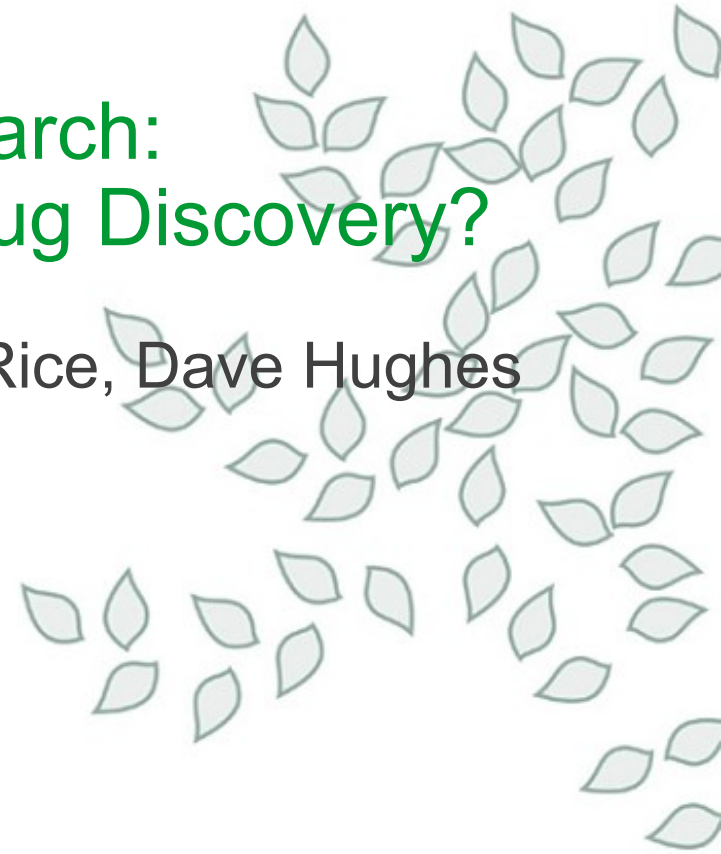




Modern Agrochemical Research: A Missed Opportunity for Drug Discovery?

John Delaney, Eric Clarke, Martin Rice, Dave Hughes



Why should we care how pharma perceives ag?

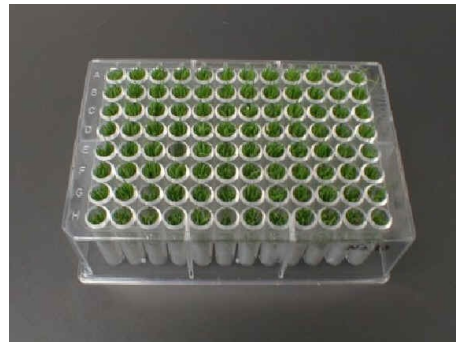
Ag screening = In-vivo screening (turnover compounds not screens).

In-vivo HTS → Feed me!

In-house synthesis, purchase, compound exchanges.

Drugs and compounds sourced from drug companies produce better pesticide leads than random compounds.

We want your compounds.



The exciting world of agrochemicals...



Agrochemicals : A short introduction...

Crop cultivation began in Neolithic times (8-10k years ago)
→ Huge increase in the number of people that could be supported in a given environment.

Cultivation brings problems – insects, fungi and weeds.

Elemental sulphur used in pre-Roman times.

Bitumen, tobacco, mercury and “gall from green lizard” were also tried...with limited success.

Inorganics became the norm (e.g. AsO_3 , HgCl_2 , FeSO_4).

High use rates, limited effectiveness, environmental damage.



The 1950s...

Synthetic pesticides! DDT, carbamates, 2,4D etc.

Much more effective than inorganics.

Not without issues...

- Toxicity – better than mercury, but not exactly clean.
- Persistence – DDT is the best known example.

Rachel Carson's book *The Silent Spring* is devoted to the environmental damage caused by the widespread use of DDT in the fifties. The book is widely credited with launching the environmentalism movement in the West.



Modern agrochemicals (1970 onwards)

Modern agrochemicals are organic compounds with single MoAs.

They are well-characterised for toxicological point-of-view (acute and chronic).

Their movement in the environment and breakdown products have been extensively studied.

Not popular with everyone...Prince Charles, The Daily Mail, The Soil Association.



Food risks – public perceptions v reality

If you ask people what they fear about their food, typically the top half-dozen concerns are food poisoning, BSE, growth hormones used in animals, animal feed, pesticides and genetically modified (GM) food (<http://www.food.gov.uk>). But how do these perceived risks stack up with the estimates of deaths caused by food? Acknowledging that these are only approximate, and that great uncertainties surround some of the numbers, two food risks tower above the rest — the dietary contributions to **cardiovascular disease** and to **cancer**. These risks, taking a fairly conservative estimate, probably account for more than 100,000 deaths per year in Britain. **Food poisoning** probably accounts for between 50 and 300 (similar in range of magnitude to the risk of **choking** to death on food or suffering a fatal accident while getting into or out of bed). As far as we know, growth hormones (banned in Europe) and **pesticides** in food, as well as GM food, are not responsible for any deaths.

John Krebs is chairman of the UK Food Standards Agency and in the Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, UK.

Nature **415**, 117 (10 January 2002)



"I feel ill Mum. I think it's the pesticides in the veges. From now on I'm going to have to eat chips, burgers and pizzas."

Why do you need to use agrochemicals?

Food quantity

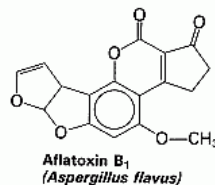
- Increased yields, less labour, lower price.

Food safety

- Fungii produce toxins such as ergotamine and aflatoxin.
- Stressed crops produce toxic defence chemicals such as solanine.

Environment

- Land usage (e.g. destruction of rainforest for farmland).
- Water usage. 70% of worldwide water usage is for irrigation.



Agrochemicals - heavy on P, Sn, metals and halogens?

Phosphorous : If we distinguish between modern (post-1970) and older compounds...

- 21% of pre-seventies compounds contain P against 9% of post-1968 compounds.
- 90% of P-containing agrochemicals were registered before 1974.

Similar stories for Sn and heavy metals.

The standard industry reference (The Pesticide Manual – ed. Clive Tomlinson) does us no favours in this regard.

Over 50% of entries have a CAS number pre-dating 1970.



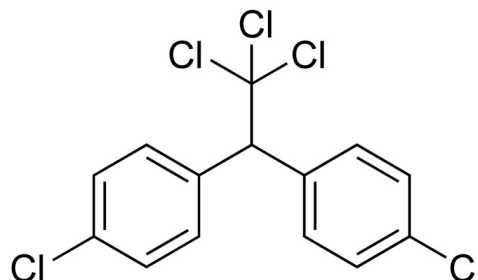
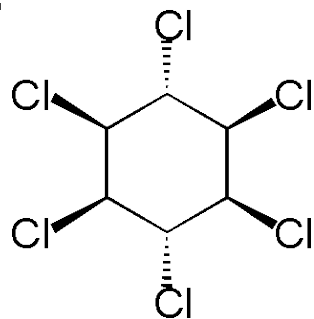
Halogens

If 2 or more halogens = heavily halogenated...

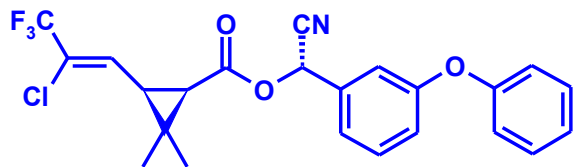
- 12% of Syngenta compound collection.
- 22% of Pesticide Manual.

For comparison, 16% of a set of 75 marketed drugs (*Oprea et al (2001), JCICS, 41, 1308-1315*) contain 2 or more halogens.

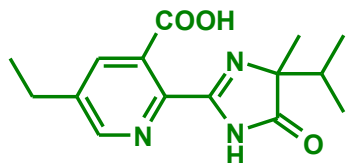
Image of excessive halogenation is a legacy from prominent insecticides from the 50s and 60s – e.g. Lindane (6 Cls) and DDT (5 Cls).



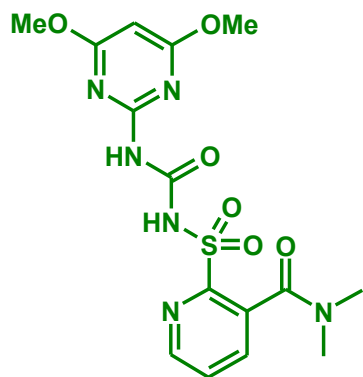
Modern agrochemicals - some examples



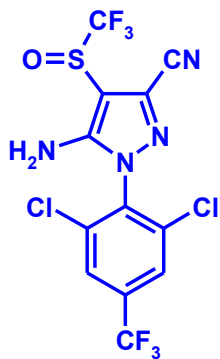
Lambda-cyhalothrin (racemic)
1984



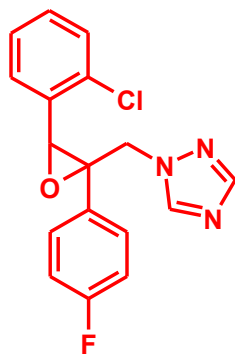
Imazethapyr
1987



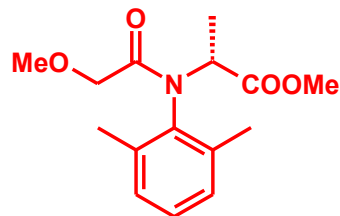
Nicosulfuron
1991



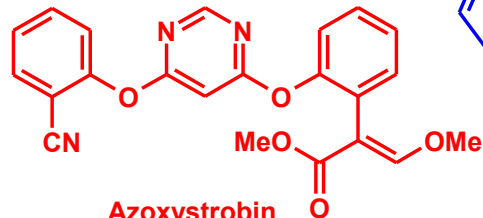
Fipronil
1993



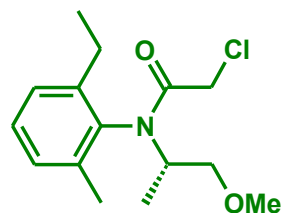
Epoxiconazole
1993



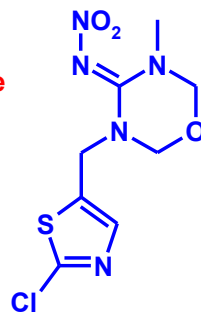
Metalaxyl-M
1996



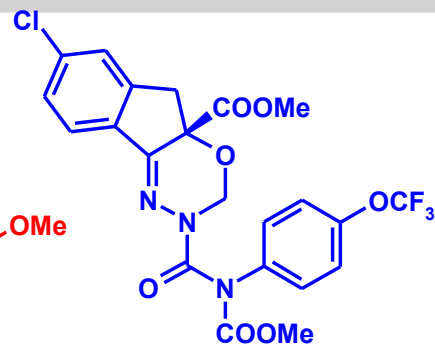
Azoxystrobin
1997



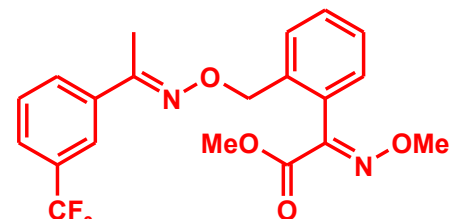
S-Metolachlor
1996



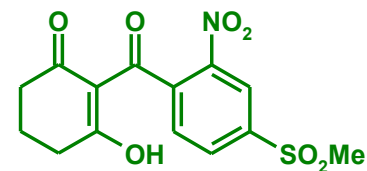
Thiamethoxam
1999



Indoxacarb
1999

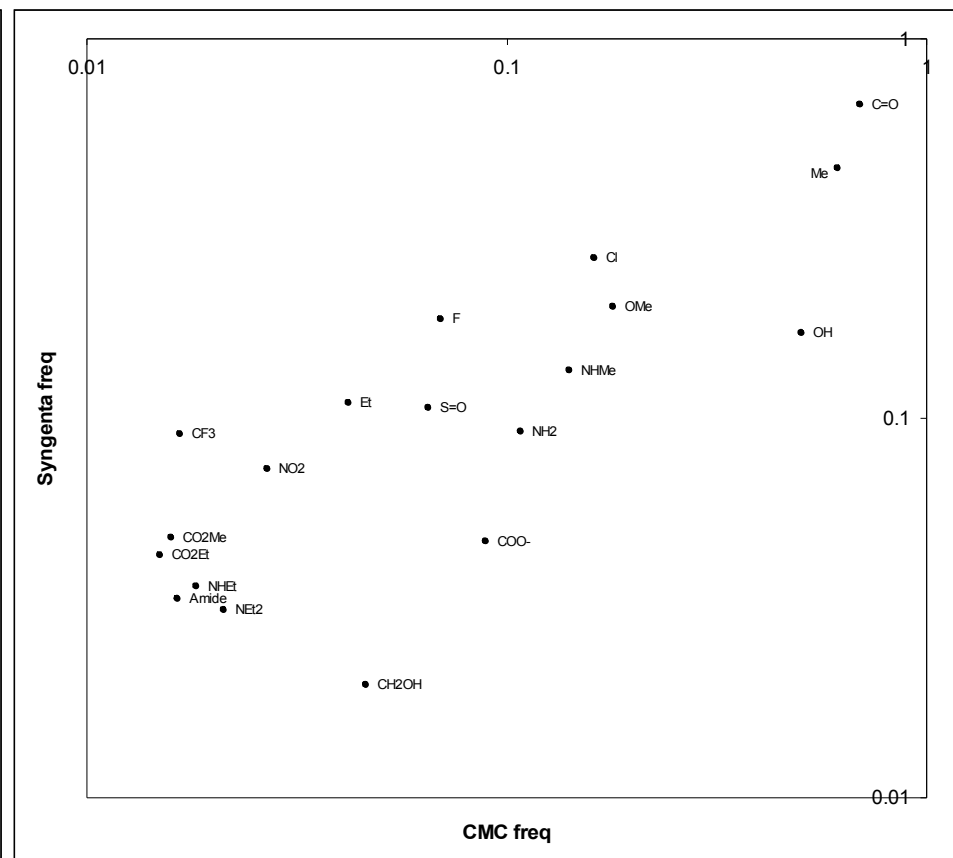
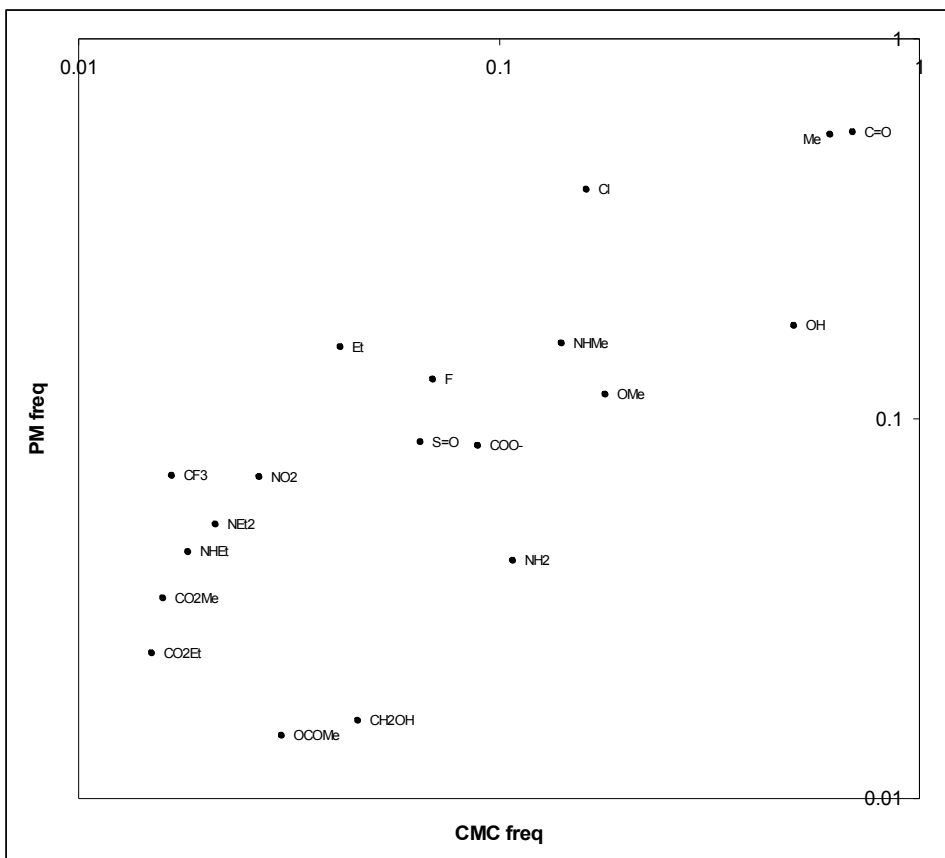


Trifloxystrobin
2000



Mesotrione
2001

Bemis and Murcko fragments (*J. Med. Chem.* 1999, 42, 5095-5099)



Drug-likeness and the modern agrochemical

Often defined by the differences between a drug-rich (WDI, CMC) and a drug-deficient database (ACD).

The Pesticide Manual has also been used as a counter example :-

“The Pesticide Manual is a yearly compendium of marketed pesticides (herbicides, fungicides, insecticides, etc.). This has been used in the past by the author as an alternative standard for non-druglikeness, primarily because nearly all of the compounds in the list are meant to cause fatality of the primary organism. While these compounds have the *druglike characteristics of bioavailability and specific mode of action, their human toxicity in most cases qualifies them as nondruglike*. It is interesting to note that fewer compounds in the Pesticide Manual than CMC fail the Lipinski rules for druglikeness (unpublished results).”

Bradley, M.P. (2002) An overview of the diversity represented in commercially-available databases. J. Comput. Aided Mol. Des. 16, 301–309

Acute oral toxicity (best-selling pesticides and drugs 2003)

Sales Rank	Pesticide	Rat acute LD50 (mg/kg)	Medicine	Rat acute LD50 (mg/kg)
1	Glyphosate	5000	Atorvastatin	5000
2	Imidacloprid	450	Simvastatin	4438
3	Acetochlor	2148	Olanzapine	175
4	Azoxystrobin	5000	Amlodipine besylate	393
5	Paraquat	143	Epoetin alfa	-
6	Tebuconazole	2850	Lansoprazole	5000
7	Chlorpyrifos	149	Esomeprazole	2210
8	Metolachlor	2780	Clopidogrel bisulfate	1914
9	2,4-D	702	Fluticasone propionate & Salmeterol xinafoate	2000
10	Mancozeb	5000	Sertraline hydrochloride	1460

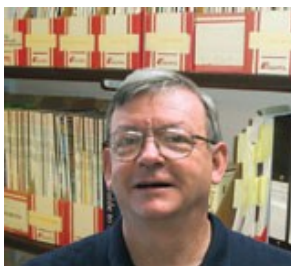
Optimal properties for drugs and pesticides

Lipinski's "rule-of-5" is well known in pharma.

Tices's rules may be rather less well-known... limits on the useable physical property limits for agchem products.

The rules are strikingly similar...main difference is the acceptable number of donors.

Property	Lipinski	Tice
Molecular weight	< 500	< 500
log P octanol	< 5	< 5
H-bond donors	< 5	< 3
H-bond acceptors	< 10	< 12



Acids

25% of the compounds in the Pesticide Manual are acids – acidic compounds move better from leaf to root (phloem mobility).

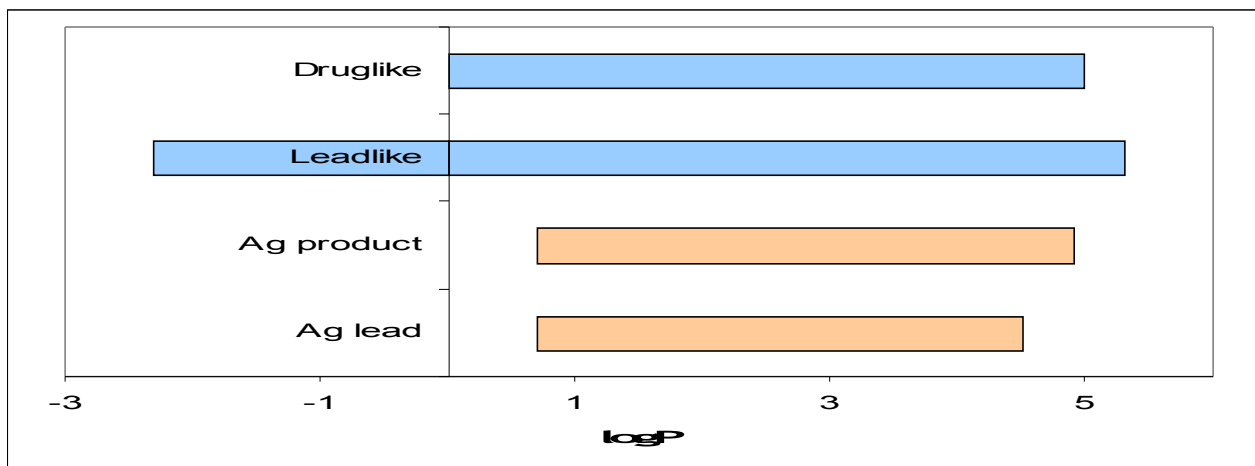
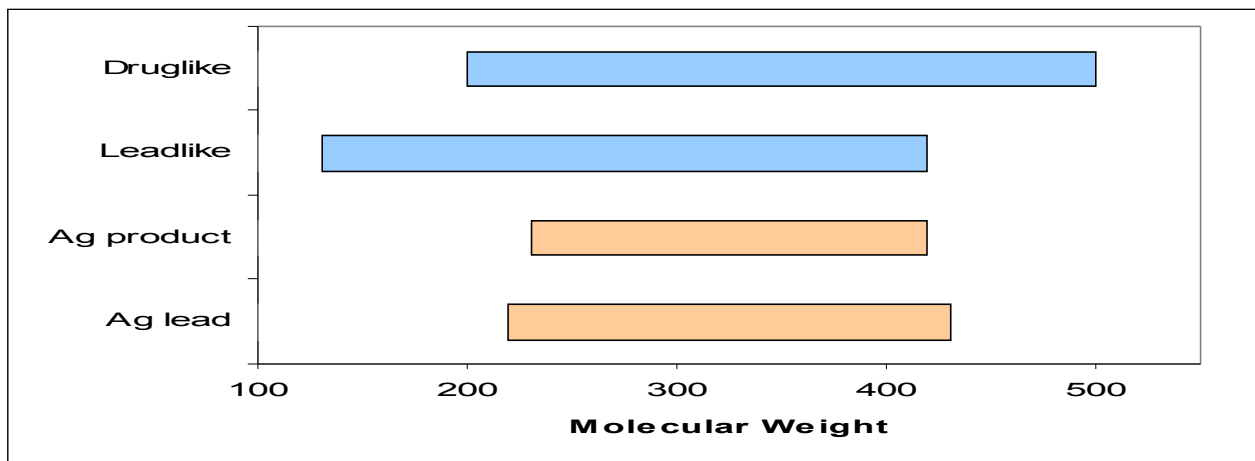
Anionics often have poor protein-binding properties in mammals – not ideal for drug development.

Recent study (Martin, Y.C. (2005), *J. Med. Chem.*, **48**, 3164-3170) nuances this – anions with a polar surface area $> 75\text{\AA}^2$ are likely to have poor availability.

Half the herbicidal acids in the PM fit this profile.



Leads and products - 10th and 90th percentiles



Oprea, T.I. et al. (2001) Is There a Difference between Leads and Drugs? A Historical Perspective. *J. Chem. Inf. Comput. Sci.*, **41**, 1308-1315.

Clarke, E.D., Delaney, J.S. (2003) Physical and molecular properties of agrochemicals: An analysis of screen inputs, hits, leads and products. *Chimia*, **57**, 731-734.

Agchems that became drug leads

Compound	Ag indication	Pharma indication	Cell Cidal MOA	Company
Epothilone	F	Anti-cancer	Y	Ciba
Triazolopyrimidines	F	Anti-cancer	Y	BASF
Fluconazole	F	Anti-fungal	Y	ICI
Fenpropidine	F	Anti-mycotic	Y	BASF
Nitisinone	H	Hereditary Tyrosinaemia Type 1 and Alkaptonuria	N	Syngenta
Anisomycin	H	Anti-bacterial	Y	Nippon Kayaku
Glyphosate	H	Anti-parasitic	Y	Monsanto
Bisphosphonates	H	Bone loss	N	Syngenta
Endothelin agonist	H	Cardio-vascular	N	BASF
Sulphonylureas	H	Anti-cancer	Y	Dupont
Nikkomycin	I	Anti-fungal	Y	Bayer
Staurosporin	I	Anti-cancer	Y	Ciba
Abamectin/Ivermectin	I	Anti-parasitic	Y	Ciba
Imizadolines	I	Hyper-tension	N	Wellcome

Not just chemistry in a rusty bucket

Our experience with HTS is that we get the best results from compounds that have been designed for some form of bioactivity. Does this work the other way too?

Agchems (esp. H) often have 'lead-like' physical properties.

F and I offer opportunities for targeting (fungal pathogens and neurological conditions).

H have potential for unexpected side-activity.

Delaney et al (2006), *Drug Discovery Today*, **17-18**, p 839-845.



Thanks to...

Eric Clarke, Martin Rice and Dave Hughes – co-authors.

Alex Gledhill – advice on tox issues.

Richard Waterman and Carine Delaney – critical reading of early drafts of the paper.

All the team leader chemists, biologists and biochemists at Jealott's Hill, Basel and Stein – examples of ags that became drug leads.



AgChem indications and pharma targets

Insecticides

- Many insecticidal MoAs are related to nerve signal transduction.
- Neurological conditions – Alzheimer's, pain, anaesthesia.

Fungicides

- Human fungal infections.
- Kinase and microtubule MoAs could be relevant for cancer and antibacterials – selective cell death.

Herbicides

- Herbicide target sites often chosen with no human equivalent – large evolutionary divergence between plants and animals.
- Off-target effects.



Drugs and agrochemicals

All living things use essentially the same chemistry to get the job done – DNA, RNA, proteins, carbohydrates, ATP etc.

All of the 300 plus pesticidal active ingredients introduced since 1980 act are believed to act via single, specific MoA.

Many metabolic and signalling pathways are conserved across phyla – e.g. Kinases, GPCRs, citric acid cycle.

A xenobiotic's point-of-view - access to its binding site is mediated through active transport, metabolic transformations and passive diffusion.

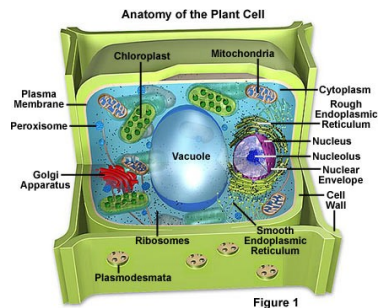
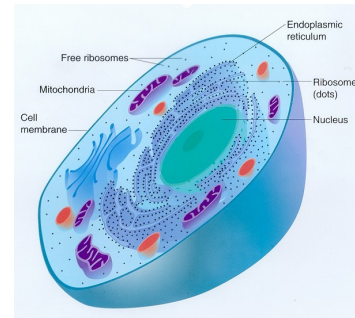


Figure 1



What I hope to cover...

What are agrochemicals and why do they matter?

Some common misconceptions about agrochemicals.

- Toxicity and mode of action.
- Chemical composition.

How similar are pharmaceutical and agrochemical research?

- Chemistry.
- Target sites.
- Bioavailability.

What opportunities do agrochemicals offer as drug leads?

- Novel chemistries.
- Lead-like physical properties.