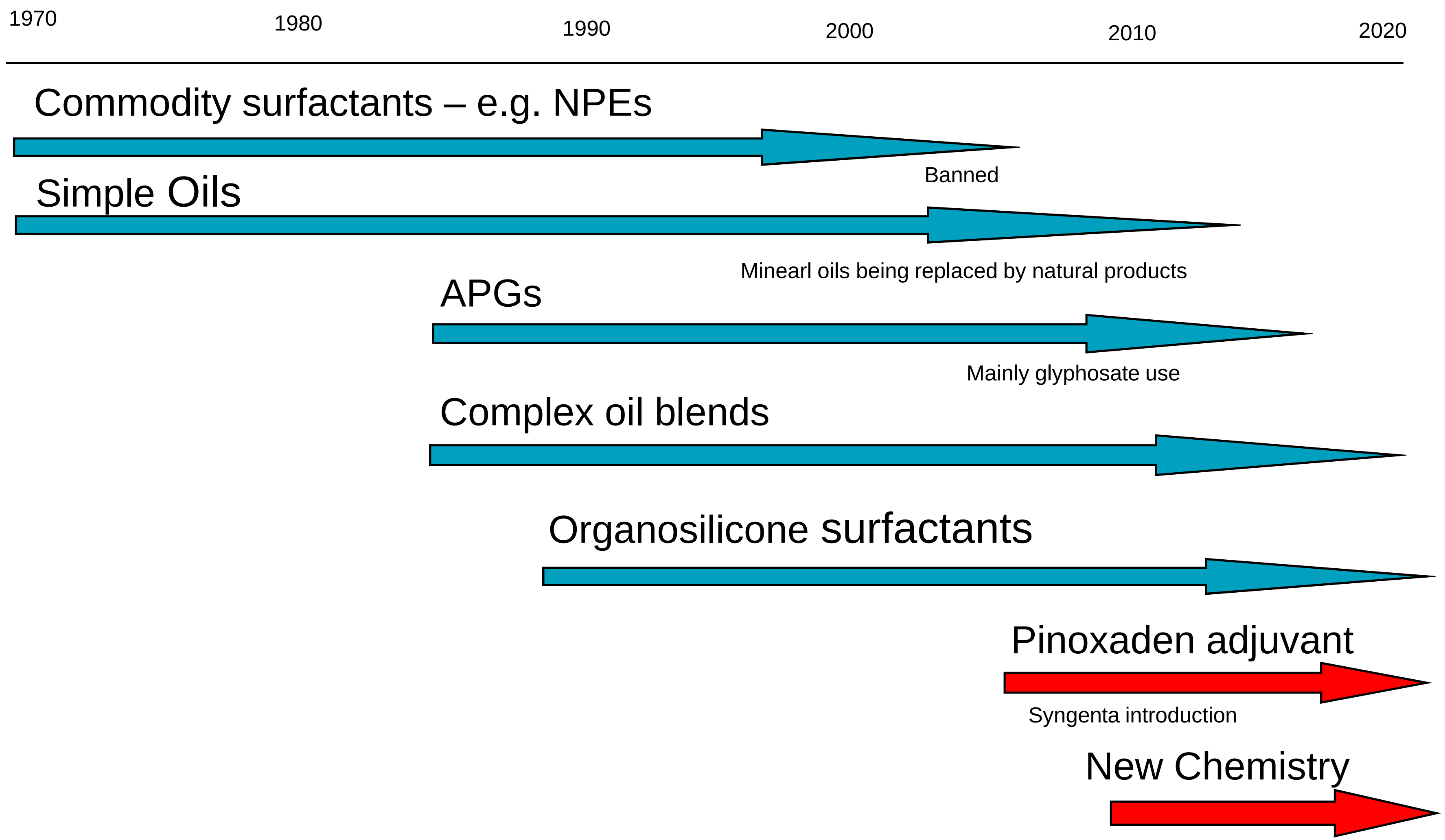
  ‘substances or preparations which consist of co-formulants or preparations containing one or more co-formulants, in the form in which they are supplied to the user and placed on the market to be mixed by the user with a plant protection product and which enhance its effectiveness or other pesticidal properties, referred to as ‘adjuvants’.

- For the USA there is a much more extensive list of terminology via the American Society for Testing and Materials Standards (ATSM).

Main chemical types of tank-mix adjuvants

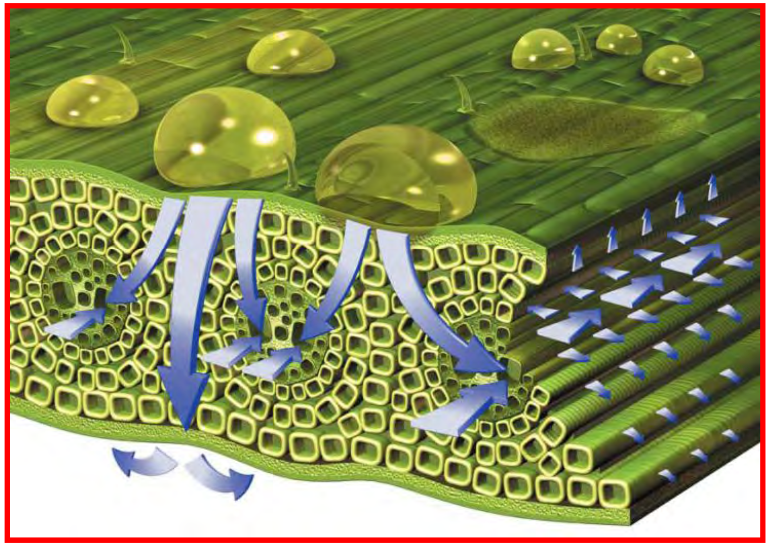
Chemistry	**Examples**	**Mode(s) of action**
Organic surfactants (ionic and nonionic)	Agral, Ethokem	Enhanced foliar retention increased penetration, coverage
Organosilicone surfactants	Silwet L-77, Sylgard 309, Break-Thru S240	Enhanced foliar coverage, stomatal flooding, enhanced rainfastness
Oils (mineral, vegetable, trans-esterified vegetable)	Codacide , Actirob B	Enhanced coverage, foliar penetration, increased availability of a.i. (insecticides)
Terpene derivatives (polymer forming compounds)	NuFilm	Increased resistance of foliar deposits to washoff. Volatility reduction.
Polymers (polyacrylamide, polyvinylalcohol) and synthetic latex	Atlas Companion, Polycote Polymer	Reduced droplet drift, enhanced foliar retention
Inorganic salts	Ammonium sulphate	Increased penetration (overcoming antagonism by divalent cations)

Historic changes in adjuvant chemistry



Adjuvant Mode of Action;-

Addressing the Delivery Challenge



Adjuvants are chemicals !

- Adjuvants have modes of action which, like pesticide active ingredients, is determined by their <u>chemistry</u>!

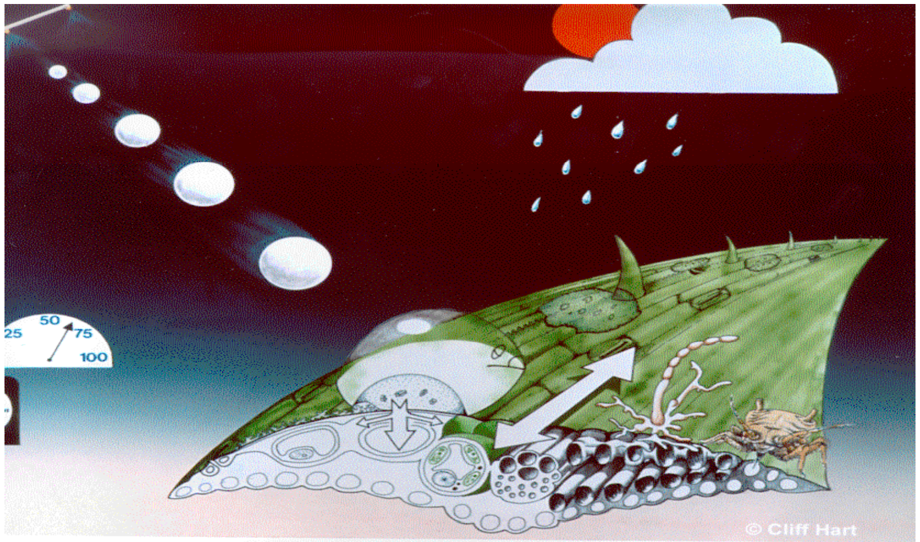
    - NIS = <u>N</u>o <u>I</u>nformation <u>S</u>upplied

(D Stock & G Briggs, WSSA Adjuvant Symposium, Toronto 2000)

- It is important to know adjuvant fate and the kinetics of the processes involved.

Why do we need adjuvants?

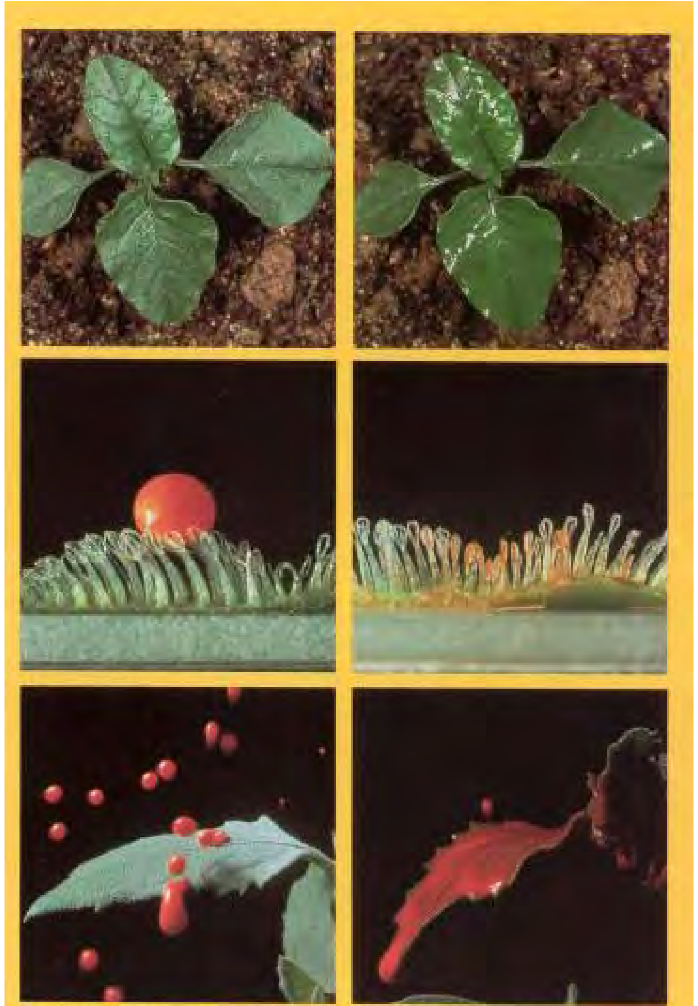
- Optimised delivery to the target site (environment benefits)
  - Maximising the dose which reaches the site of action.
  - Minimising loss processes to the environment.
    - Rain washing
    - Lack of foliar retention
- Minimising dose requirement of the AI
  - Reduced manufacturing, packaging.
  - Cost reduction.



How to select the most appropriate adjuvant;-

- **It depends** on;-
  - What is the delivery problem with the formulated product?;-
    - Uptake
    - Coverage
    - Retention
    - Rainfastness
- Mode of action studies and Biokinetic investigations for the Active Ingredient should provide key information on;-
  - Where is the AI needed (surface/contact activity, systemic etc)?
  - Uptake rate and likely loss to rainfastness or UV degradation.
  - Is coverage an issue (vapour redistribution may compensate for poor coverage, e.g. pirimicarb).
- Based on such considerations, there is no such thing as a “good” general adjuvant.

Spreading:- Retention / wetting /spreading



Formulation chemicals provide for uniform wetting and spreading of the active ingredient over the leaf surface.

Good foliar spreading

Good wetting properties needed to ensure spreading across rough leaf surfaces

Foliar retention a priority

Foliar retention:- Impaction and retention process

•Droplet impaction/ retention process highly complex,
- -may retain on initial impact
- -may bounce one or more times then retain
- -may bounce off
- -may shatter

•Retention occurs when adhesion energy + energy dissipated during impaction is greater than kinetic energy of impaction

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Foliar retention:- Important parameters

- Process is dependent on
  - -droplet size (most material is in the large droplets that retain the least readily)
  - -droplet velocity
- Timescale of the process may be as small as 1ms.

- Amount retained may be correlated to two spray liquid properties

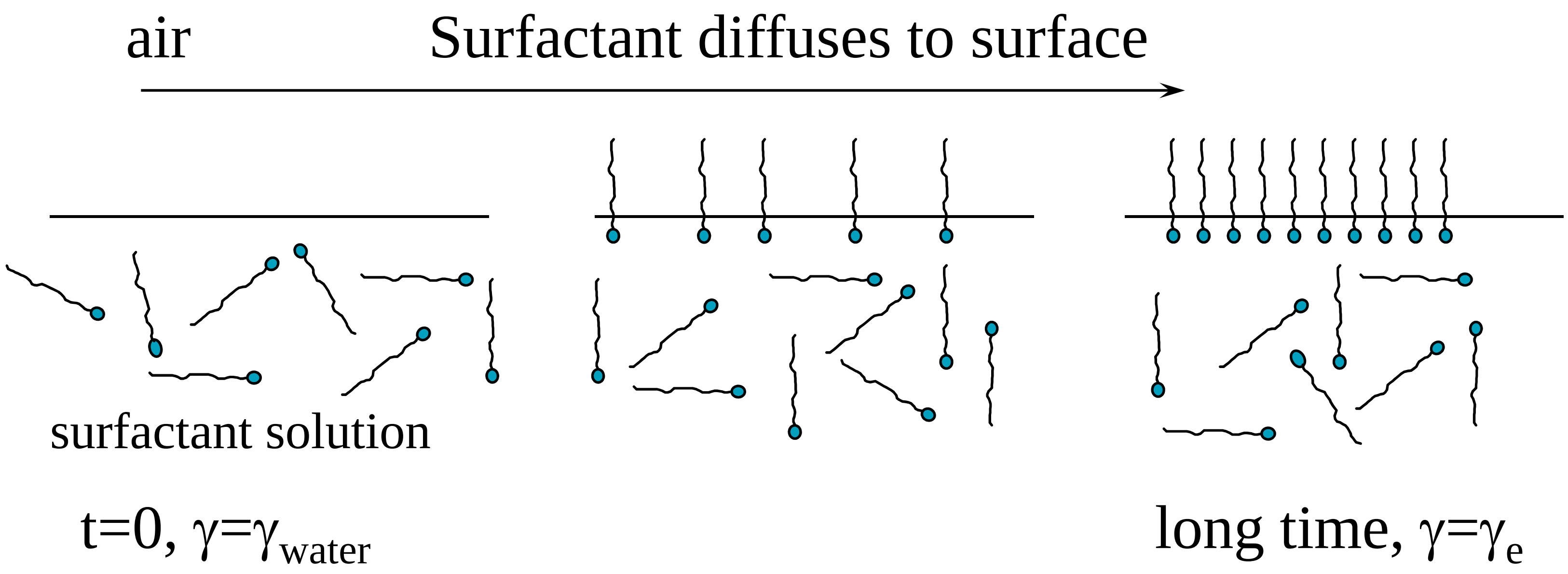
Dynamic Surface Tension

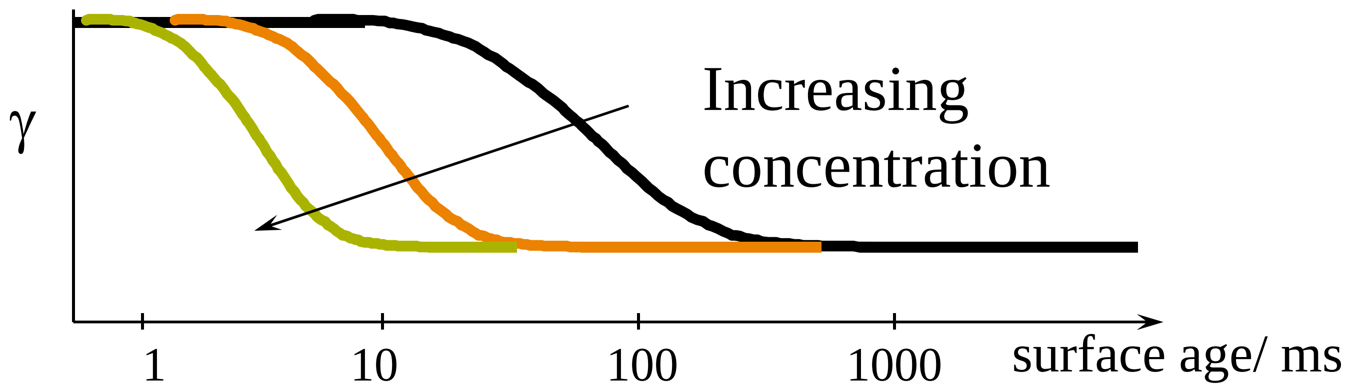
-a low DST allows droplet to wet surface, increases adhesion and displaces air from between droplet/ leaf

Extensional viscosity

high viscosity dissipates energy during process

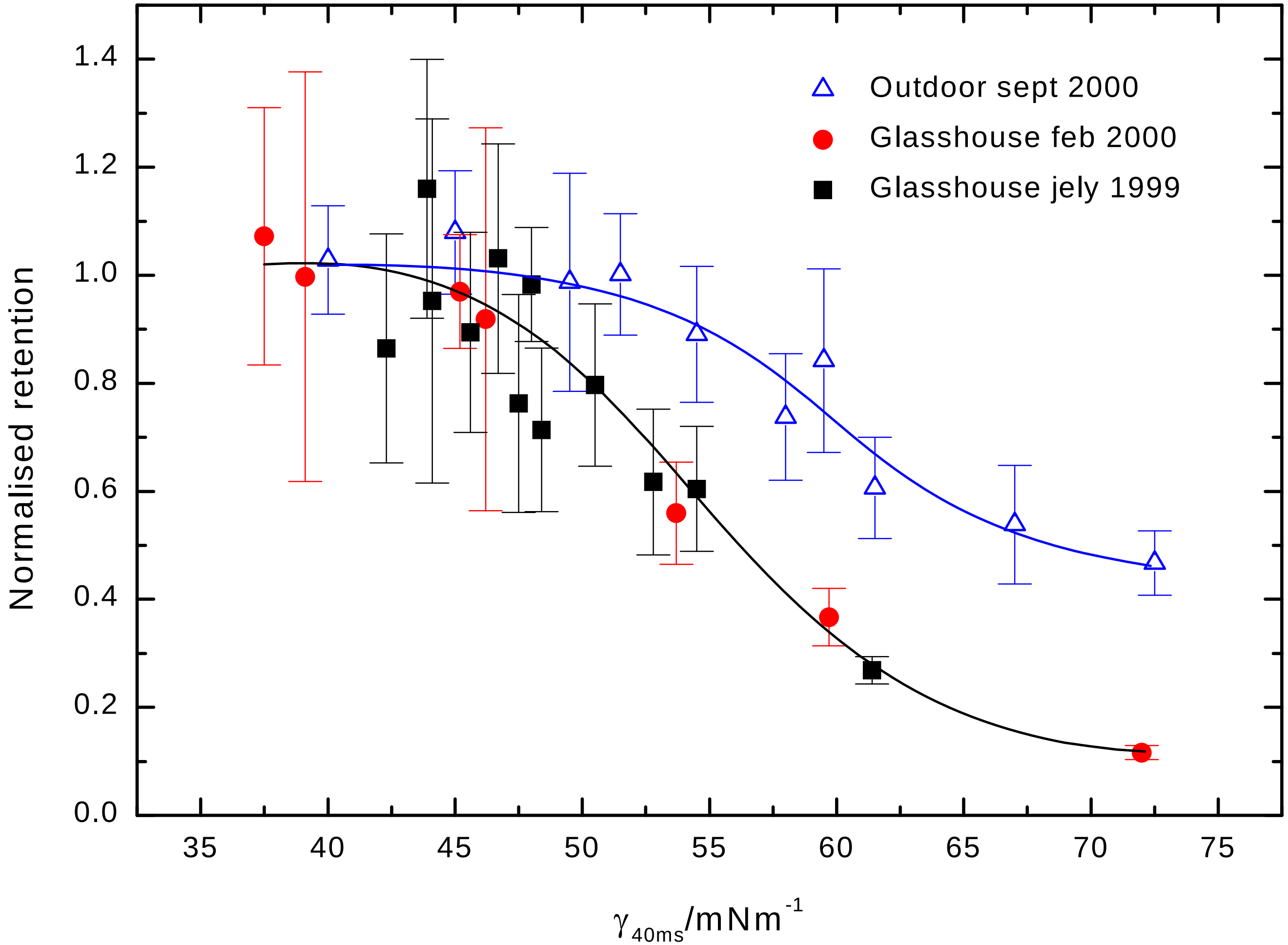
Foliar retention:- Dynamic Surface Tension





•Retention can be correlated to DST at a surface age of 40ms

Foliar retention:- Comparison of retention on glasshouse and outdoor grown HORVS



Addition of a good retention aid has smaller effect on outdoor plants

	Norm. ret. water
OD	0.47
GH	0.12

Retention aid increases retention cf water by factor of 8 in GH but only by 2 on OD

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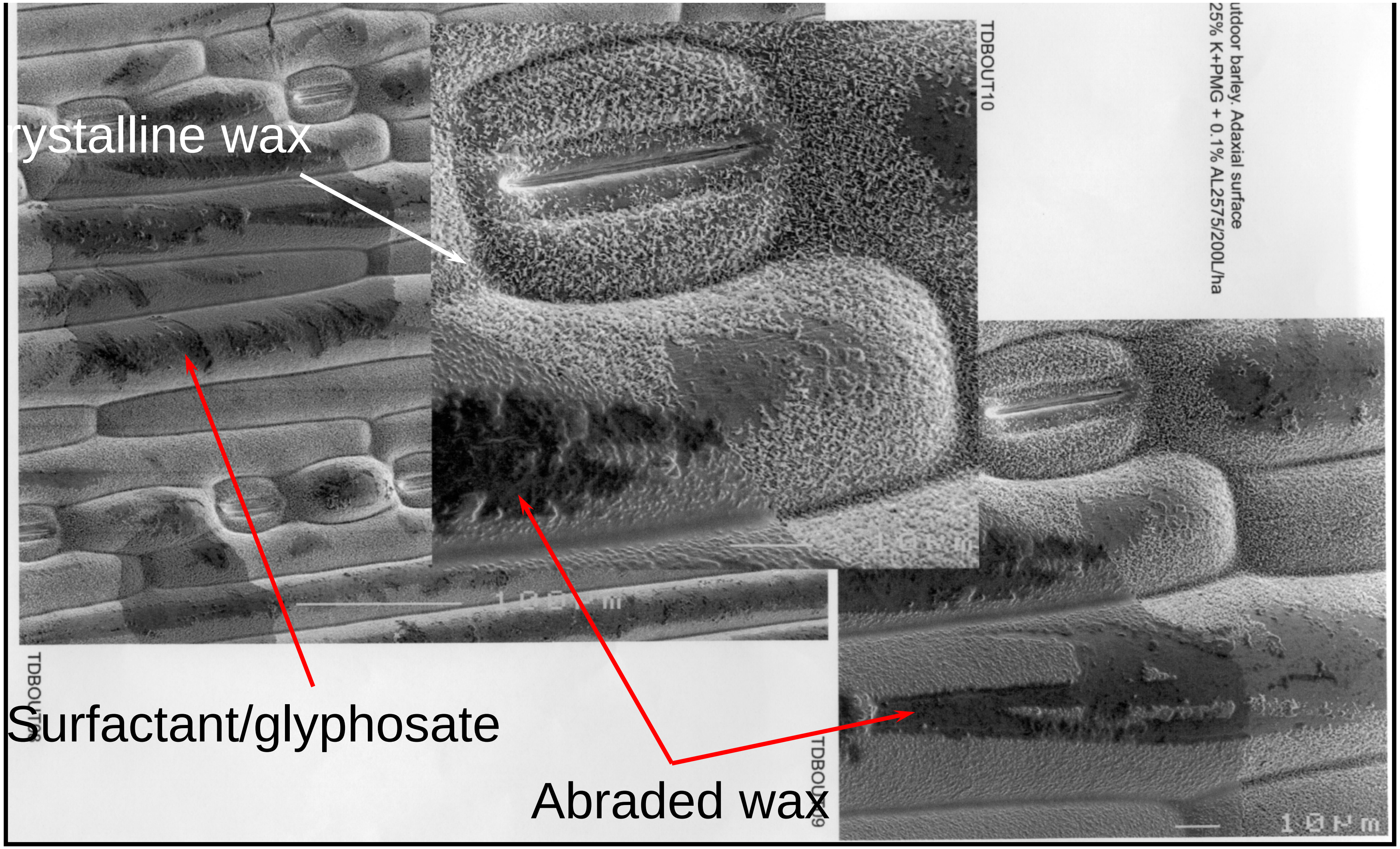
Foliar retention: SEM pictures of abraded wax on outdoor grown HORVS



Adaxial surface-abraded wax easier to wet than undisturbed crystalline wax

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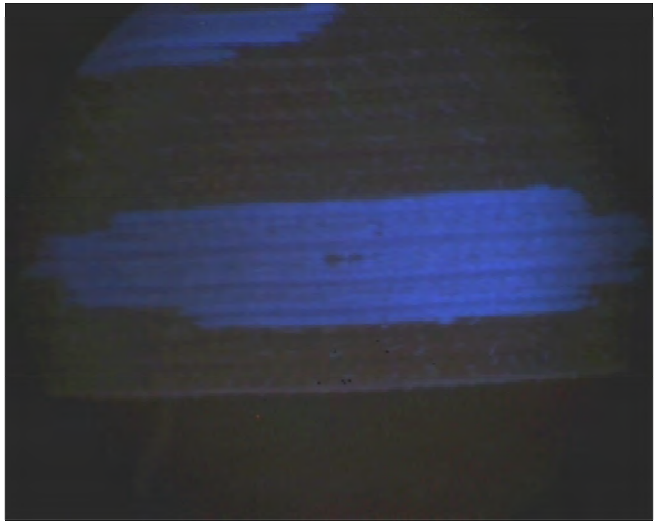
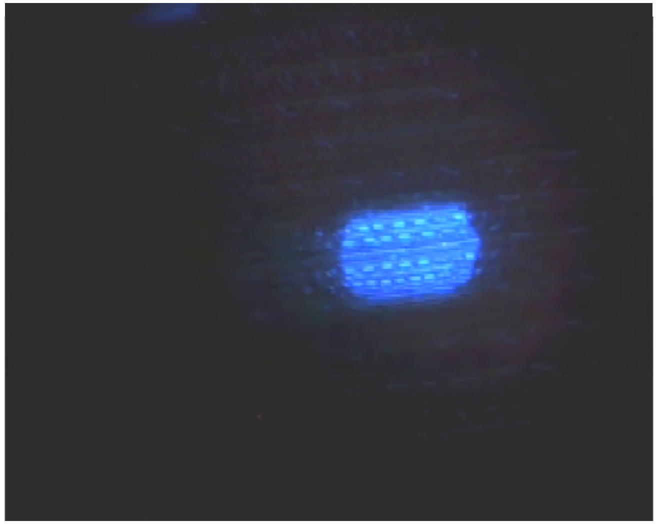
Spreading of oils on wheat (applied as emulsions)

0.2µl droplets with 0.5% emulsions EW applied to wheat in 25%v/v isopropanol, spread areas determined 2HAT

Lower magnification than other image



Wheat with 0.5% methylated rapeseed oil EW



Wheat with 0.5% castor oil EW

Treatment (emulsions in water)	Average spread area on wheat (mm2)
0.5% methylated rapeseed oil	4.96 +/- 1.08
0.5% rapeseed oil	2.31 +/- 0.57
0.5% castor oil	0.65 +/- 0.11

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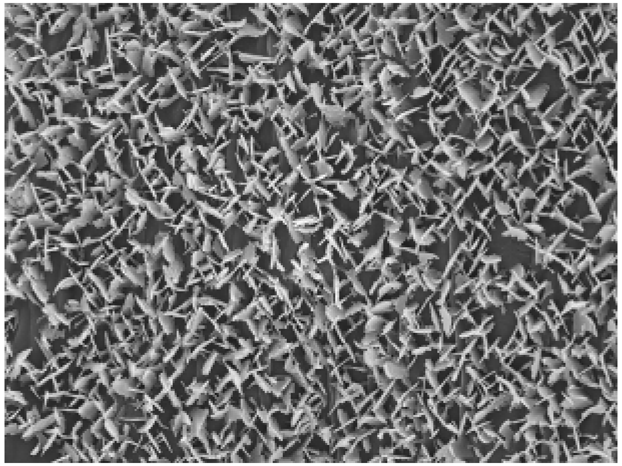
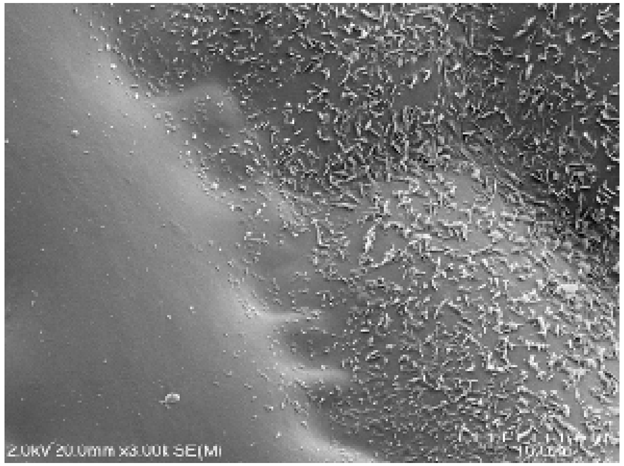
Microscopy of leaf surfaces

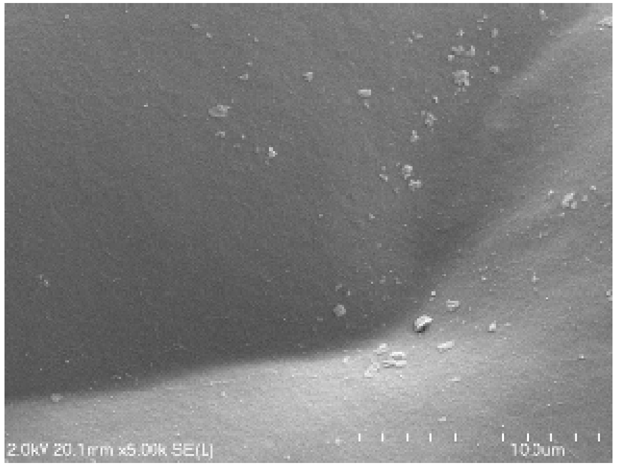
FESEM images of adaxial surfaces of leaves with varying degrees of microroughness



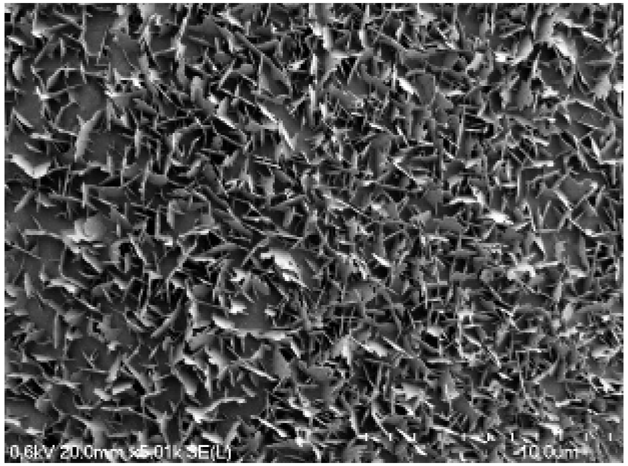
Wheat



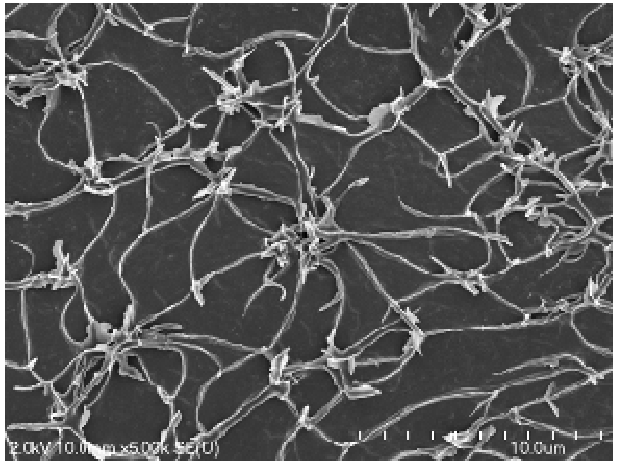
Maize



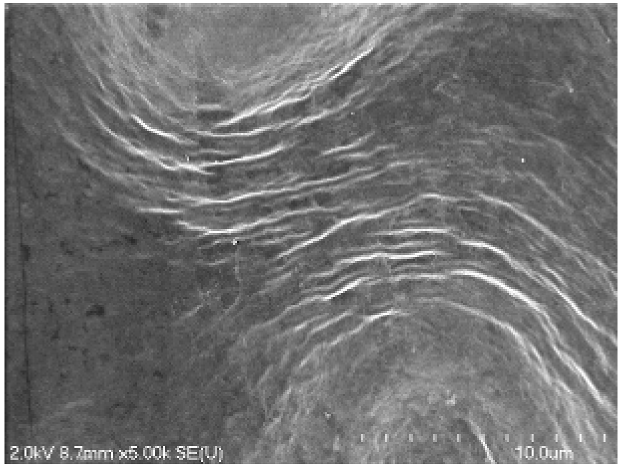
Sugar beet



Pea



Strawberry



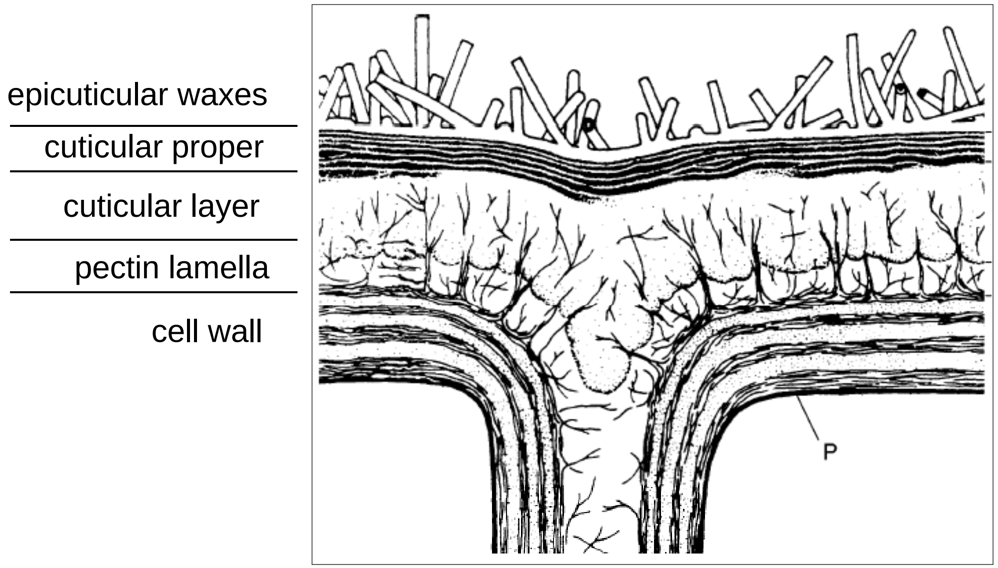
Vine

Difficult to wet ⟷ **Easy to wet**

The Challenges of Foliar Uptake

The Cuticle:- Barrier to Penetration

outer layer between aerial plant parts and their environment:

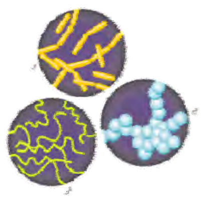


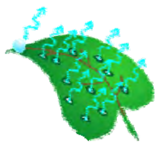
- stabilises tissues

- protection against outer influences

- minimises leaching of nutrients

- habitat for microorganisms



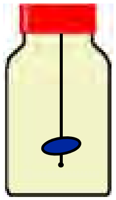


- <u>transpiration barrier</u>

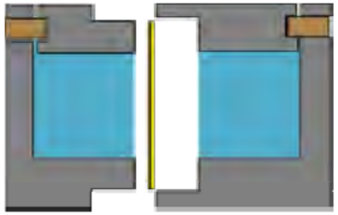
Physicochemical Window of Crop protection Compounds

Property	Range
Melting Point	-20^{O}C to >250^{O}C
Molecular weight	160 to 1000
Organic solubility	Negligible to Miscible
Aqueous solubility	Negligible to 1005g/l
Log P (octanol / water partition coefficient	-3 to >6
Vapour Pressure	mPa to non-volatile

Choice of Methods



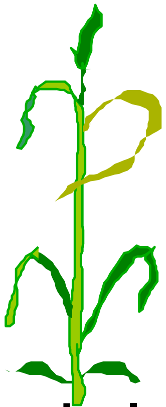
Reconstituted waxes



Transport through cuticles

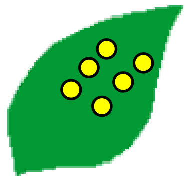
Uptake/Desorption from cuticles

Modelling



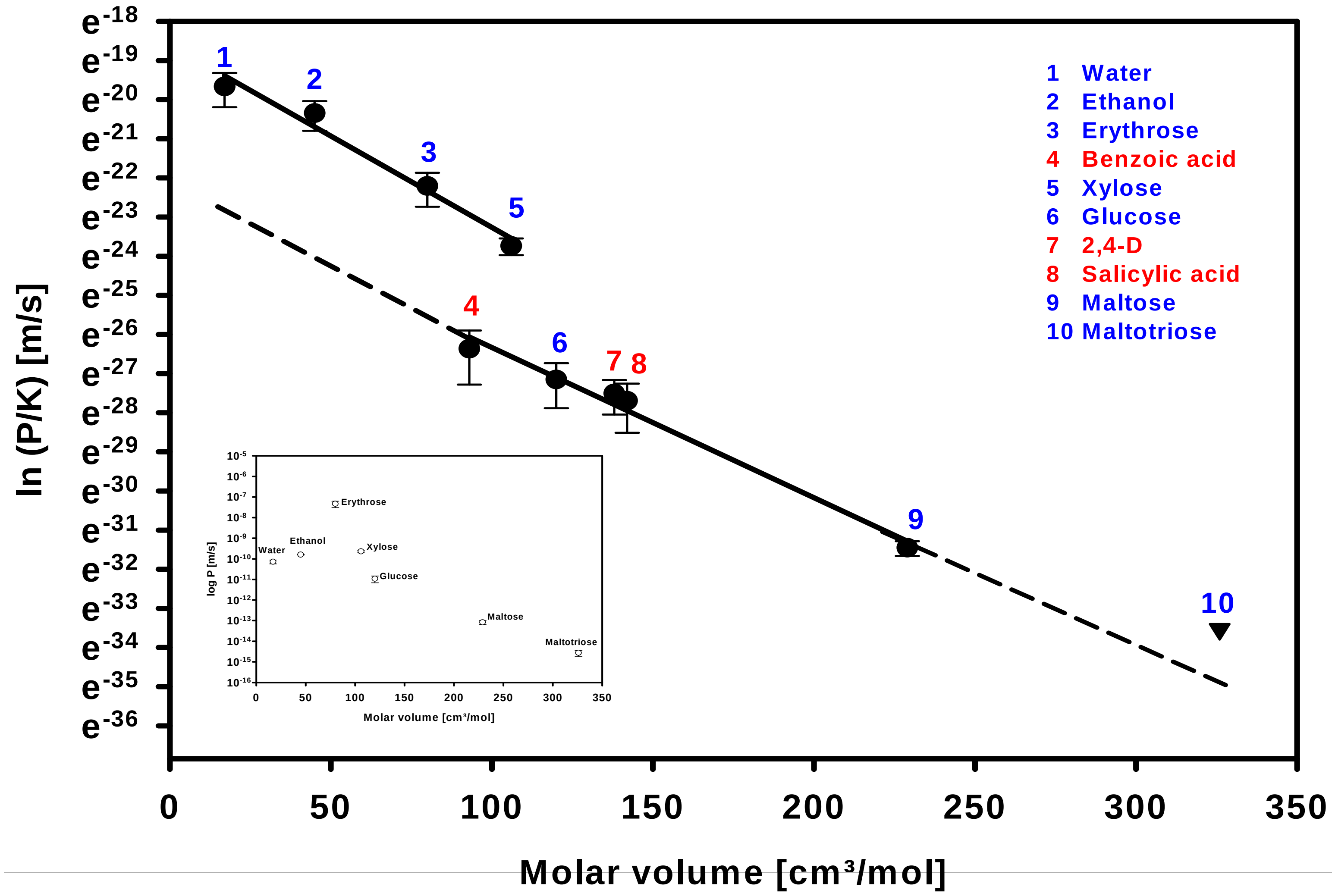
Biological efficacy

Confocal Microscopy



Uptake into leaves

Hydrophilic uptake routes & adjuvancy



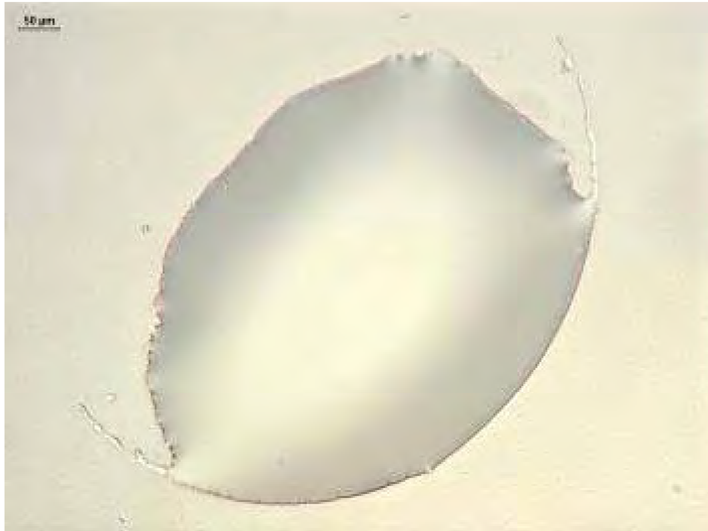
C Popp *et al.* (2005). Journal of Experimental Botany, Vol 56, Nol 421, pp2797-2806)

Humectancy

- Humectants hold onto water which helps to keep water-soluble active ingredients in a liquid form suitable for foliar uptake.
  - There is now good evidence that hydrophilic channels pass through the leaf cuticle. Maintaining water soluble materials in a liquid form enhances access to such channels.
- Humectants are only effective if the Relative Humidity is above a critical value (varies between different humectants).
- Numerous types of chemicals act as humectants;-
  - Glycerol
  - Sugars

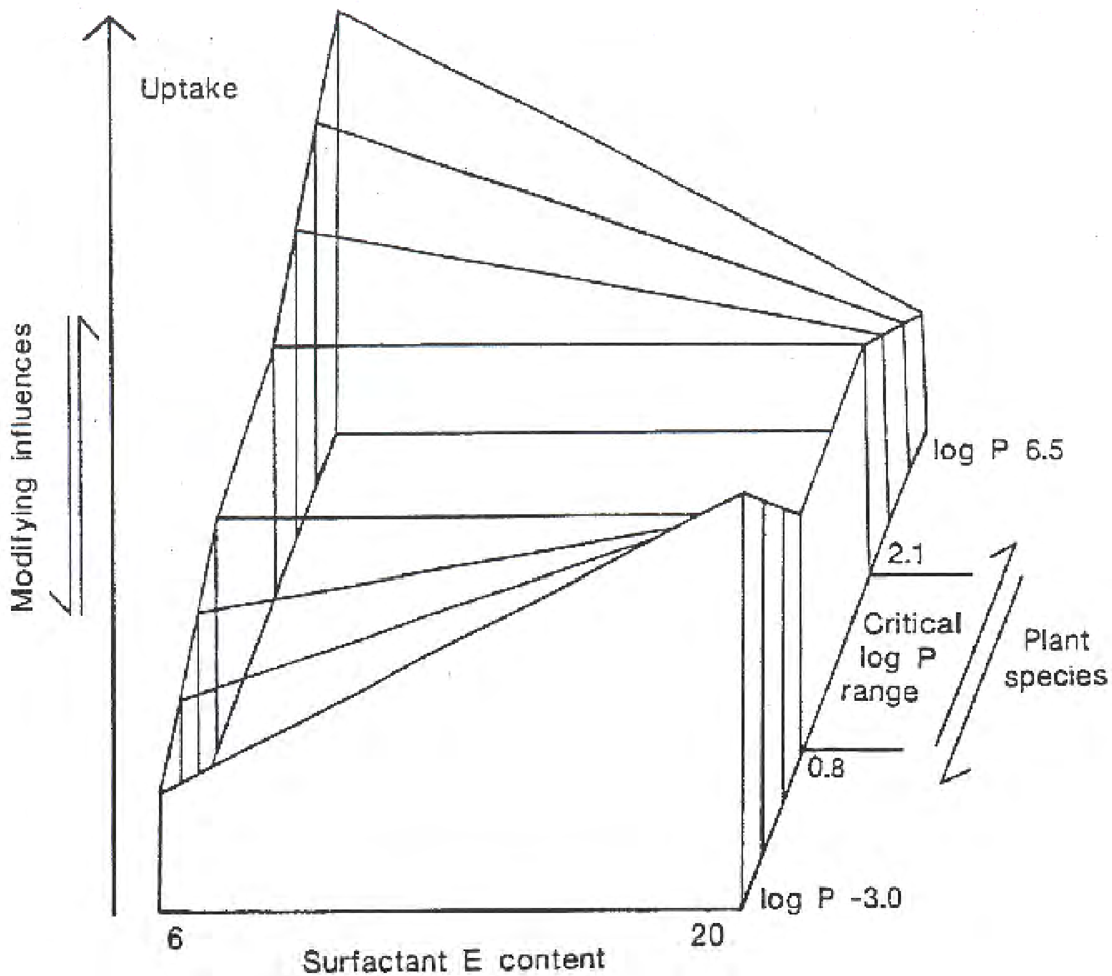
Humectancy (2);- Example of 2 paraquat deposits at 50% RH

Sodium chloride



Monoethanolamine chloride

Development of a Predictive Uptake Model to Rationalise Selection of Polyoxyethylene Surfactant Adjuvants for Foliage-applied Agrochemicals



Stock *et al*, Pestic.Sci, 1993, 37, 233-245

Interrelationship between surfactant and AI physicochemical properties during foliar penetration

- A qualitative model is available for nonionic ethoxylates
  - Higher ethoxylates preferred for water soluble, low log P, compounds
  - Ethoxylation is less important for intermediate log P compounds
  - Lower ethoxylates optimal for high log P compounds
- Superficial relationship to HLB within a surfactant series
  - Use of this surfactant parameter is meaningless in isolation.
- No unified penetration-enhancement mechanism is implied
  - More recent studies on cuticles has provided valuable information to understand penetration mechanisms and adjuvant impact.
- Optimal structures for penetration not necessarily ideal for other key adjuvancy processes.

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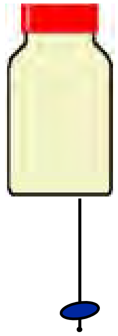
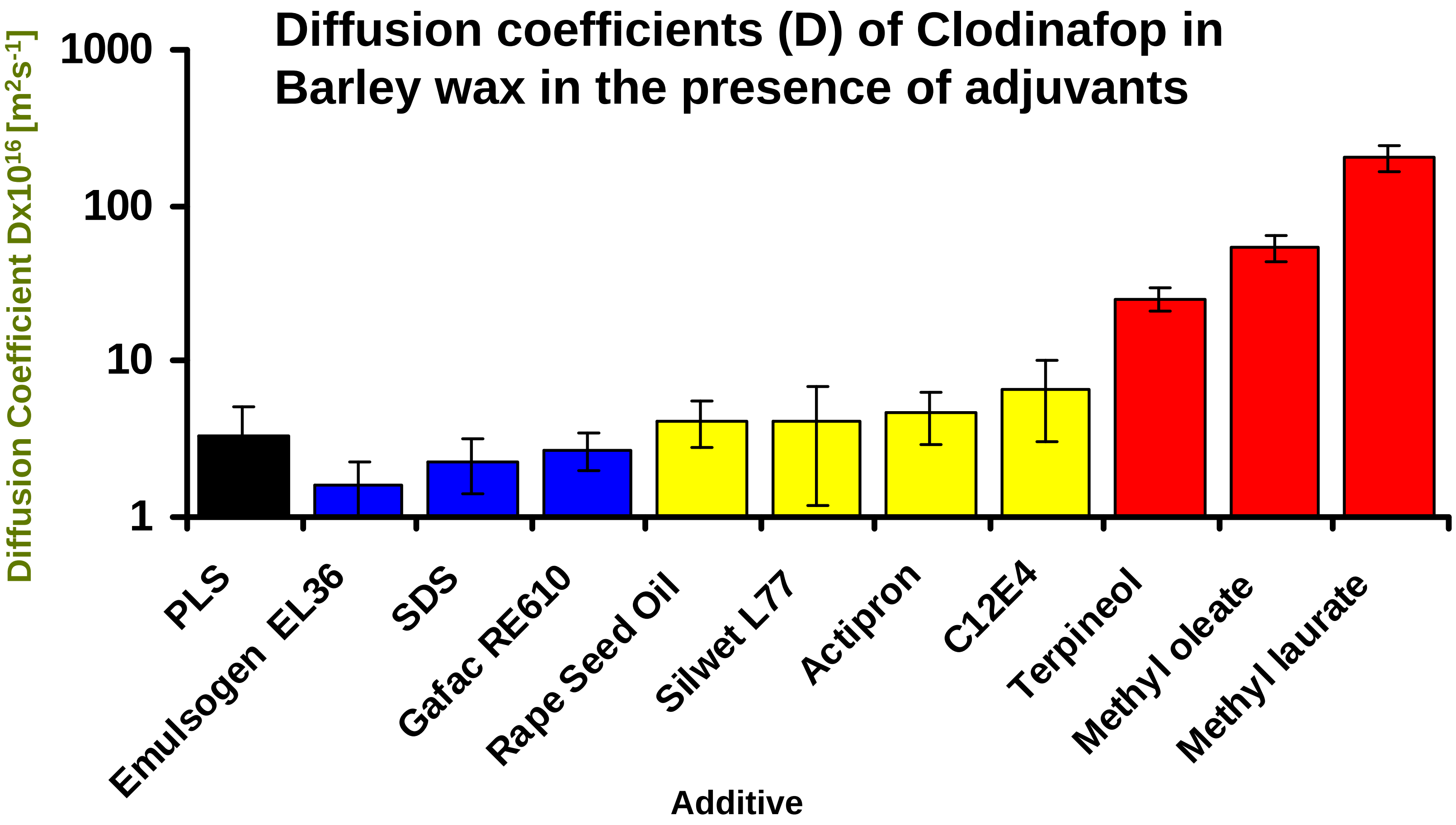
Diffusion in Plant Waxes





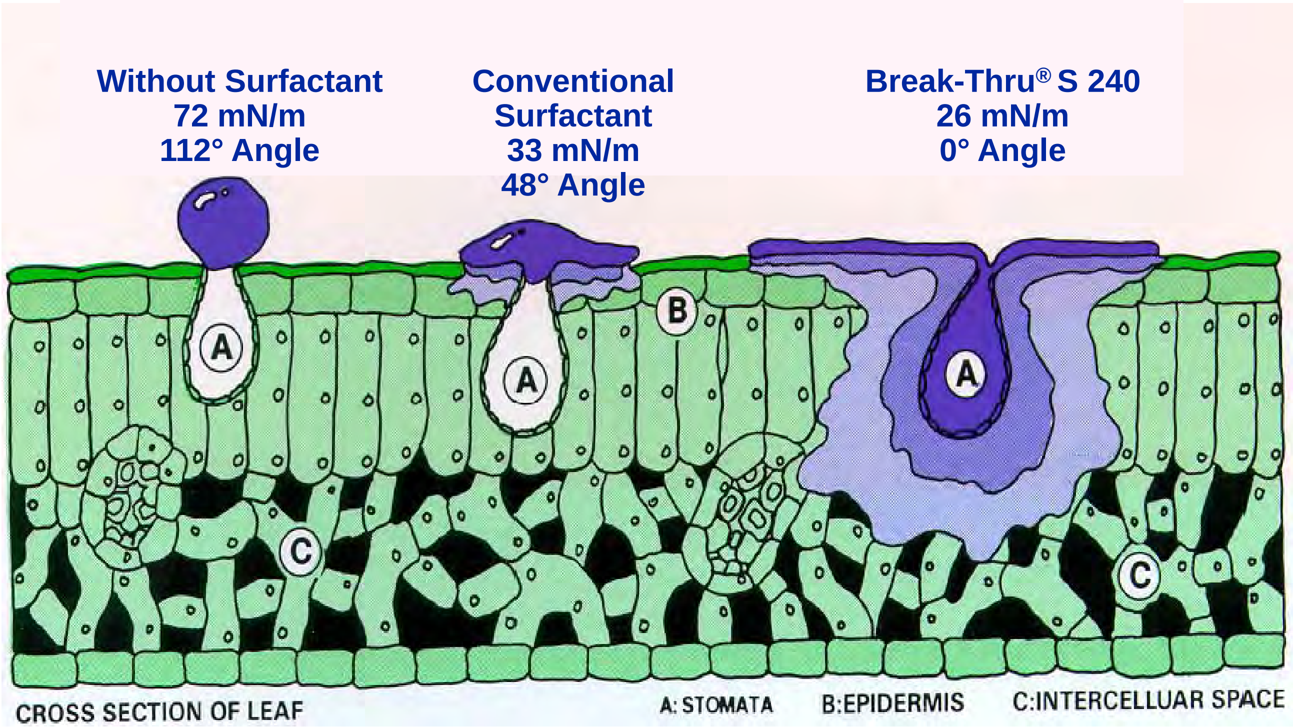
Activity on Real Plants

Clodinafop on Alopecurus myosuroides 24 days after application (climate chamber, 6-8°C)

No Adjuvant (minimalistic formulation) | **Rapeseed Oil** | **$C_{12}E_4$** | **Me-Oleate**

Stomatal infiltration – organosilicone surfactants

Spray Droplets On Leaf Surface



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Volatility $t_{1/2}$ values for a selection of adjuvants

Hydrocarbon	VP (Pascal)	VP (mm Hg)	Volatilisation (Kg/ha/day)	$t_{1/2}$ on leaf for 1 Kg/ha
EH 10	400	3	68,000	<<<1 min
EH 15	9	7×10^{-2}	1,400	< 1 min
EH 20	0.1	1×10^{-3}	30	30 min
EH 25	4×10^{-3}	3×10^{-5}	0.5	1 day
EH 30	8×10^{-7}	6×10^{-7}	0.01	50 days

Material	Equivalent Hydrocarbon (EH)
C12 paraffin	12
C15 paraffin	15
N-methylpyrrolidone	13
Methyl oleate	21
Butyl oleate	24
Triolein	>>30
C8E2	19

Briggs, G.G & Bromilow, R.H. (1994). In: *Interactions between adjuvants, agrochemicals and target organisms*, Proceedings of the 12th Schering Foundation Workshop, P.J. Holloway, R.T. Rees & D. Stock (Eds), Springer Verlag. pp 1-26.

Adjuvant properties and plant surface behaviour

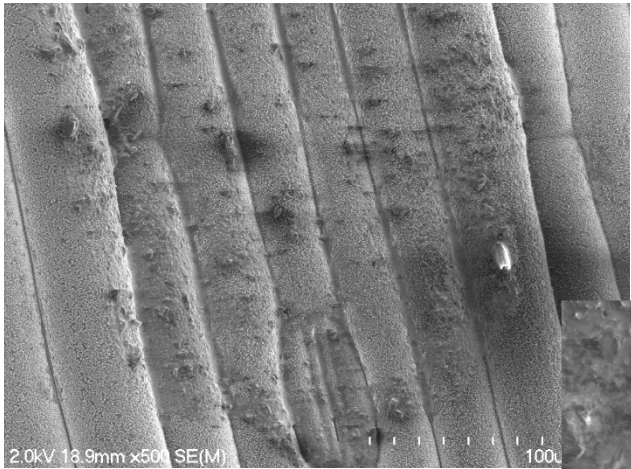
Adjuvant	EH	Log P	Δ log P	% Water content	Plant uptake	Function	Predominant fate process
Me oleate (Me seed oil)	22	8	0.2	Zero	Rapid	Solubiliser	Volatilisation, plant metabolism
Triolein (seed oil)	>50	25	0.6	Zero	V slow	Solubiliser	Surface deposit
NP ethoxylate 5EO	35	4.5	3	4	Rapid	Solubiliser	Plant uptake, metabolism
NP ethoxylate 10EO	50	4	5	14	Medium	Solubiliser + water retention	Plant uptake, metabolism
NP ethoxylate 20EO	>50	3	9	25	Slow	Water retention	Plant uptake, metabolism, surface deposit
Typical mineral oil	13-17	7-9	0	Zero	Medium	Solubiliser + spreader	Volatilisation
EP-PO (30:70) polymer Mr 4950	>50	7	V large	High	Zero	Water retention + deposit form	Surface deposit
PVA 17% acetyl Mr 14000	>50	>0	V large	High	Zero	Water retention + deposit form	Surface deposit

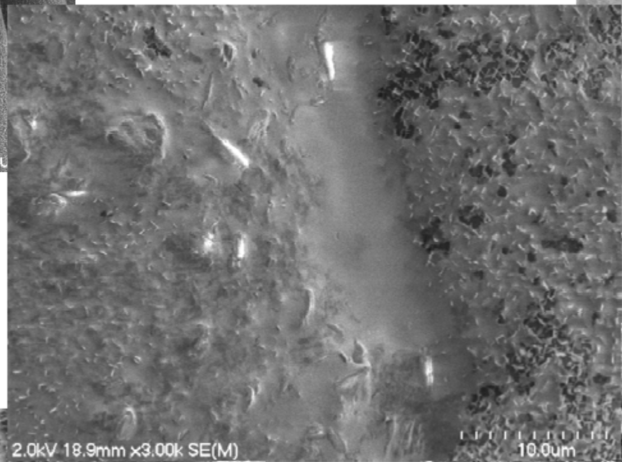
Stock, D. & Briggs, G.G. (2000). Physicochemical properties of adjuvants; values and applications. *Weed Technology*, 14, 798-806.

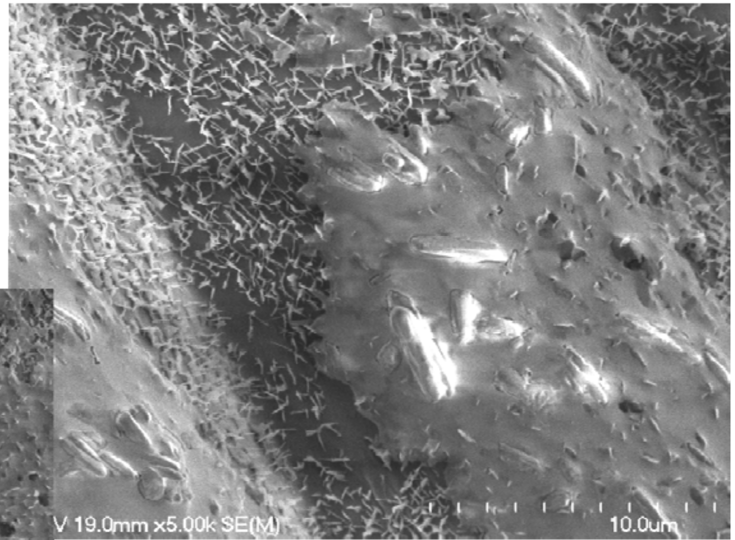
Ambient temperature FESEM images of controlled evaporation tralkoxydim formulations sprayed at 120g ai/ha onto AVEFA plants

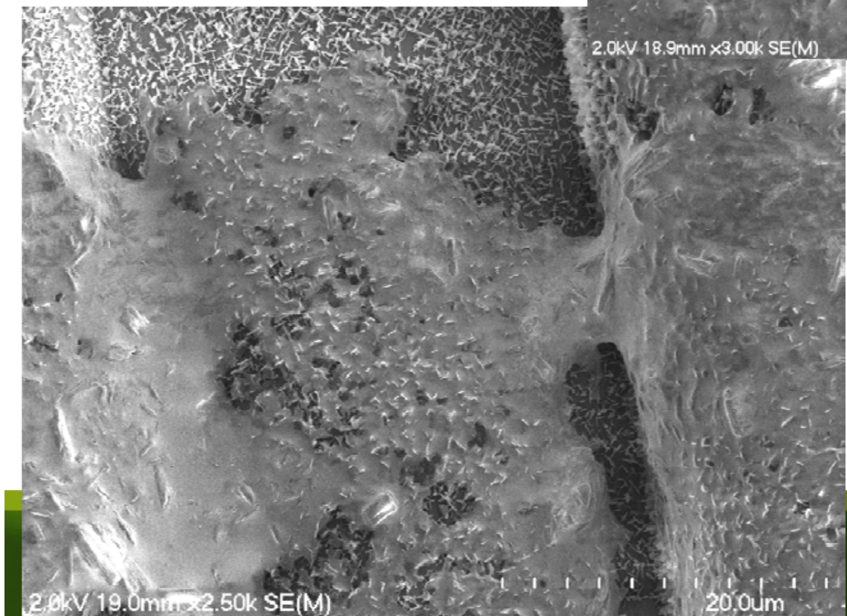
Grasp Standard SC : 109296 (Treatment 20)

< 8 HAT









Ambient temperature FESEM images of controlled evaporation tralkoxydim formulations sprayed at 120g ai/ha onto AVEFA plants

Grasp Standard SC : 109296 (Treatment 20)

1 DAT

Examples of Activity Improvement

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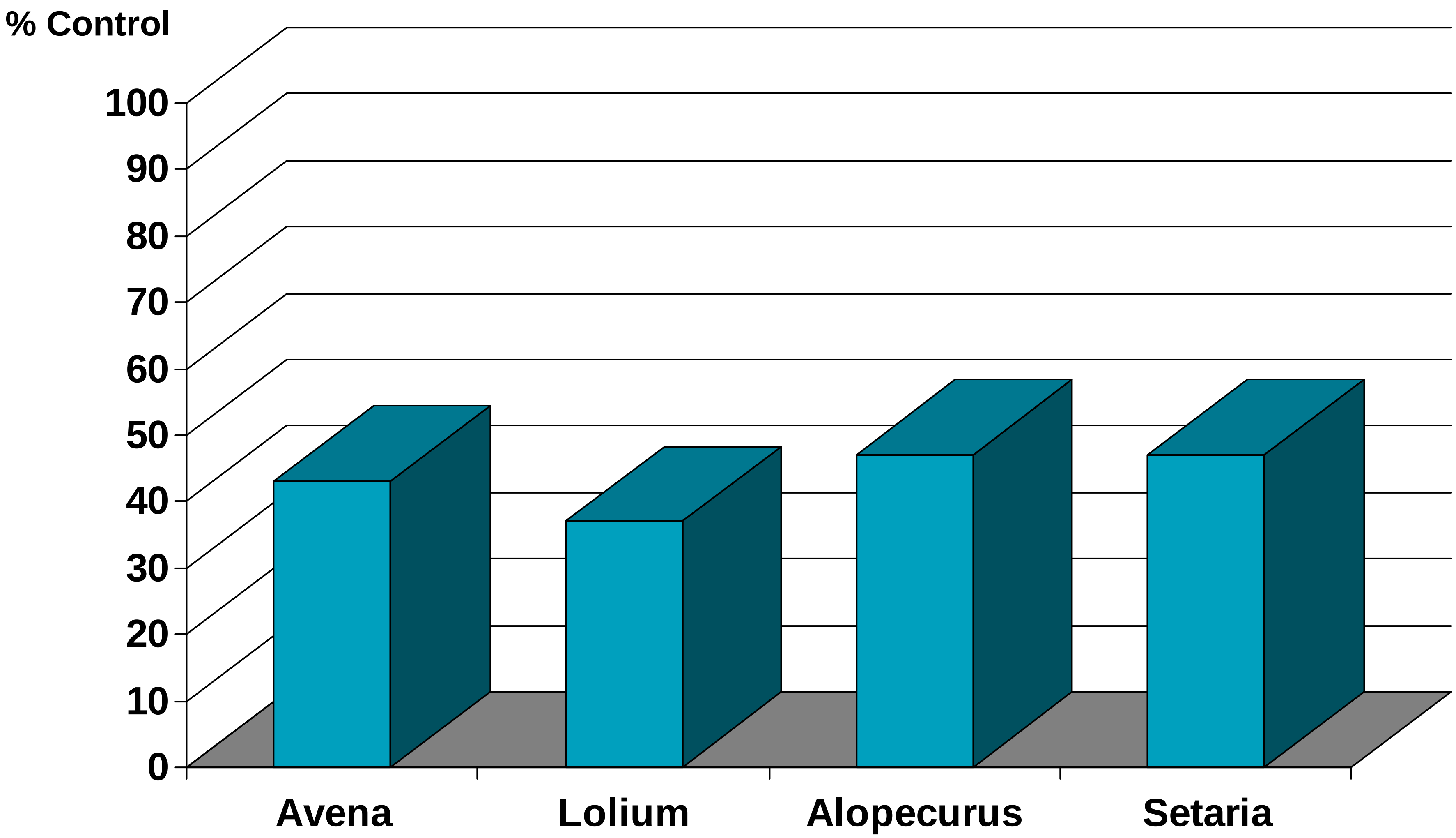
Pinoxaden

No wetting (No Retention aid, No adjuvants)



Pinoxaden.. Average of 3 rates (4, 8 & 16g/ha)

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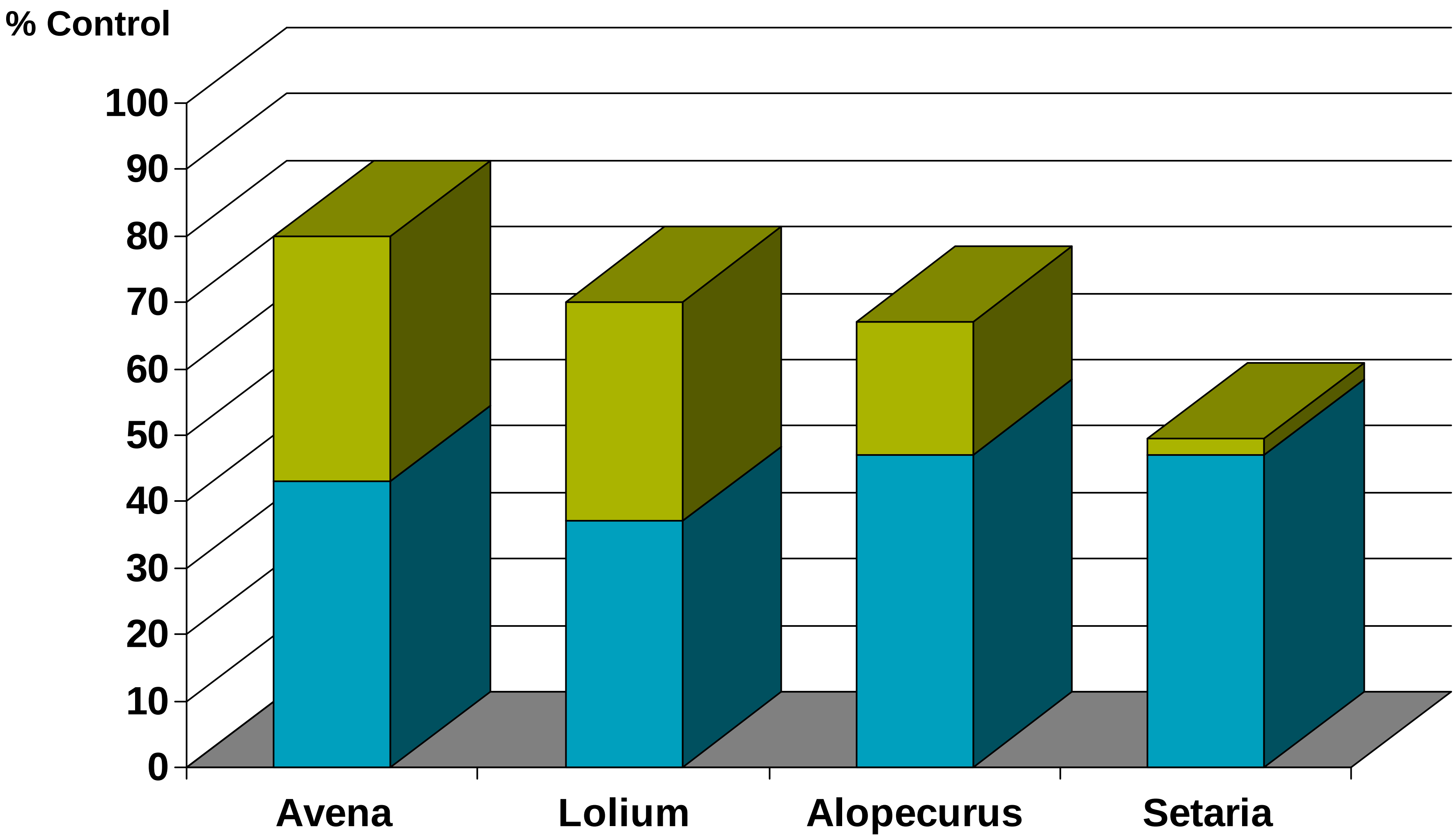
Pinoxaden

Good Wetting (Retention aid, No adjuvant)



Pinoxaden.. Average of 3 rates (4, 8 & 16g/ha)

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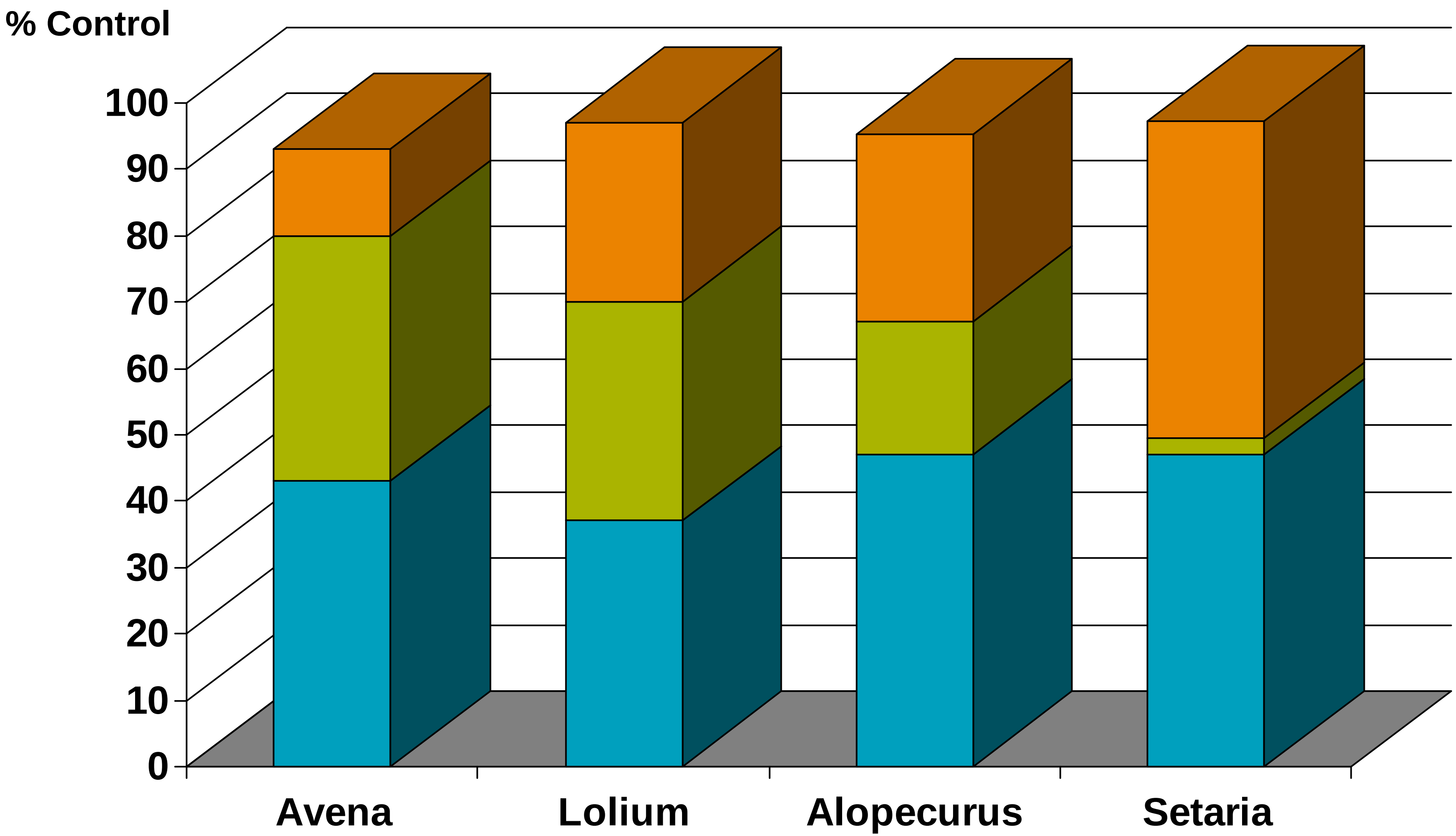
Pinoxaden

Wetting + Adjuvancy (Retention aid + Novel adjuvant)

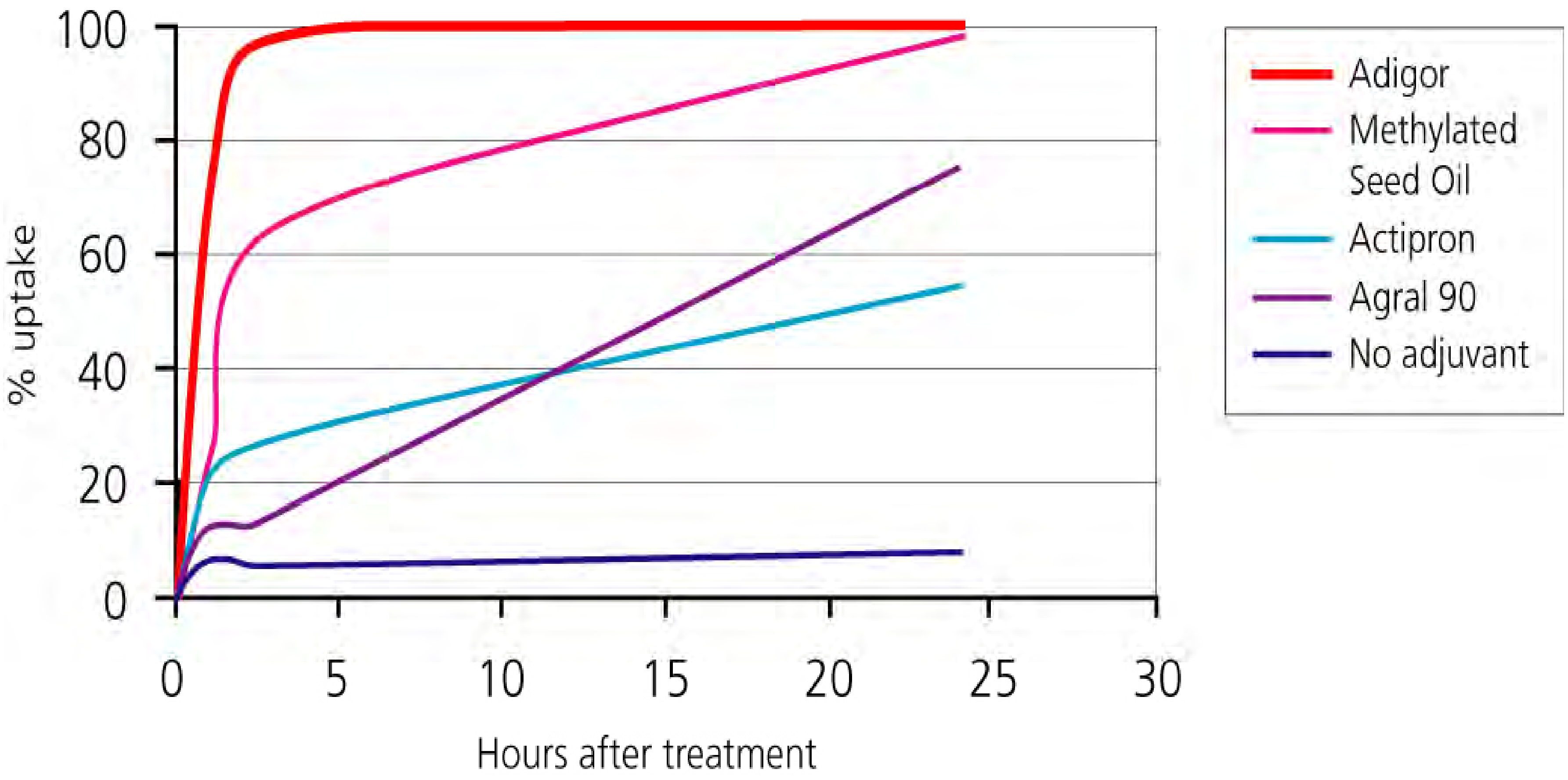


Pinoxaden.. Average of 3 rates (4, 8 & 16g/ha)

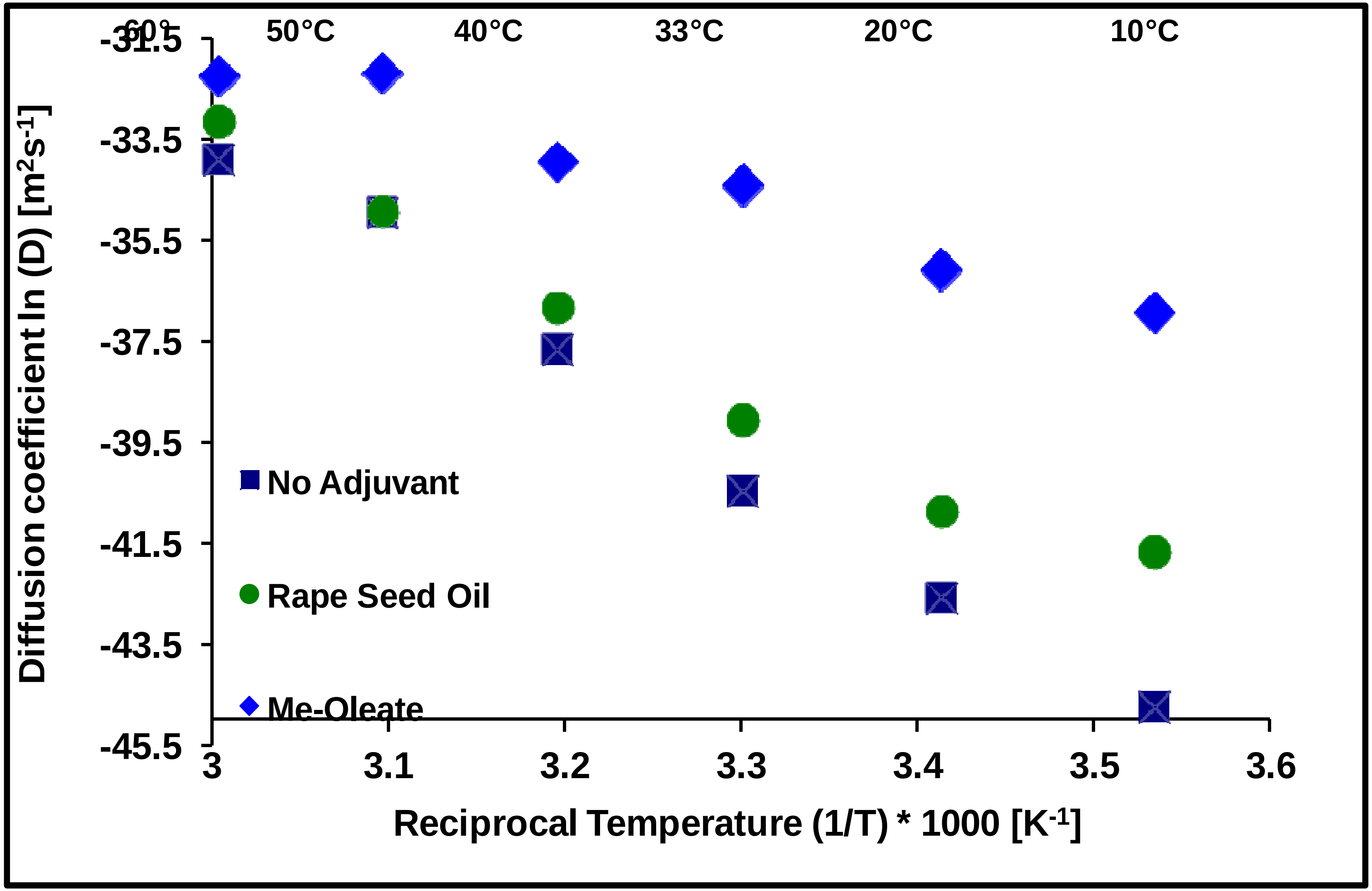
Adjuvancy: the “on-off“ switch for pinoxaden

- The adjuvant increases uptake and performance of pinoxaden
- Uptake is primarily through leaves
- Necrosis and death of green tissue within 2-5 weeks

Impact of a range of adjuvants on uptake of pinoxaden into wild oat leaves.



Impact of adjuvants on mobility of pinoxaden



Rainfastness; Comparison of **BRAVO**® vs. competition

The scanning electron micrographs illustrate the difference in deposits of **BRAVO**® and competitor after 127 mm of simulated rain. Note that although the deposits of both products appear similar prior to rain (top row), only the **BRAVO**® deposit is clearly distinguishable after 127 mm of rain (bottom row).

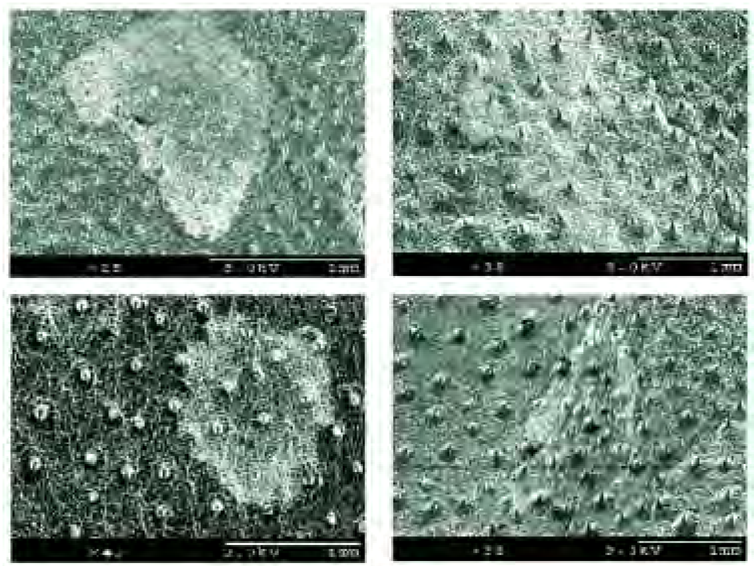
Scanning electron micrographs of **BRAVO**® and competitor on the surface of

cantaloupe leaves before (no rain) and after 127 mm of simulated rain.

BRAVO® Competitor

No rain

127 mm rain



Practical considerations in Adjuvant chemistry

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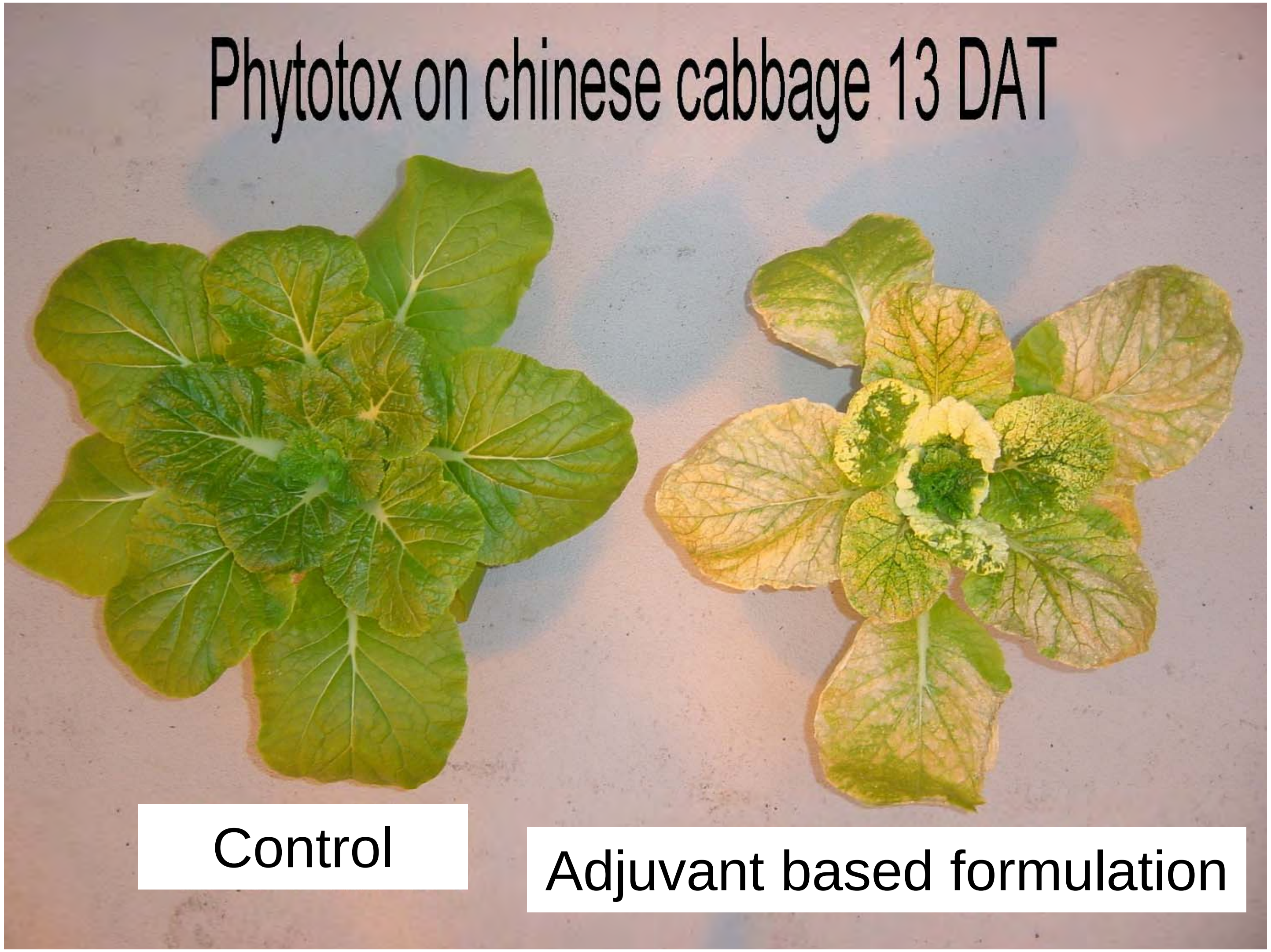
Impact of some penetration enhancers on sensitive plant species



Phytotoxicity from Surfactants

- Surfactant toxicity to plants has been demonstrated in different ways including:
  - Suppression of leaf growth
  - Induction of cellular necrosis on leaves
  - Flower and fruit abscission
  - Root development

- Surfactant toxicity can have deleterious effects on the translocation of pesticides in the tissue beneath the spray deposit.

- The most common mechanism identified is surfactant disruption / solubilisation of biological membranes

How will the choice of surfactant influence phytotoxicity?

- Only a few generalisations can be made (from studies in literature):

Cationics>Anionic>/=Nonionic

→ Lower phytotoxicity

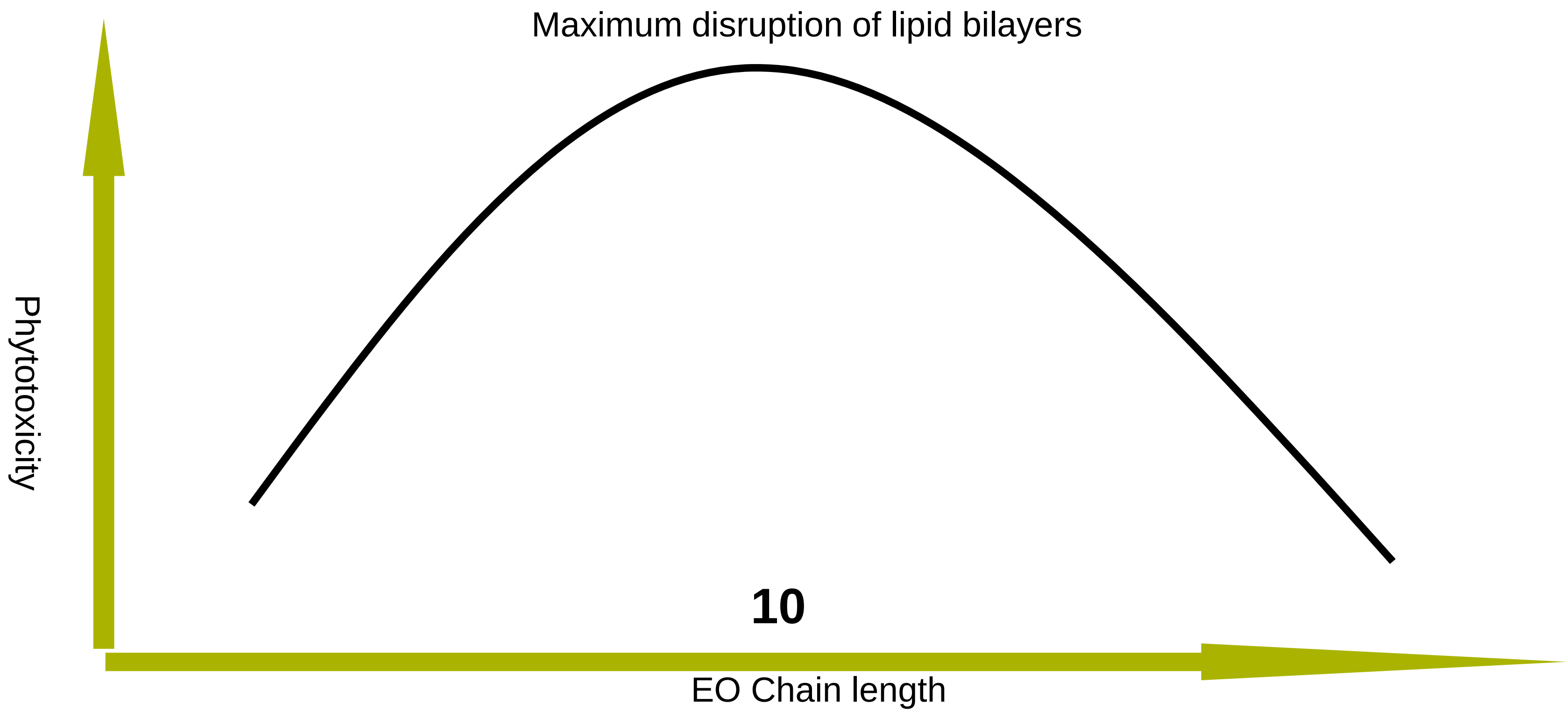
Increasing hydrophobe size

High EO content for nonionics

(Increasing MW)

Nonionic surfactants

- For alcohol ethoxylate surfactants, membrane disruption potential typically follows a parabolic relationship.



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Cont…

- Significant differences seen between membrane disruption studies and whole plant visual assays
  - Short chain ethoxylates show higher level damage;- they can rapidly penetrate the leaf cuticle!
  - High plant species variability in ability to metabolise/conjugate surfactants

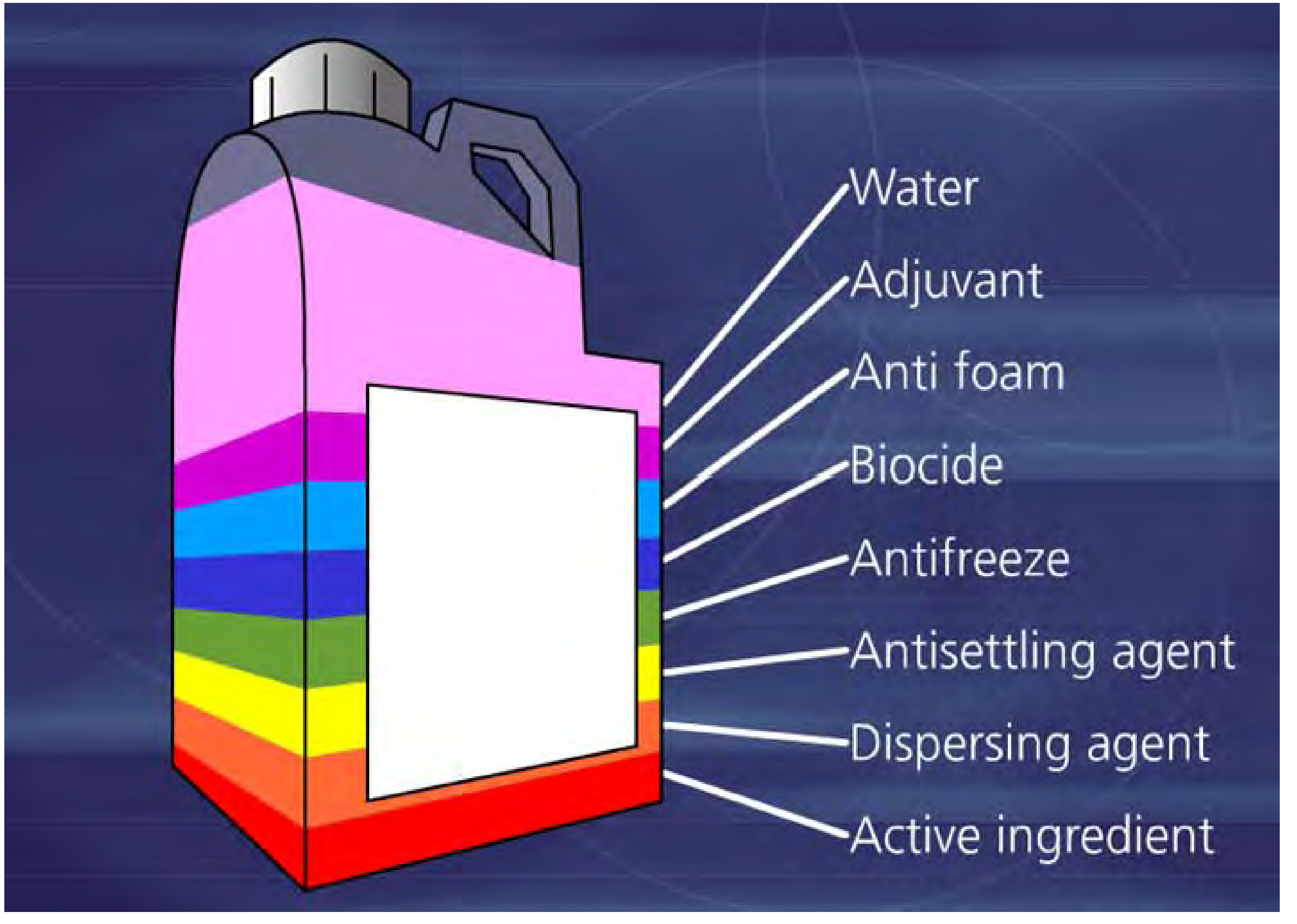
Build-In Versus Tank-Mix

- Technical Considerations.
  - Physical & Chemical Compatibility.
  - Space within the formulation.
- Regulatory Considerations.
  - (Will address later in presentation).
- End user considerations & flexibility
  - Different acceptance levels according to market segment;- e.g. Common practice to tank-mix adjuvants with many herbicides..
  - Built-in products have a fixed adjuvant:AI ratio;- potential issues for reduced dose application and in high volume applications.

Build-in adjuvant approaches.

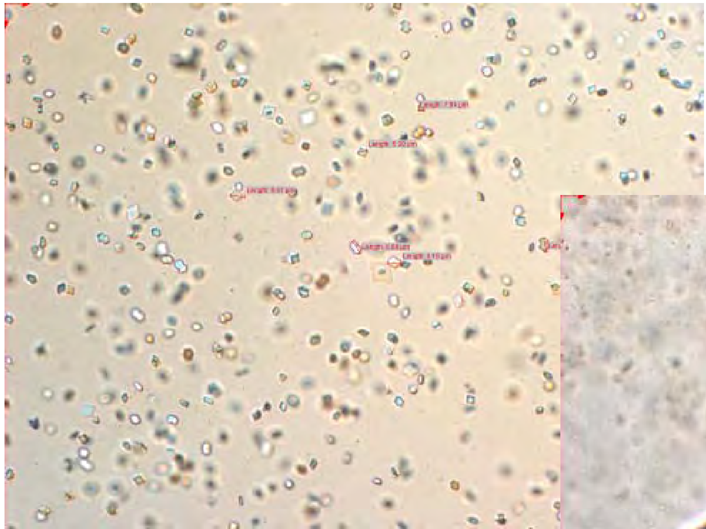
- High surfactant loaded aqueous formulations.
  - SL Formulations (e.g. Touchdown, glyphosate products).
  - Aqueous SC formulations (Amistar, azoxystrobin formulations).
- Solvent based formulations.
  - EC based formulation (Fusilade Max/Forte, fluazifop P butyl).
- Oil based formulations.
  - OD formulations (OTeq, ODesi brand formulations, Bayer Cropscience)

Spatial consideration – is there room in the formulation?



Other formulation considerations

- Physical compatibility & handing
- Chemical compatibility issues;- adjuvant and Active Ingredient



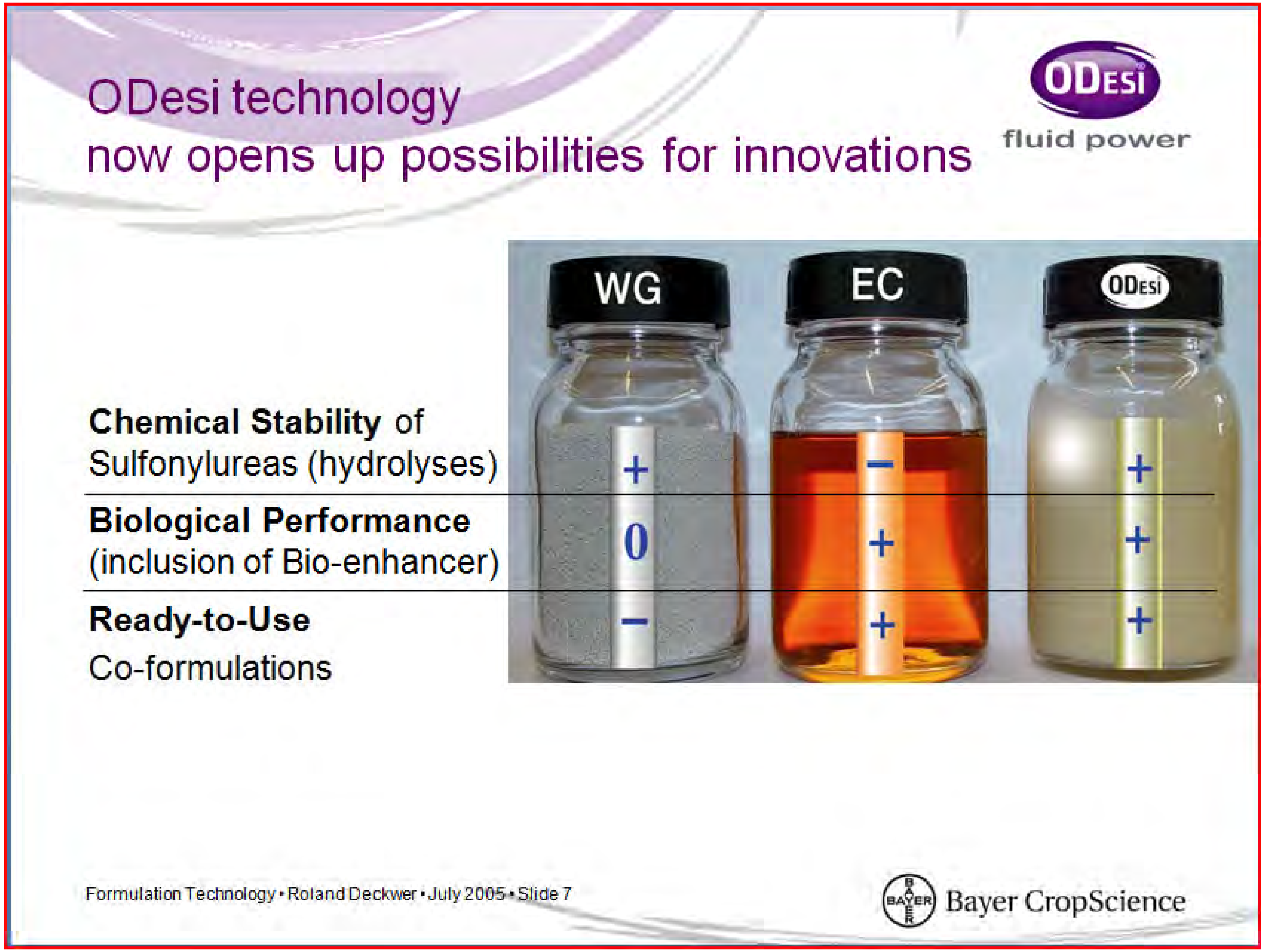
Finely dispersed particles

5 microns

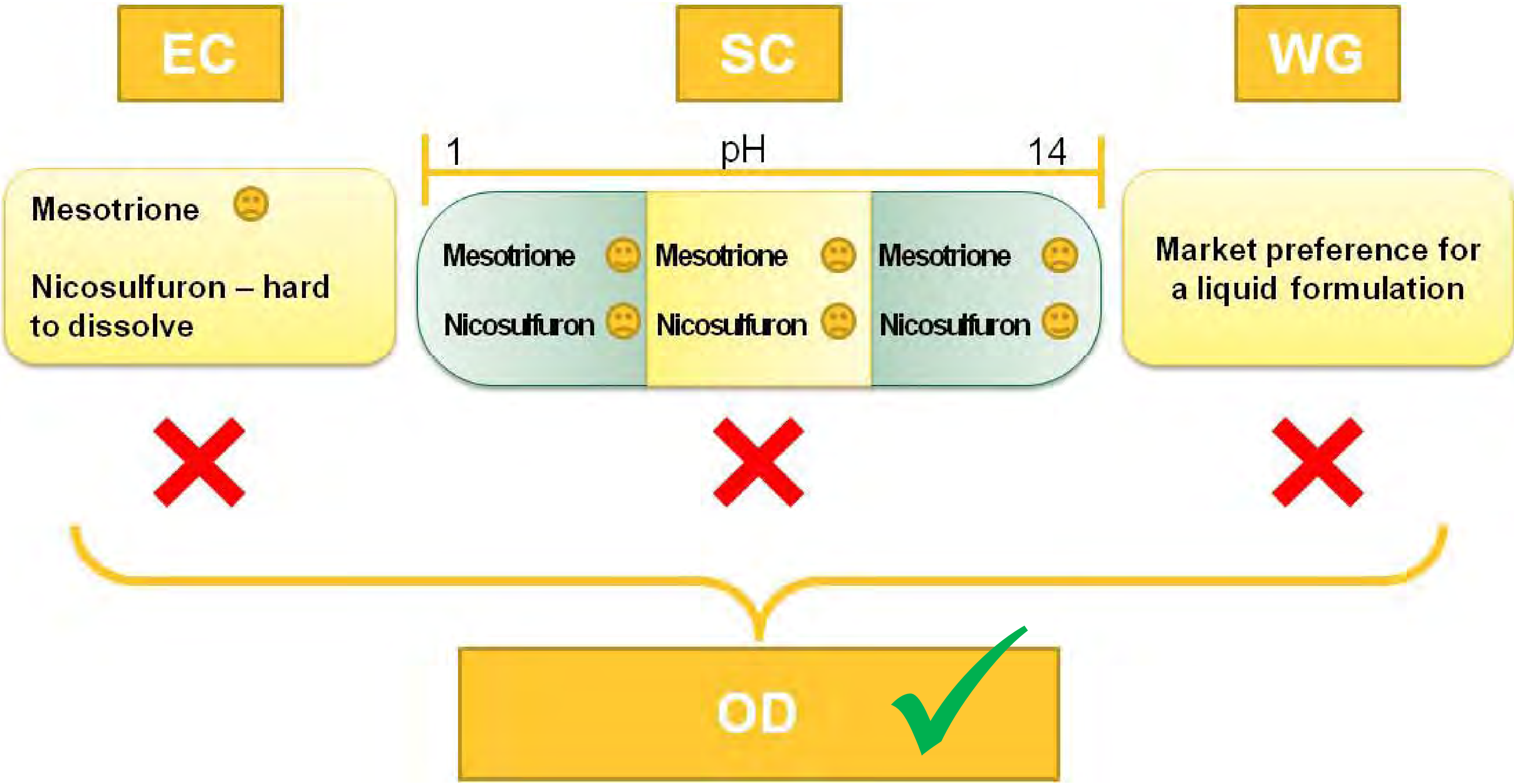
Dramatic crystal growth

200 microns

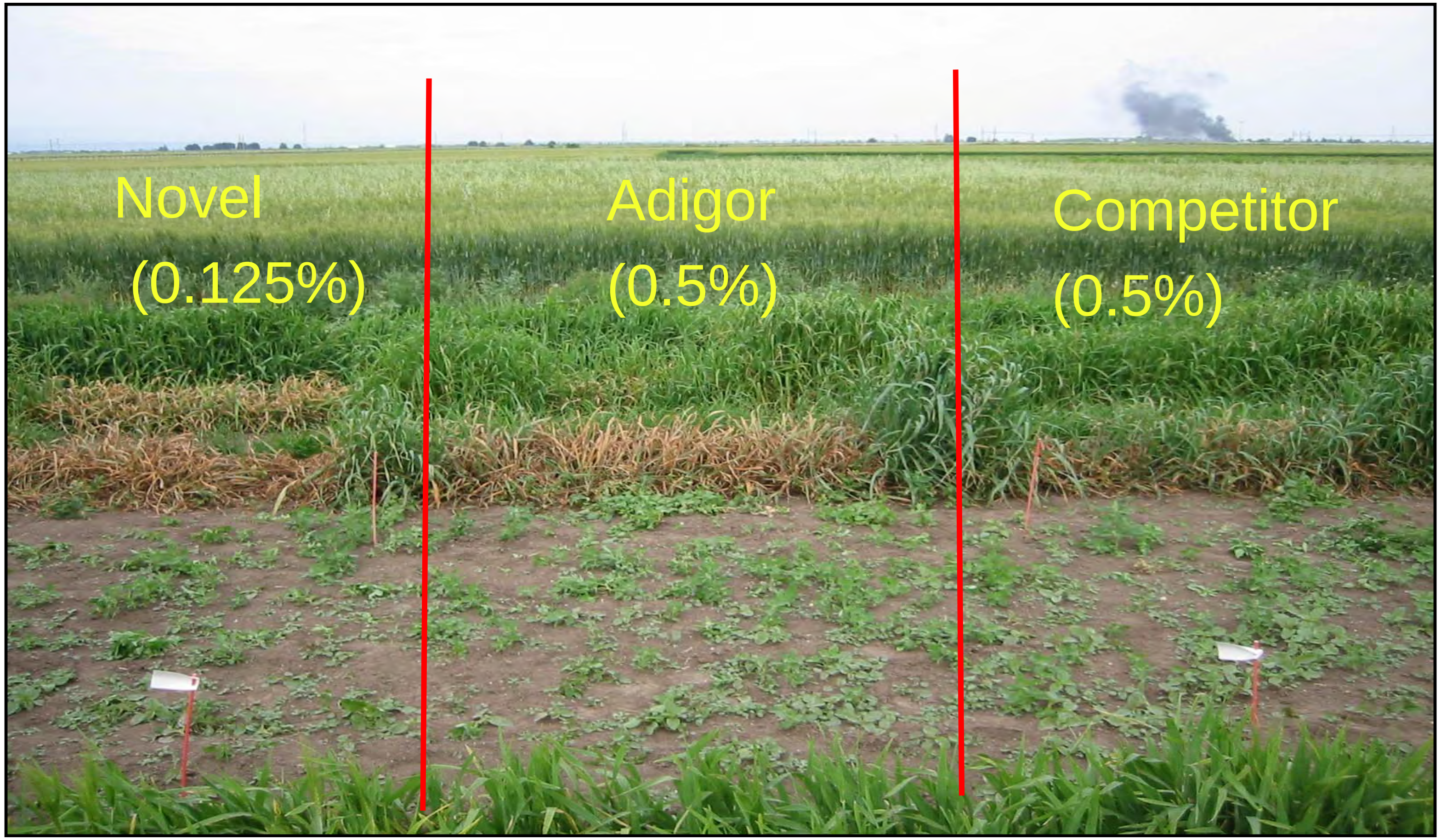
Use of OD technology to balance requirements



OD: solution to a physical compatibility challenge



Built-in next generation....



"Inert" Regulations

Regulatory situation of Adjuvants / Inerts

- Significant differences between EU and USA
  - REACH regulations impact current EU trends.
  - USA situation complicated by in-can versus tank-mix adjuvants.
    - Tank-mix adjuvants do not need to comprise EPA approved Inerts.
- Regulatory consideration will be a significant driver in terms of new chemistry and commercial strategy.
  - Environmentally “friendly” adjuvants.
- Pesticide sales often underpinned by adjuvant chemistries of modest commercial value to suppliers.
  - Major uses of current adjuvant chemistries often driven by other industries.
  - [Use of tank-mix adjuvants often destructive in terms of commercial impact.]

Core Data Requirements

- Product Chemistry
- Structural Activity Relationship
- Acute Toxicity (6 Pack)
- Genotoxicity (Ames +)
- One Generation Repro Screening Test (OECD 422)
- Biodegredation
- Ecotox (daphnia, fish)
- Risk Assessment
- Additional Data May Be Needed
  - up to full A.I. package
  - Endocrine Effects (a particular issue for some Inerts)

Identification of new solvent tools

- Various new solvents and cosolvents promoted within the Ag industry.
  - Propylene carbonate. (e.g. Huntsman).
  - Short chain fatty acid esters.
  - Rhodiasolv® Polarclean (Vidal et al, 9th International Symposium on Adjuvants for Agrochemicals)
  - Dimethyl lactamide.
    - Based on natural materials processed within Biochemical systems of mammalian system.

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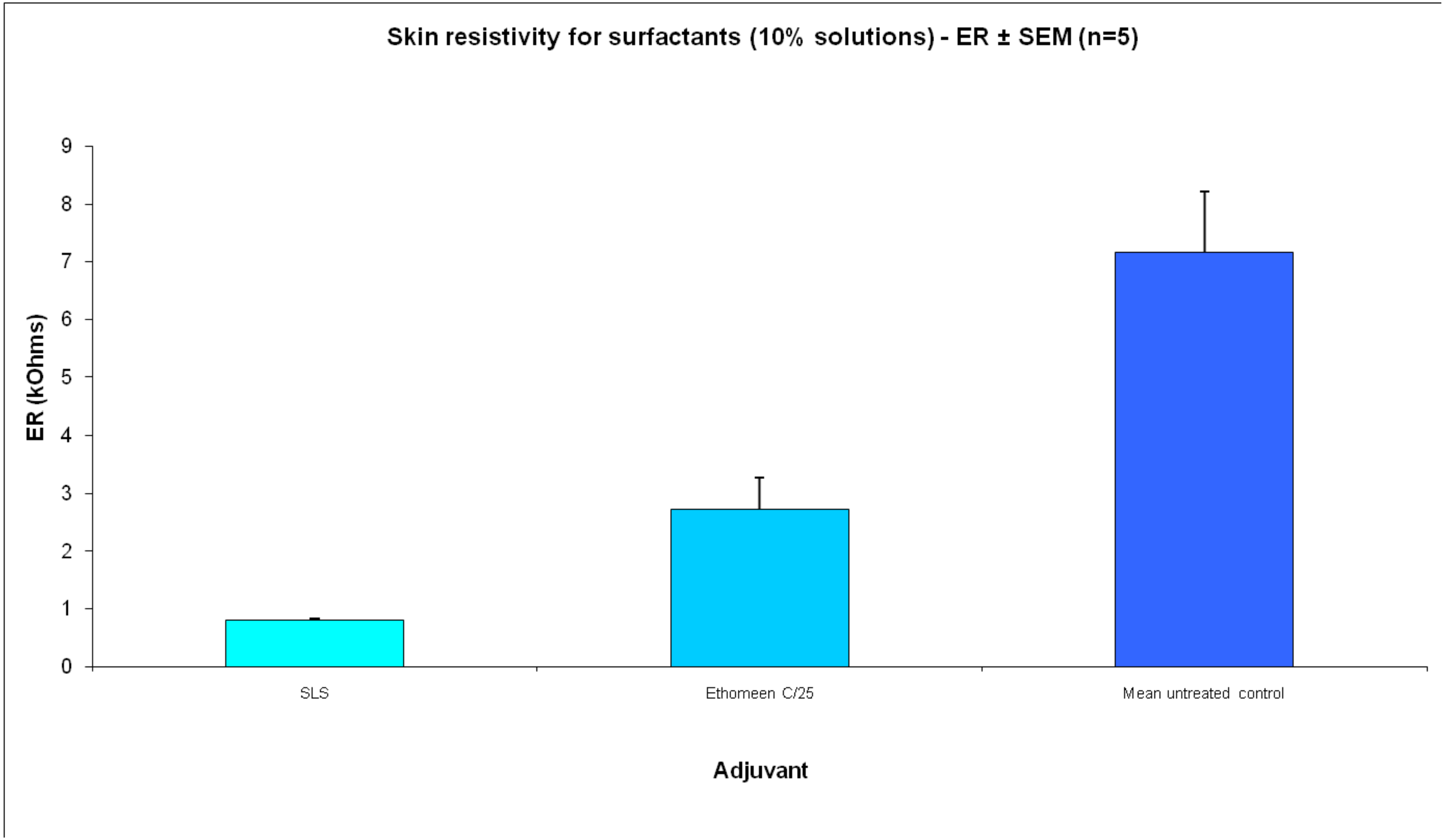
Cont

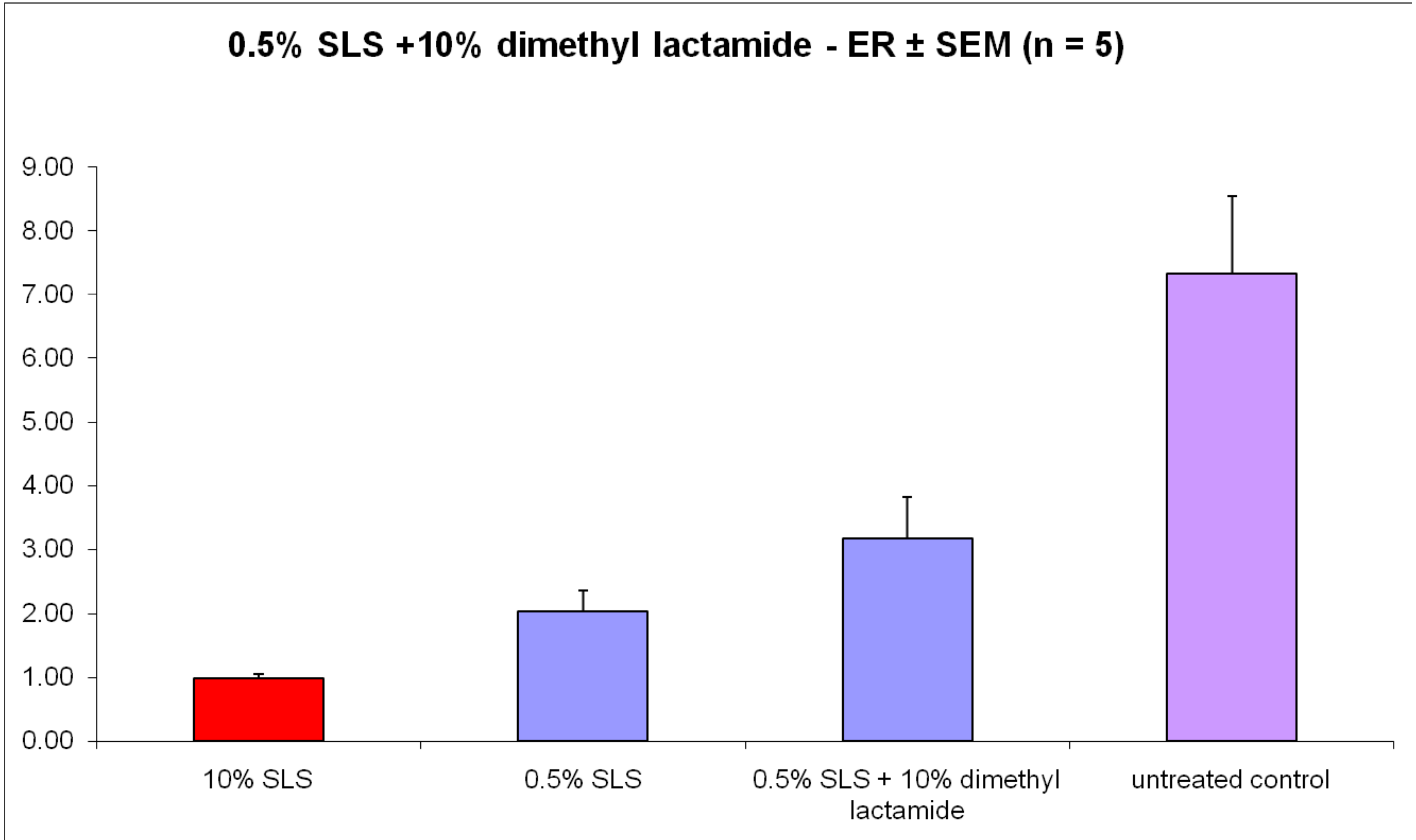
Improvements in or relating to pesticide formulations with lactamides. Bell, Gordon Alastair; Harris, Clair Louise; Tovey, Ian David. (Syngenta Limited, UK). PCT Int. Appl. (2009), 21pp. CODEN: PIXXD2 WO 2009027624 A2

Improvements in or relating to organic compounds used in agrochemical formulations. Bell, Gordon Alastair; Harris, Clair Louise; Tovey, Ian David. (Syngenta Limited, UK). PCT Int. Appl. (2009),
Preparation of lactamides as agents for reducing the toxicity of pesticides. Bell, Gordon Alastair; Tovey, Ian David. (Syngenta Limited, UK). PCT Int. Appl. (2007), 19 pp. CODEN: PIXXD2 WO 2007107745 A2

Skin function test for surfactants



Safening effect of dimethyl lactamide



How do you choose the “best” delivery system ?

- It depends!....
- What are the problems to be addressed?
- What is acceptable in terms of a Product Strategy?
- Need to consider other trends
  - Regulatory
  - Market preference.

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Acknowledgements

- Phil Taylor
- Gordon Bell
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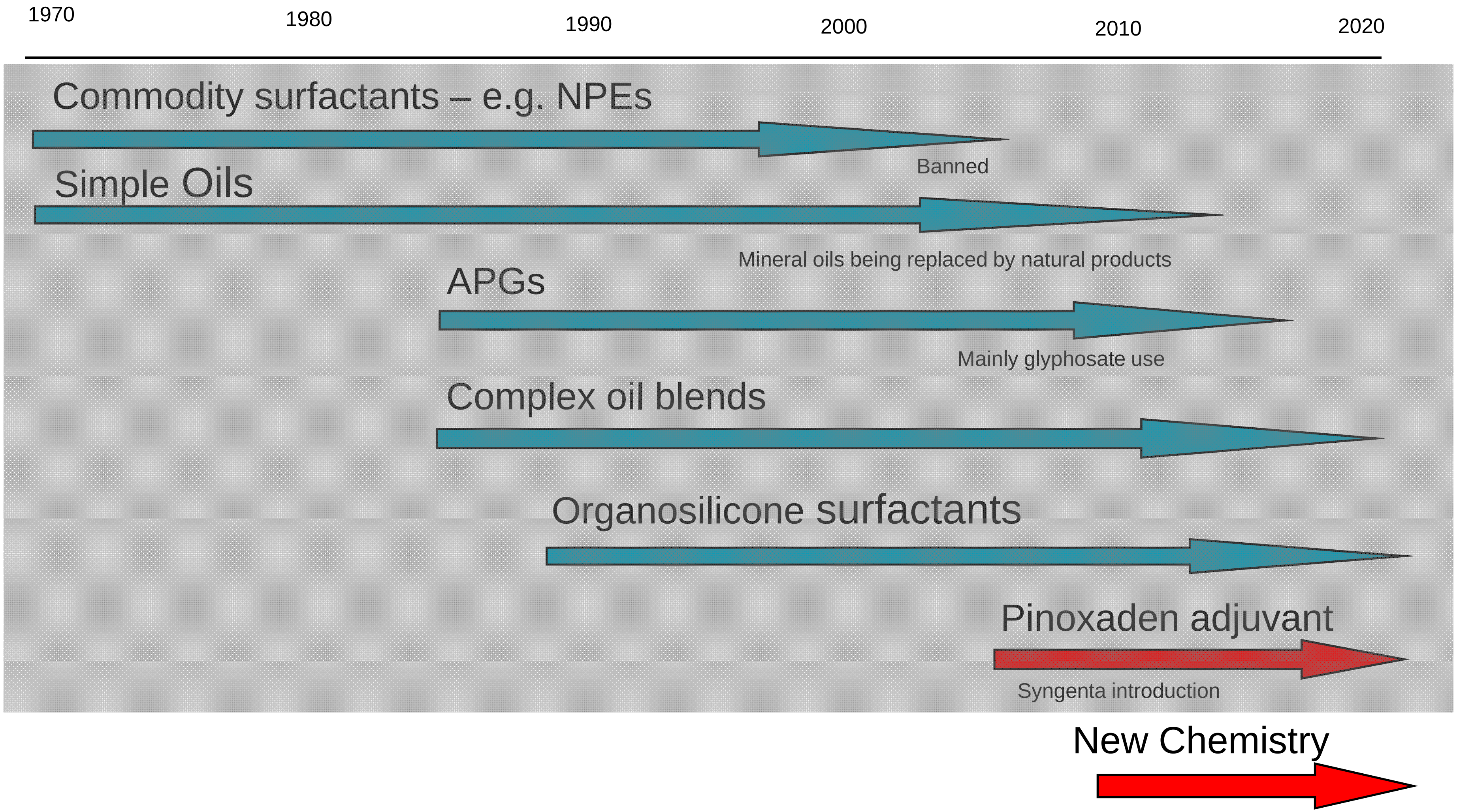
- Ian Shirley

......where are we going?......



What will the changes be?

- There will/must be some!
- Changes are already underway.
  - Some are Regulatory driven (see next section).
  - Others are technical or market-driven in terms of in-can development.
    - E.g. Introduction by Bayer of Oil-Dispersion formulations (OTeq, ODesi).
- Patenting activity competitive as this is a key aspect of portfolio defence.

Non-target effects: direct impact on phtytotoxicity.

- Surfactant-type adjuvants
  - Cationics>Anionic>/=Nonionic
- Ionic surfactants
  - Phytotoxic effects often not well understood
  - Charge interaction with membrane proteins considered a key factor (disruption of folding impacting on functionality)
    - Note:- SDS surfactant (sodium dodecyl sulphate) is used in gel-electrophoresis for proteins for this reason!

Data Package Generation

- Search of Public Data Bases, MSDS, etc.
- Conduct Studies to Fill Gaps

Regulatory data requirements: EU

Country	Toxicology	Efficacy	Residues
Austria	Y	Y	N
Belgium	Y	Y	N
Denmark	N	Y	N
Finland	N	N	N
France	Y	Y	N
Greece	Y	Y	N
Germany	Y	Y	Y
Ireland	Y	N	N
Italy	Y	Y	Y
Netherlands	N	N	N
Portugal	Y	N	N
Spain	Y	Y	Y
Sweden	N	N	N
UK	Y	N	N/Y

(Butselaar & Newman, 1998)

...not much harmonisation yet!

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General comments

- Globally there is increasing regulatory concern regarding the non-target environmental effects of “inerts” including adjuvants.
  - Oestrogenic effects of Nonylphenol ethoxylates (NPEs).
    - Loss of NPE emulsifiers and the Agral tank-mix adjuvant from the Syngenta range.
  - Amine ethoxylate surfactants an increasing issue in EU, especially Germany;-
    - Tallow amine ethoxylates classically used with original glyphosate formulations have ecotox. issues in terms of effects in aquatic systems.