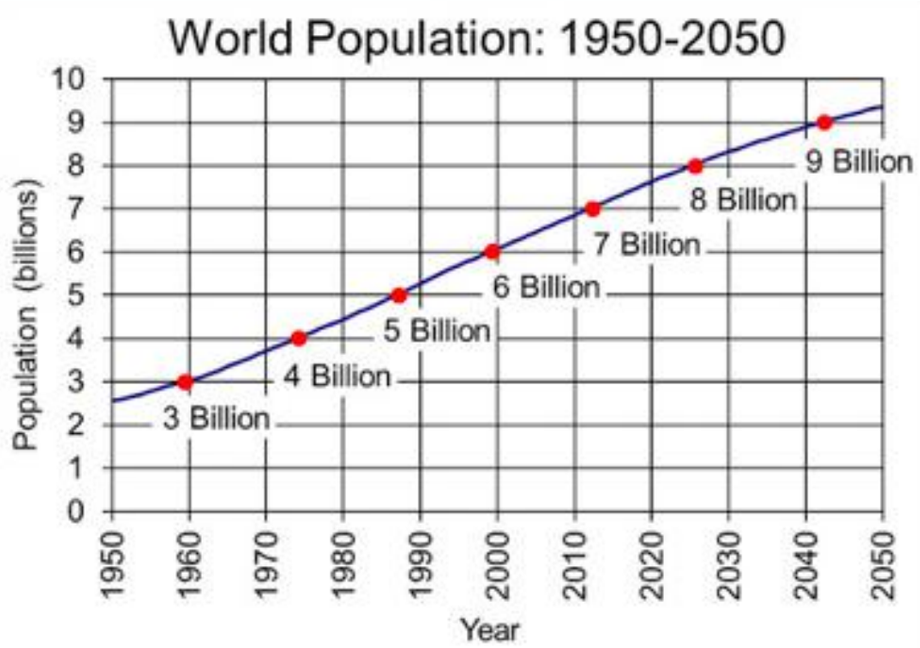
Pesticides in Agrochemical Research & Development

Robert Pipal

MacMillan Group Meeting

May 5, 2020

The Challenge of Feeding 9 Billion People



possible solutions for food security

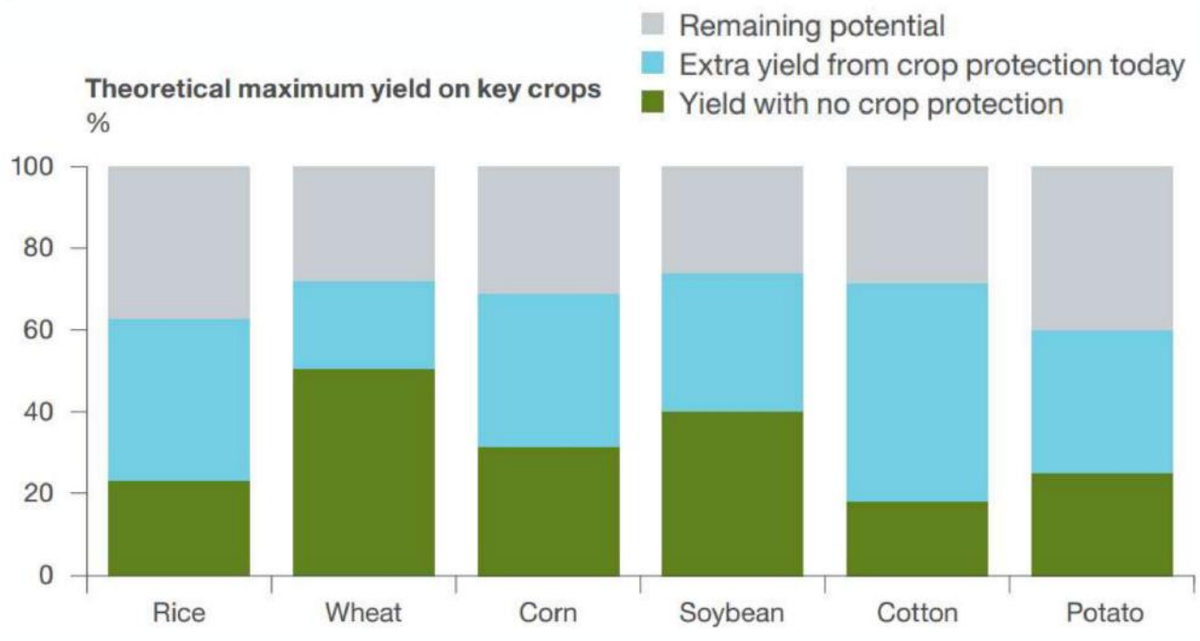
- reducing food waste
- changing diets
- increasing productivity

studies suggest world needs 70–100% more food by 2050

crop protection includes biotechnology

solutions (plant breeding & genetic modification)

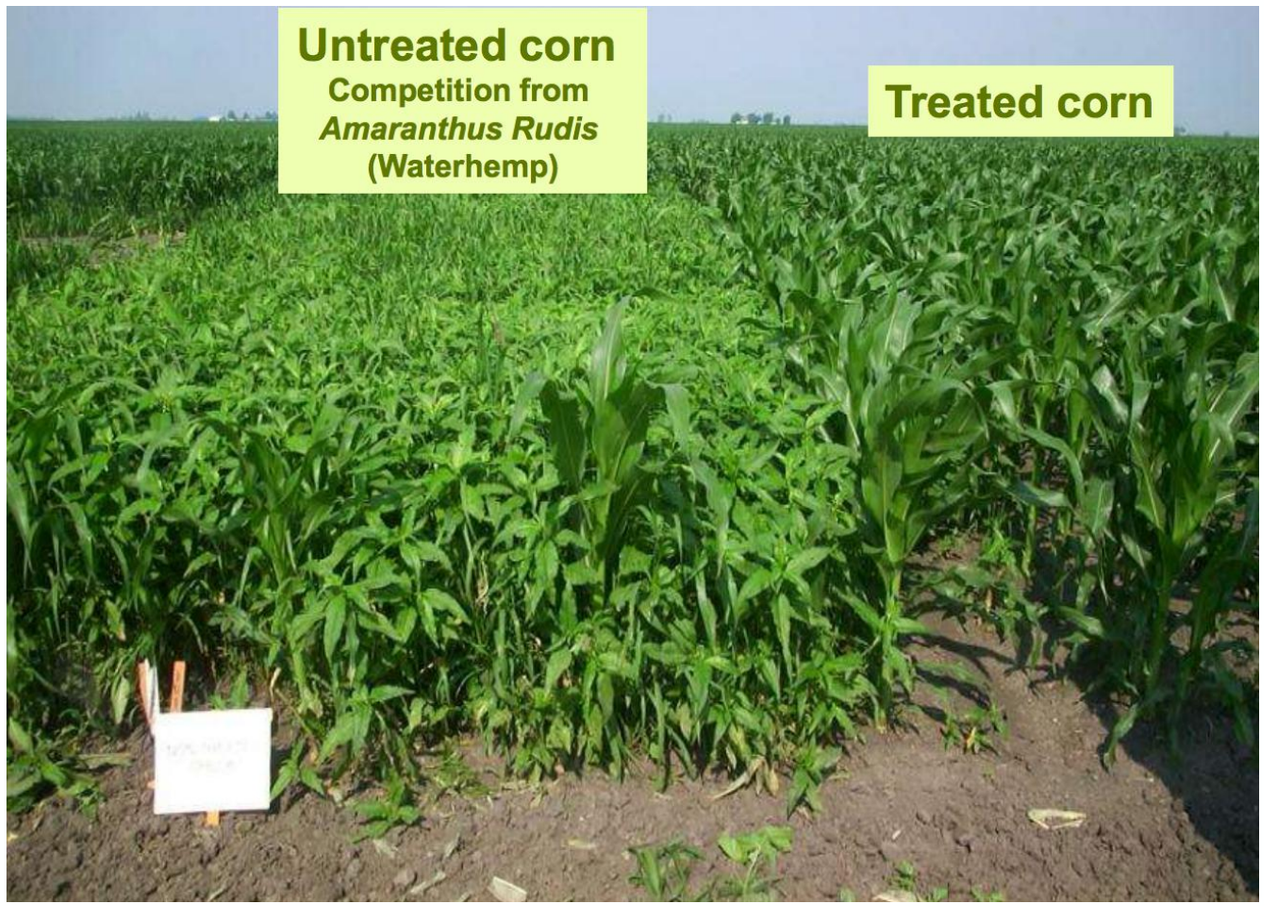
and ***pesticide solutions***



Godfray, H. C. J. *et al*, *Science.* **2010**, *327*, 812–818.

Uses of Pesticides

Pesticide – a substance used for destroying insects or other organisms harmful to cultivated plants or to animals



Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Various Types of Pesticides

herbicides

- weeds compete for light and nutrients
- selective and non-selective varieties

insecticides

- protection for pre- and post-harvest
- also used to control disease vectors

fungicides

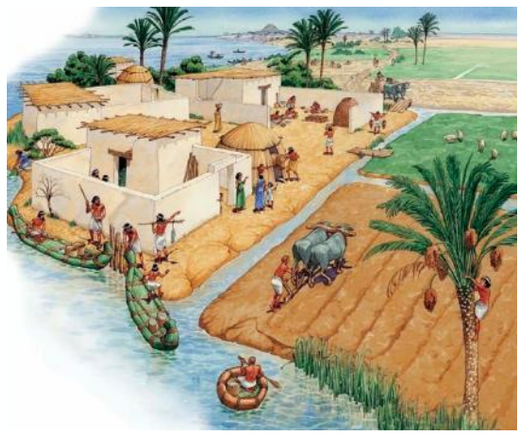
- some fungi produce carcinogens
- fungi responsible for potato famine

fumigants

- volatile chemicals to eliminate pests
- e.g. bromomethane (phased out)

Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

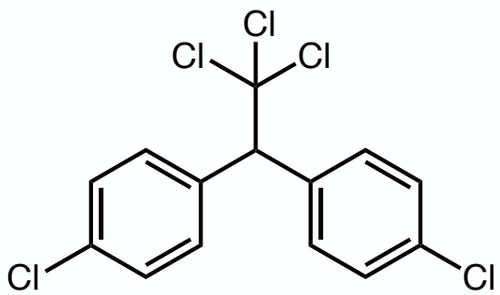
Timeline of Pesticide Use



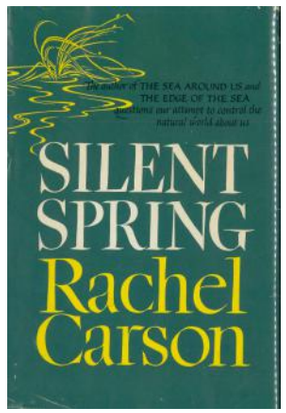
8000 BC: agriculture begins in Mesopotamia

2500 BC: Sumerians use sulfur to contol mites and insects

1800s: documenting of pest control methods begins

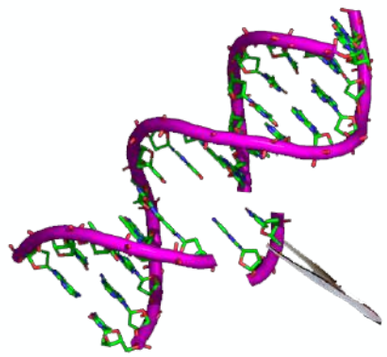


1940s: DDT developed as first synthetic pesticide



1962: *Silent Spring* by Rachel Carson published

1950–60s: The Green Revolution



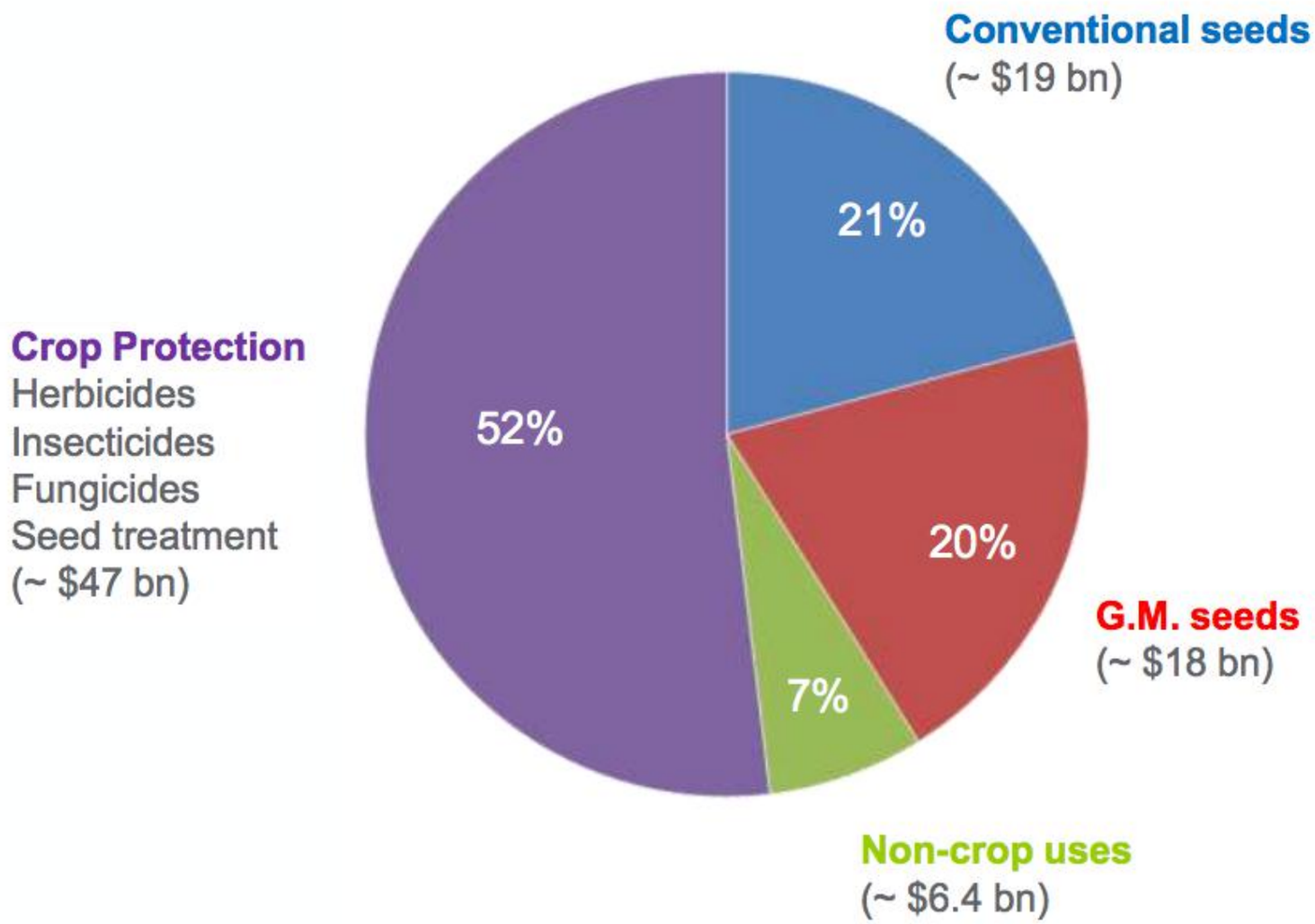
1996: first GMO crops commercialized

1970: Environmental Protection Agency (EPA) established

Pesticides in Agrochemical Research & Development

- **Background of Agrochemical Industry**
  - Factors shaping industry
  - Landscape of agrochemical companies
- **Methods for Research & Development**
  - Plant biology & ag-like properties
  - Discovery process
  - Development process
  - Utility of radiolabeled pesticides
- **Pesticides of Note**
  - Glyphosate
  - DDT
- **Outlook on Pesticide Development**

Agrochemical Industry Breakdown



global agrochemical industry in 2012: ~$91 billion

Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Factors Shaping Agrochemical Research

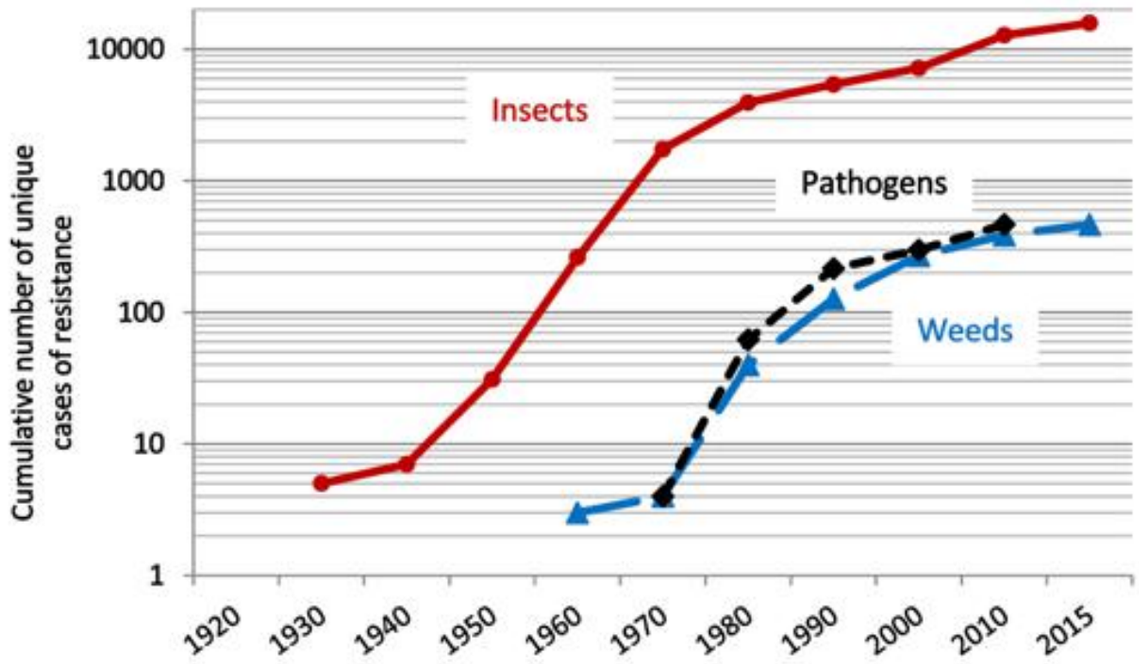
major factors shaping agrochemical research

- growing resistance of species to pesticides

how do we overcome this challenge?

- develop new pesticides, especially with novel mechanisms/modes of action (MOAs)
- rotation of pesticides with different MOAs

evolution of resistance for insects, plants, and pathogens

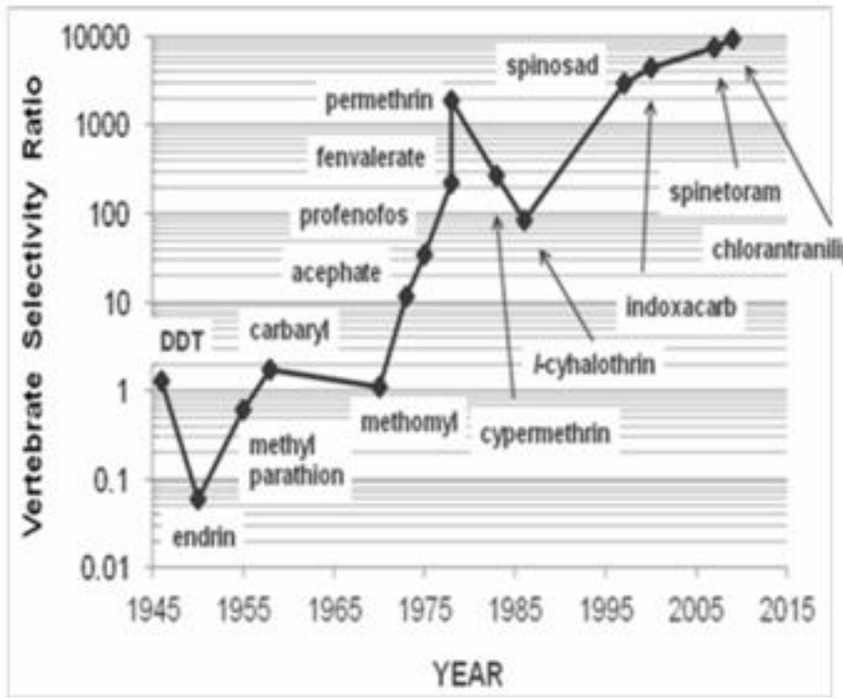


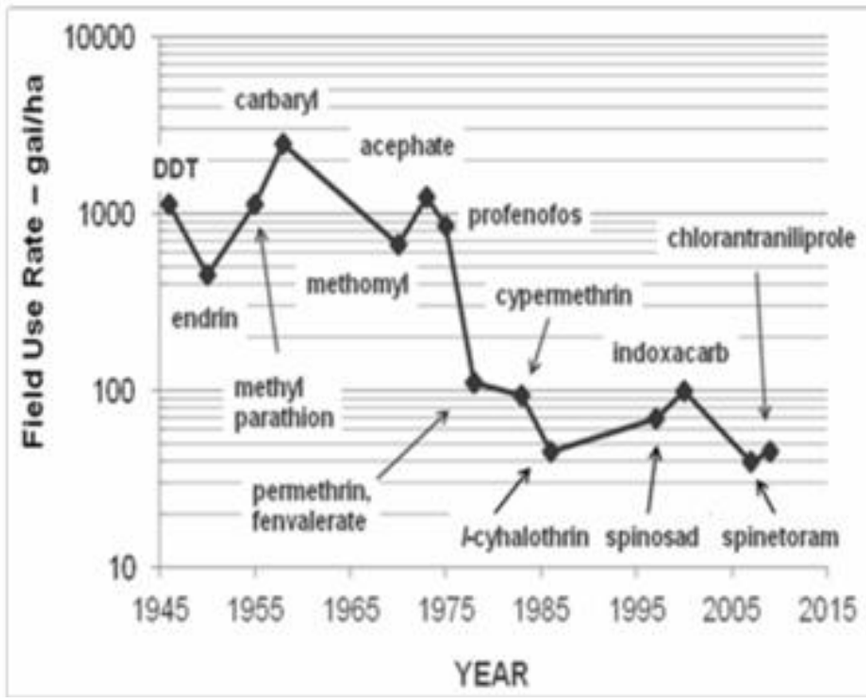
Sparks, T. C.; Lorsbach, B. A. *Pest Manag. Sci.* **2017**, *73*, 672–677.

Factors Shaping Agrochemical Research

major factors shaping agrochemical research

- growing resistance of species to pesticides
- increasingly stringent regulatory standards





- need for more favorable environmental, non-target, and toxicological profiles

Sparks, T. C. *Pestic. Biochem. Physi.* **2013**, *1*, 8–17.

Sparks, T. C.; Lorsbach, B. A. *Pest Manag. Sci.* **2017**, *73*, 672–677.

Factors Shaping Agrochemical Research

major factors shaping agrochemical research

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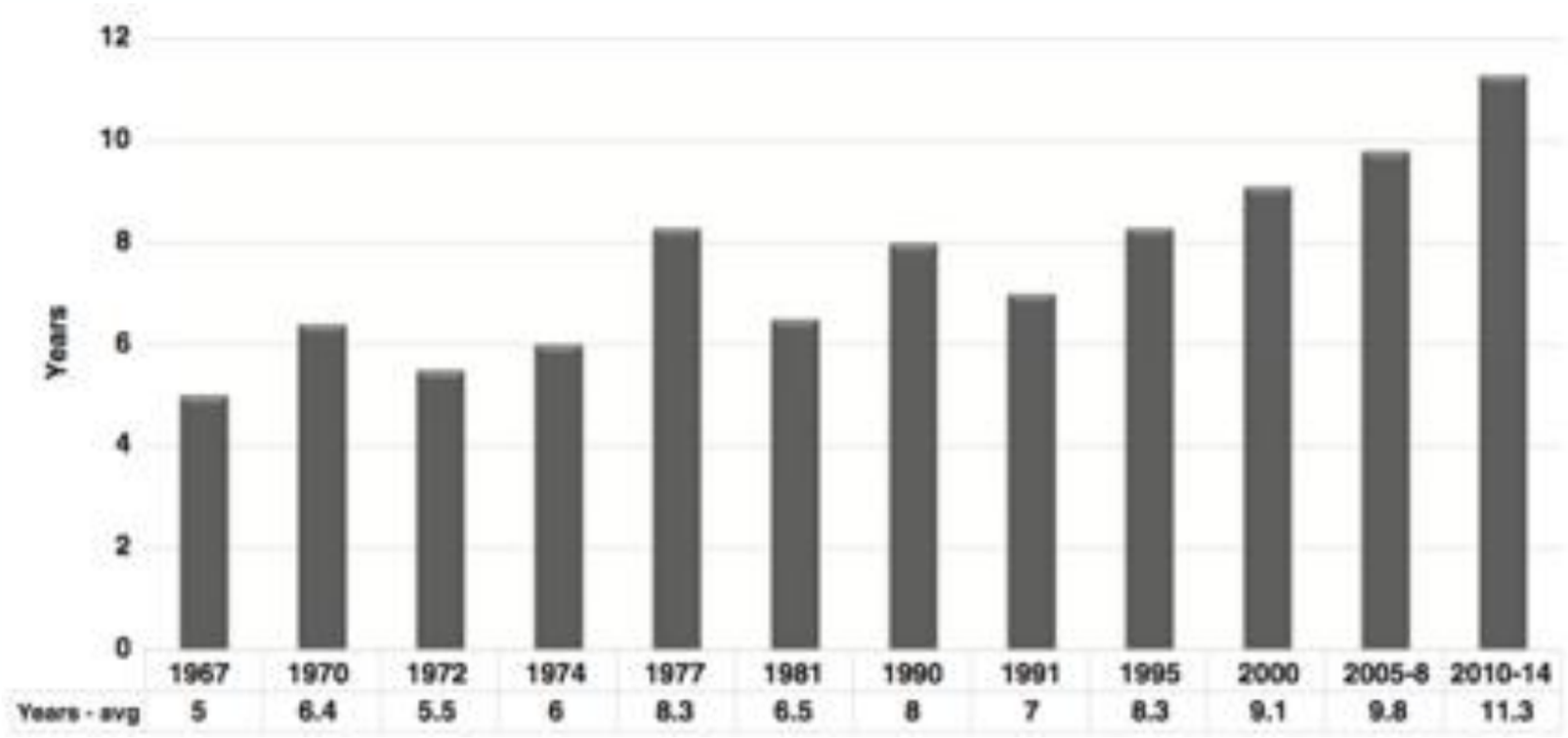


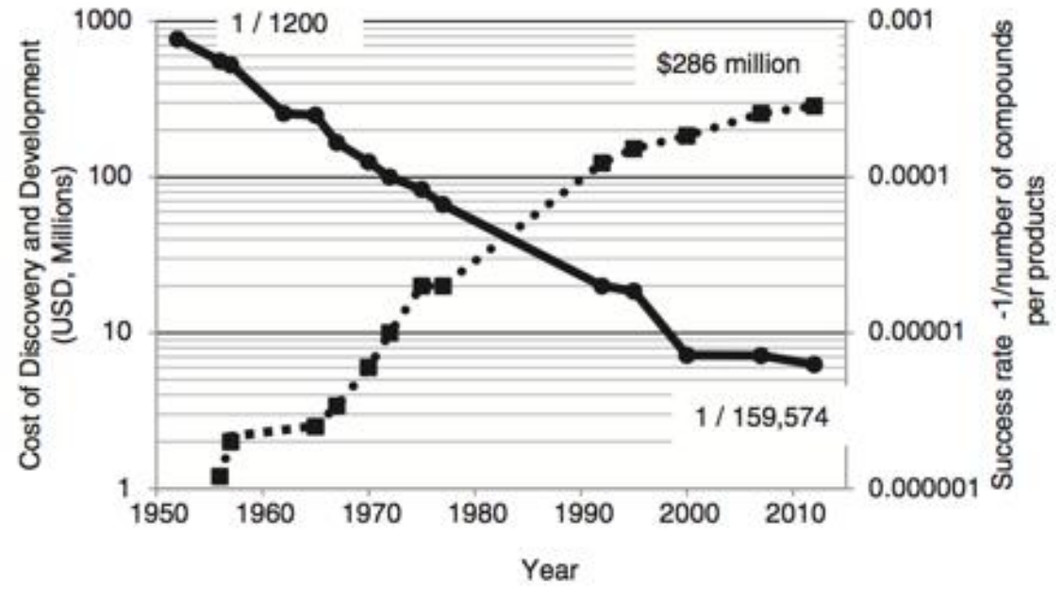
- finding molecules with improved efficacy, selectivity, and favorable environmental profiles takes longer

Sparks, T. C.; Lorsbach, B. A. *Pest Manag. Sci.* **2017**, *73*, 672–677.

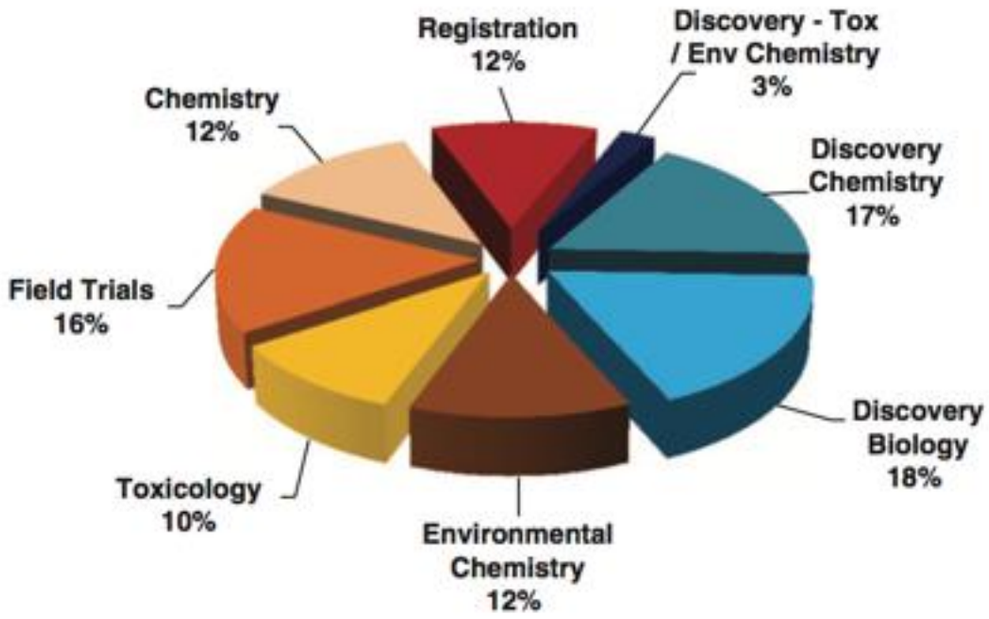
Factors Shaping Agrochemical Research

major factors shaping agrochemical research

- growing resistance of species to pesticides
- increasingly stringent regulatory standards
- cost of discovery/development



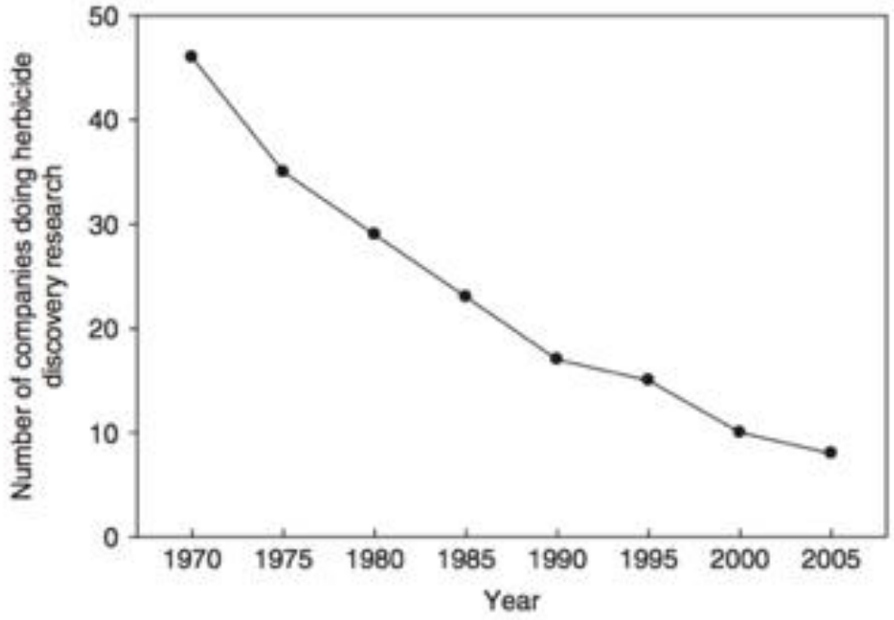
cost of pesticide development and screening success



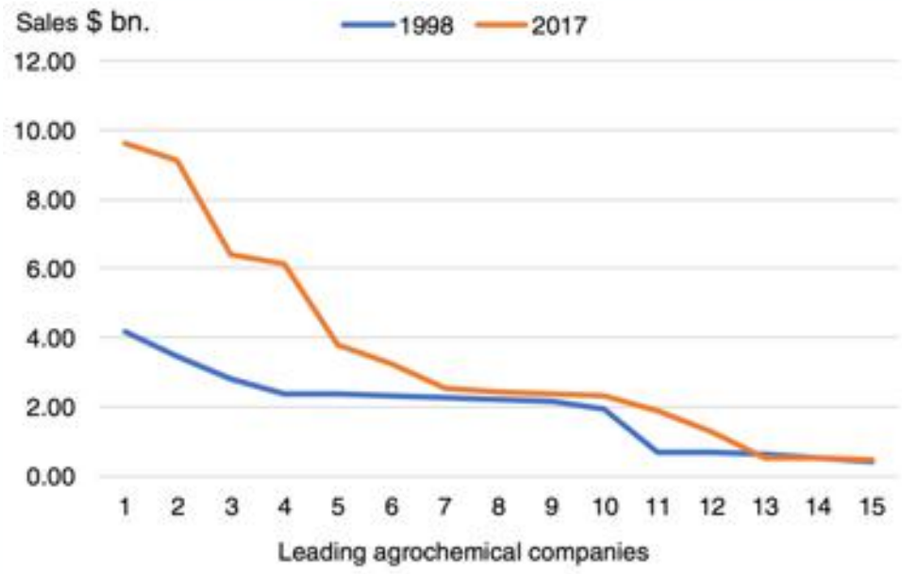
- 37% discovery, 51% development, 12% registration
- $286 million to develop pesticide
- cash flow after launch often negative for 10+ years

Sparks, T. C.; Lorsbach, B. A. *Pest Manag. Sci.* **2017**, *73*, 672–677.

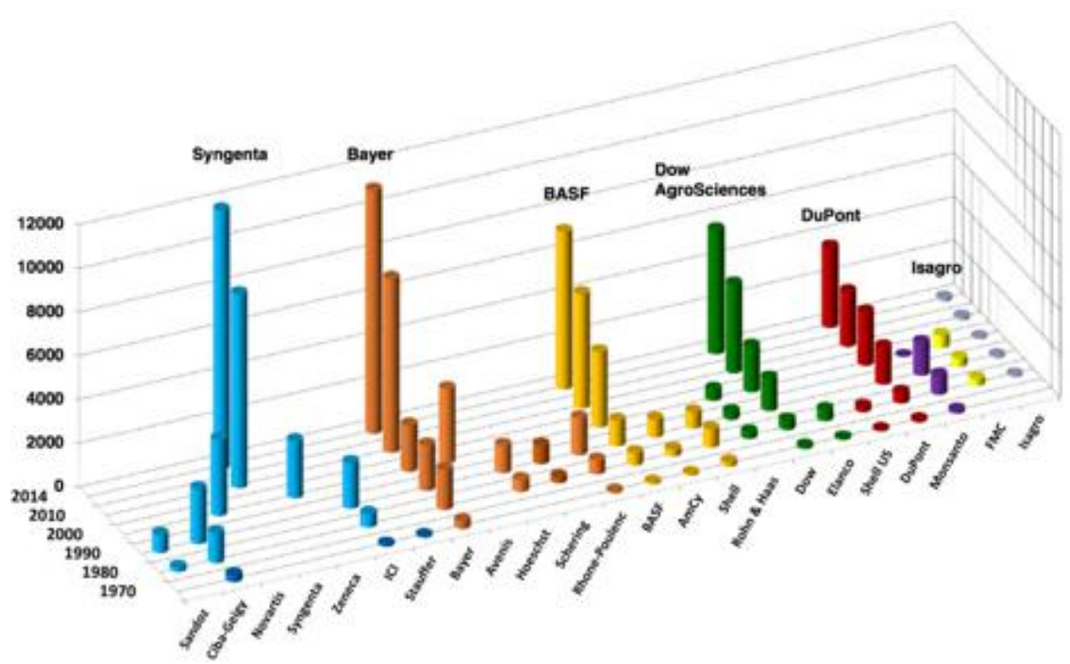
Landscape of Agrochemical Companies



- trend toward fewer agrochemical companies



- fewer companies control more of agro sales



Dow and DuPont agrochemical research sectors combined to form Corteva in 2019

- increasing consolidation of agrochemical companies

Phillips, M. W. A. *Pest Manag. Sci.* **2019**, DOI: 10.1002/ps.5728.

Sparks, T. C.; Lorsbach, B. A. *Pest Manag. Sci.* **2017**, *73*, 672–677.

Pesticides in Agrochemical Research & Development

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  - DDT
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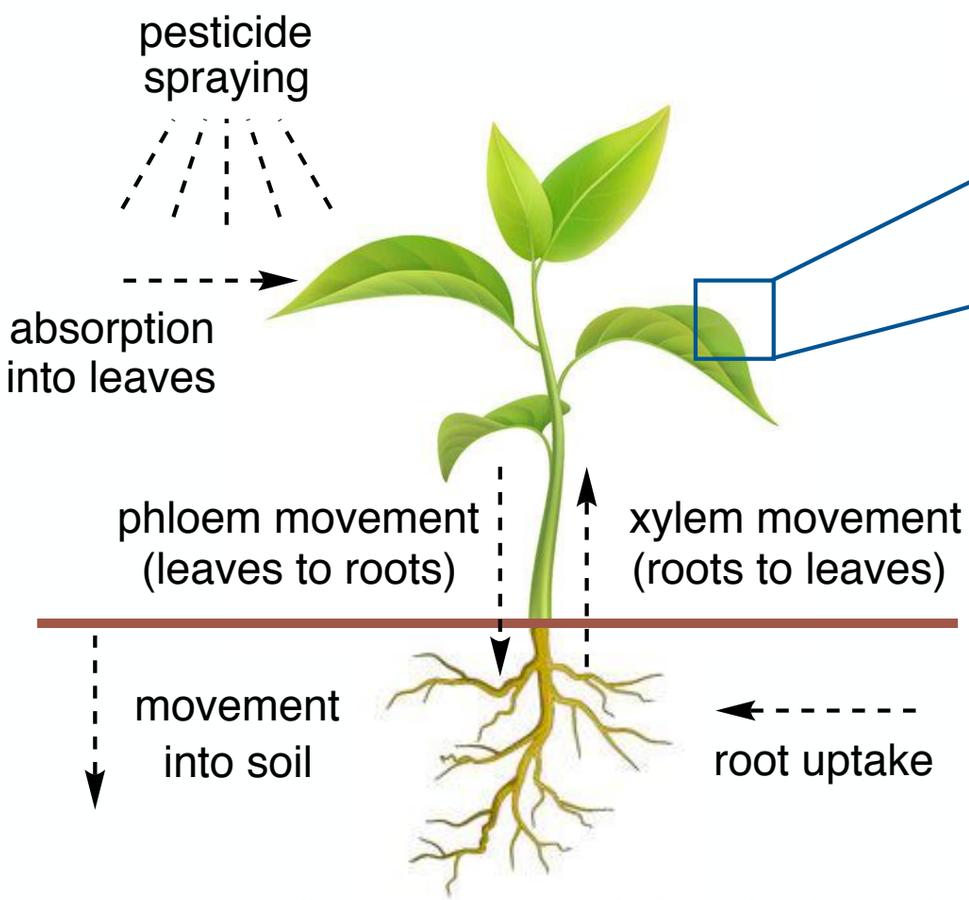
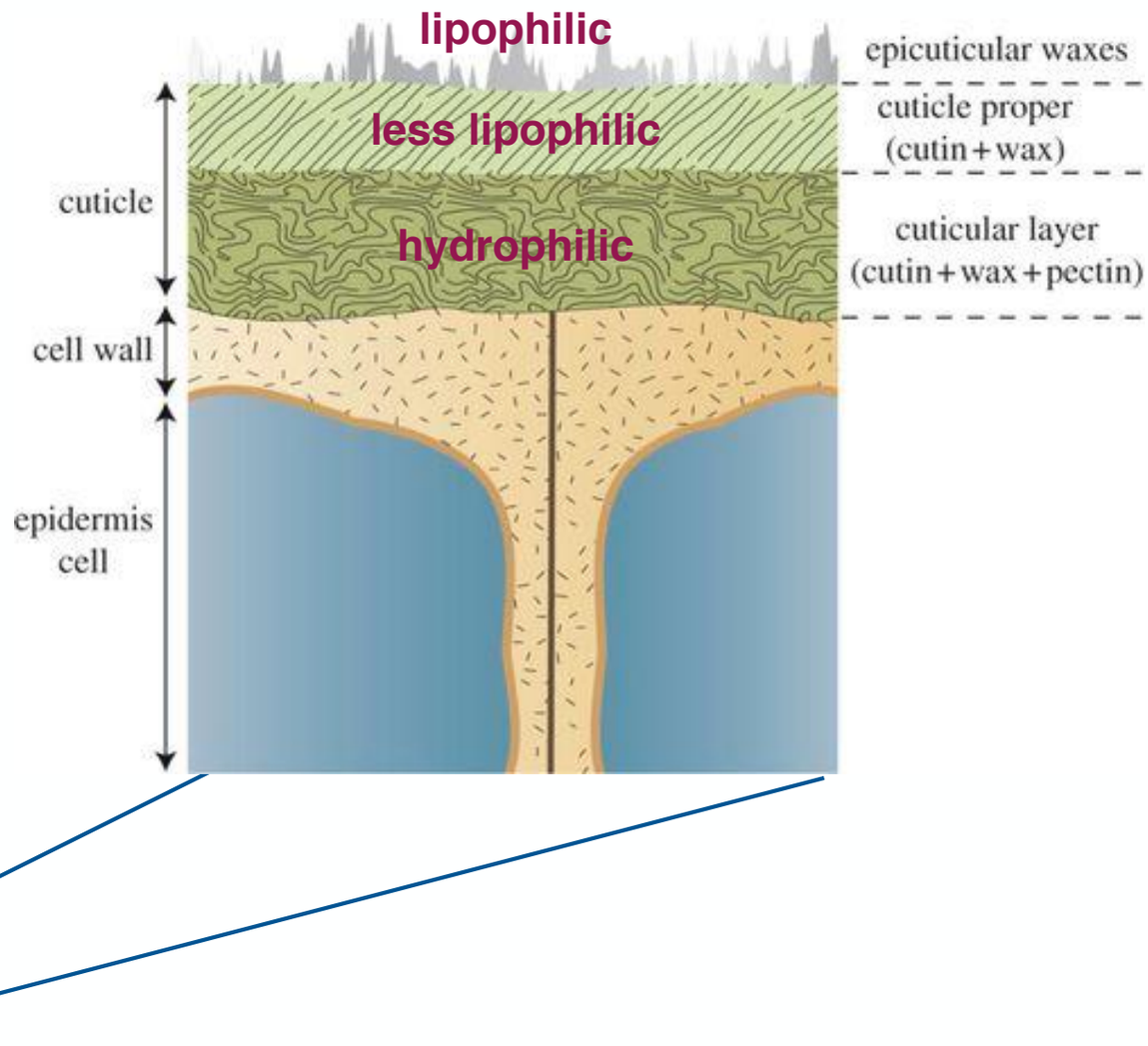
Methods for Pesticide Discovery

post-emergent pesticide spraying

(after plant germination)

most common method for application





agrochemicals require a balance

between hydrophilicity & lipophilicity

Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Lipinski's Rule of 5 for pesticide development

Parameter	Pharmaceuticals	Herbicides	Insecticides
Molecular mass	$\leq$ 500	$\geq$ 150 and $\leq$ 500	$\geq$ 150 and $\leq$ 500
mlog *P*	$\leq$ 4.15	$\leq$ 3.5	$\geq$0 and $\leq$ 5.0
H-bond donors	$\leq$ 5	$\leq$ 3	$\leq$ 2
H-bond acceptors	$\leq$ 10	$\geq$ 2 and $\leq$ 12	$\geq$ 1 and $\leq$ 8
Rotatable bonds	—	$\leq$ 12	$\leq$ 12

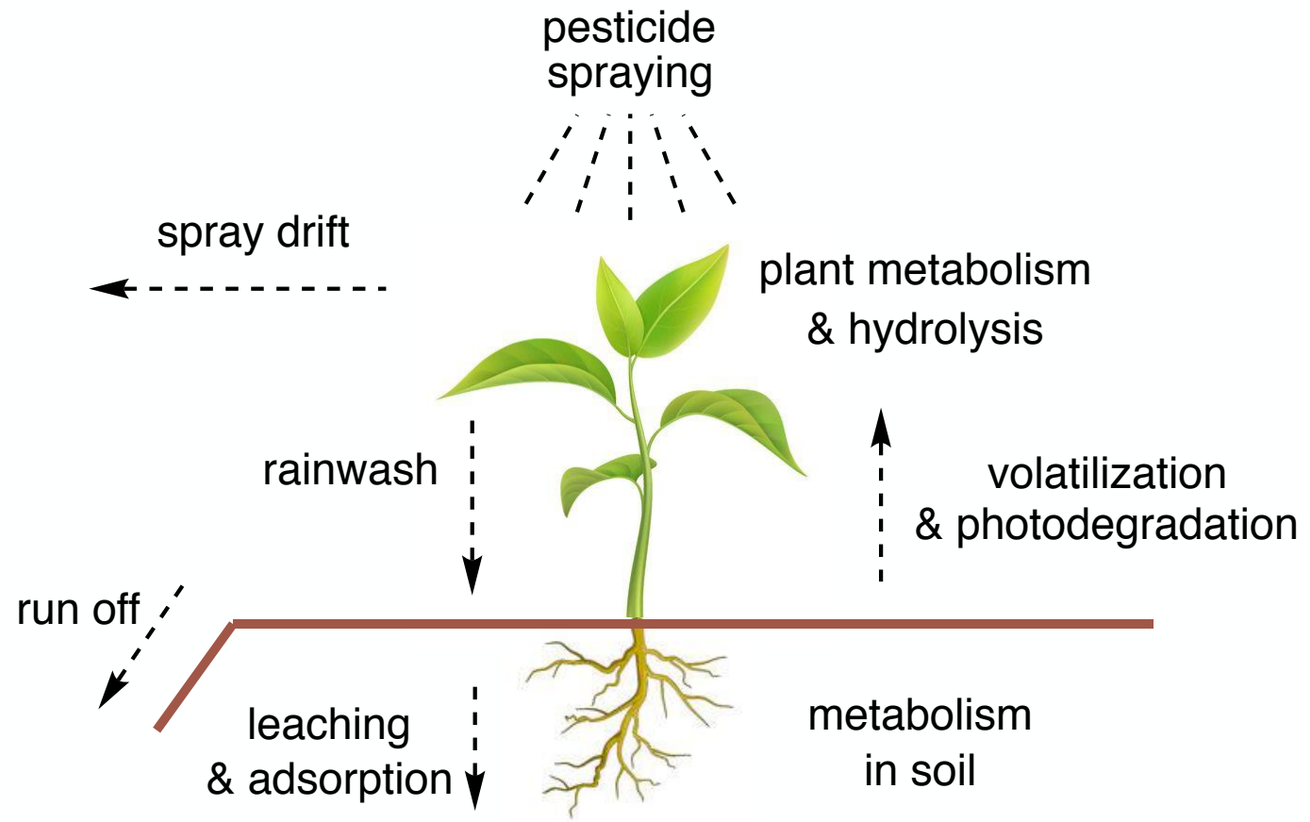
different chemical environments require different physicochemical properties

Tice, C. M. *Pest. Manag. Sci.* **2001**, *57*, 3–16.

Methods for Pesticide Discovery

Other requirements of pesticides:

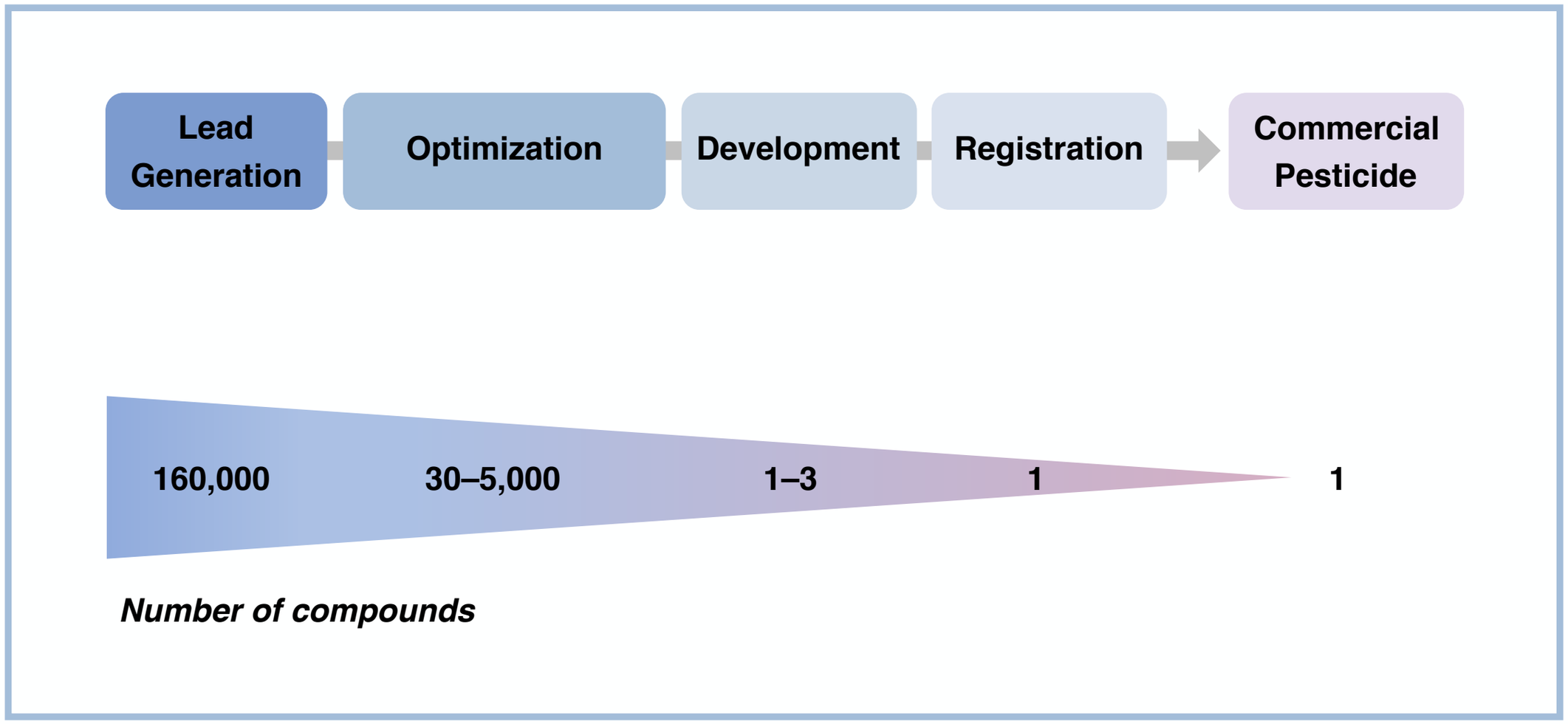
- long lasting activity and persistence
- very low cost of production
- safe for environment & human health



challenges of pesticide application

Lamberth, C.; Jeanmart, S.; Luksch, T.; Plant, A. *Science* **2013**, *341*, 742–746.

Agrochemical Discovery Process



Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Methods for Lead Generation in Pesticide Discovery

agrochemical companies utilize several methods for effective risk-benefit balance

methods for pesticide discovery

data mining

competition inspired

NP inspired

target-site based

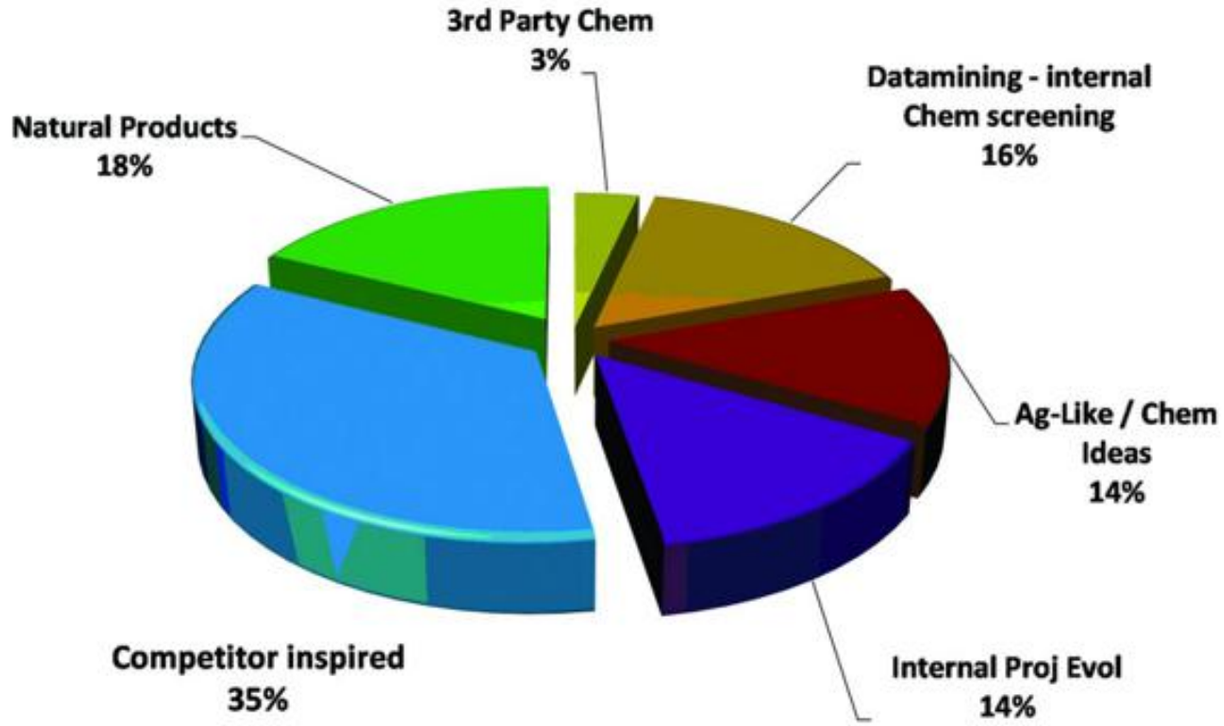
fragment based

novel scaffolds

diversity screening

bioinfo

novelty

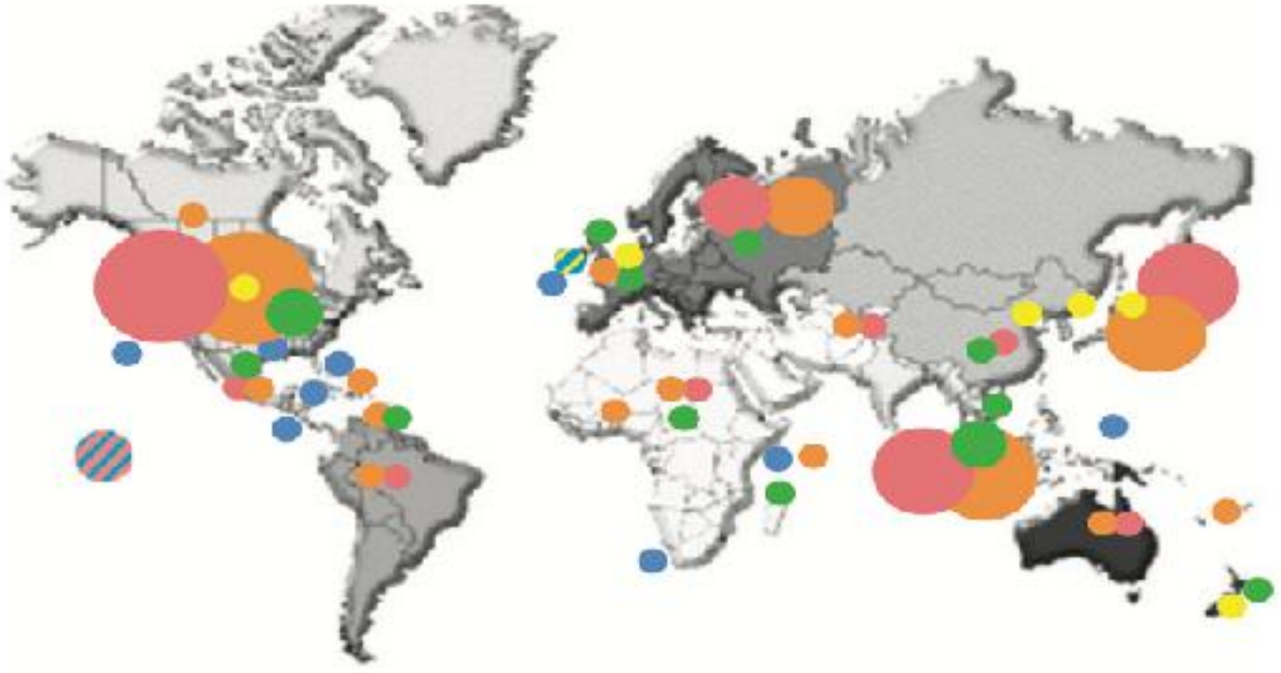


origins of insecticides introduced since 1990 (n = 57)

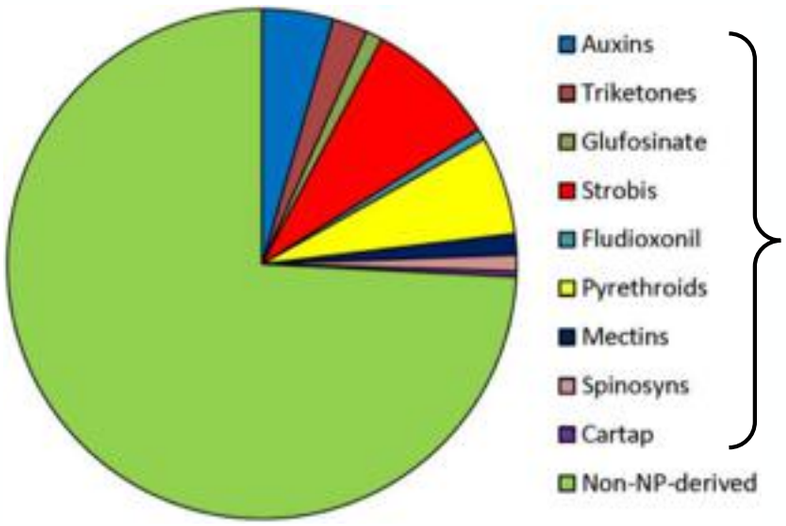
Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Sparks, T. C. *Pestic. Biochem. Physi.* **2013**, *1*, 8–17.

Natural Product Inspired Pesticides



sources of natural products used for screening at Dow AgroSciences



natural product-derived pesticides (~$10 billion)

market for crop-protection chemicals in 2011

rich source of new Modes of Action

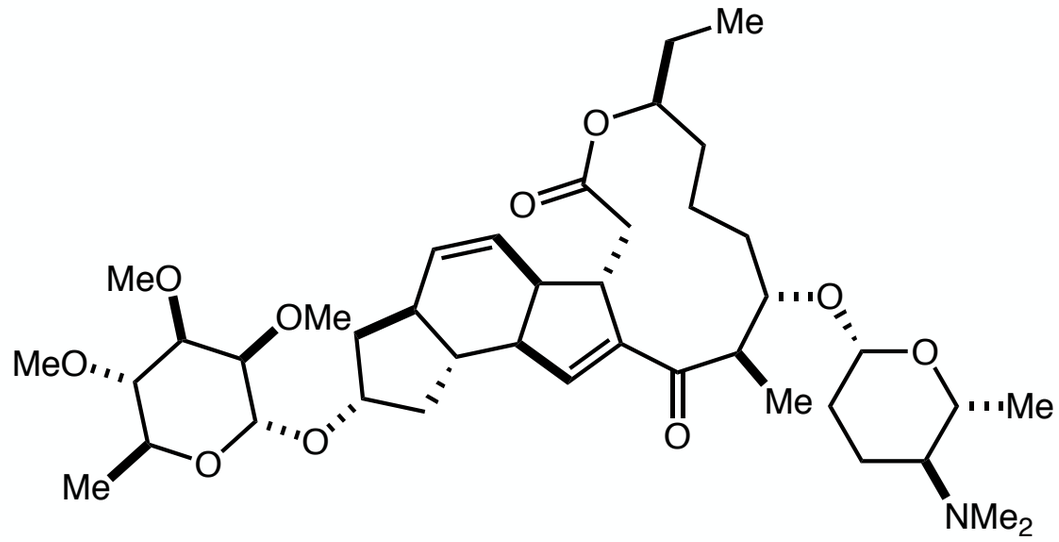
60% of MOAs contain natural product inspired chemical

Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Natural Product Inspired Pesticides

NP derived pesticide classes

- Natural products



spinosad
insecticide

NP possess all required properties of effective agrochemical product

extremely rare event

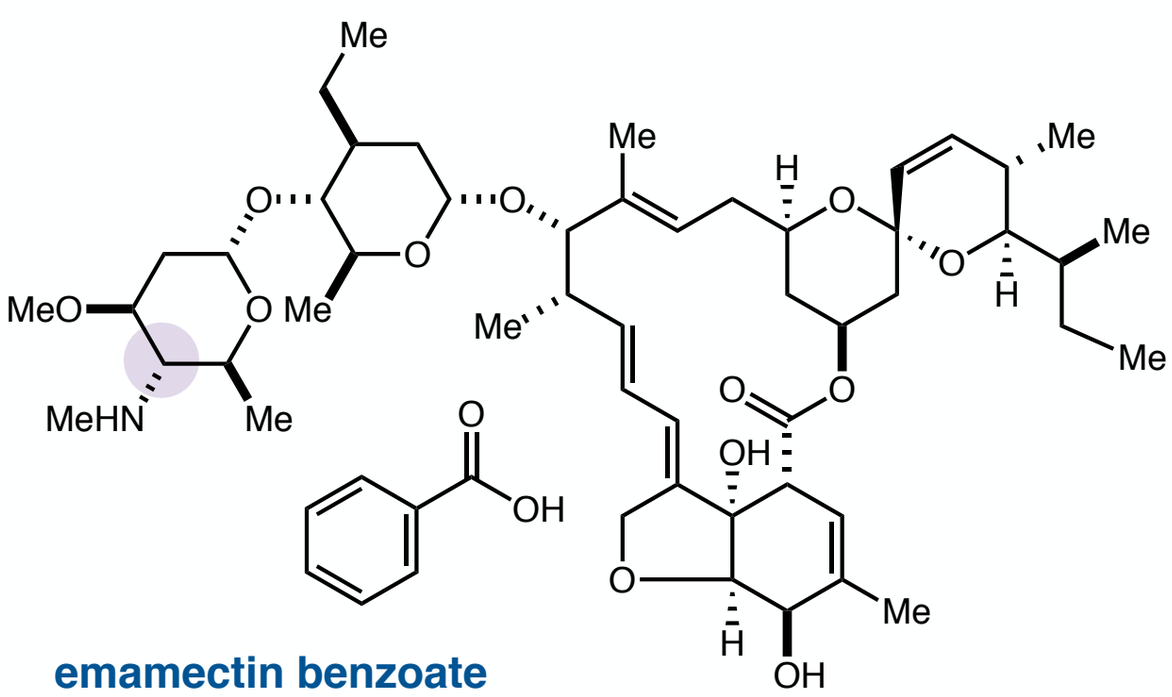
Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Natural Product Inspired Pesticides

NP derived pesticide classes

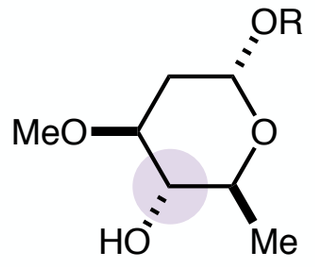
- Natural products
- Semi-synthesis

- requires synthetic manipulations to NP to enhance activity or stability
- requires ample supply of natural product



emamectin benzoate

insecticide



abamectin

natural product

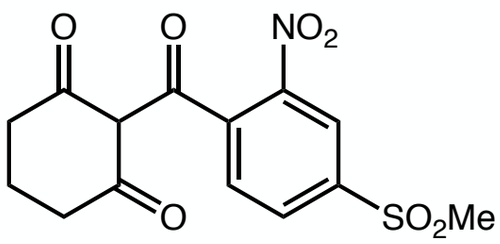
Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Natural Product Inspired Pesticides

NP derived pesticide classes

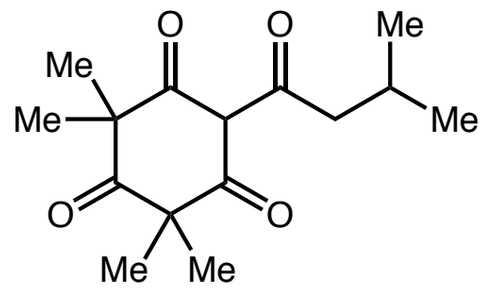
- Natural products
- Semi-synthesis
- Synthetic mimics

- physical properties such as solubility and photostability unsuitable as pesticide
- usually low-probablility approach due to molecular complexity



Mesotrione

natural product



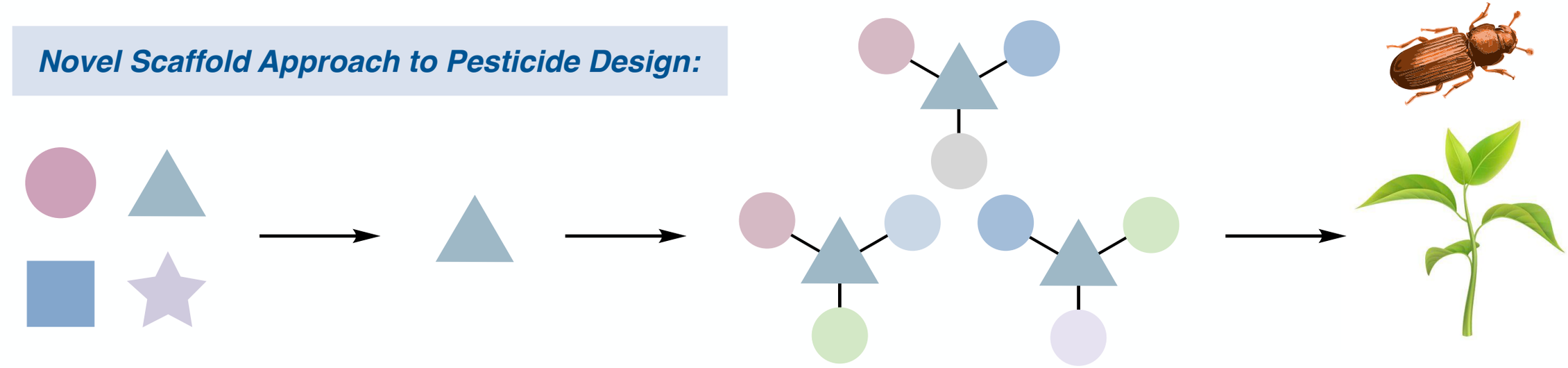
Leptospermone

herbicide

Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Scaffold-Based Approach to Pesticide Discovery

Novel Scaffold Approach to Pesticide Design:



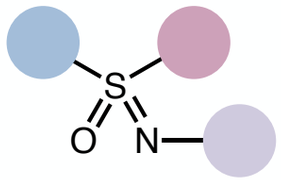
novel scaffolds | **selected scaffold** | **library synthesis** | **plant/organism screening**

- scaffold selected based on novelty, synthetic versatility, physical properties

significantly divergent from known structures in literature (*de novo* design), leads to new MOAs

Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

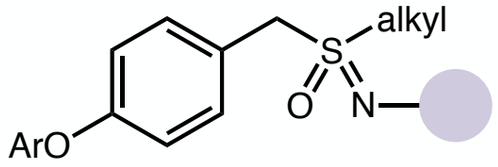
Scaffold-Based Approach to Sulfoxaflor Discovery



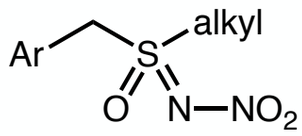
sulfoximine scaffold

identified by Dow AgroSciences

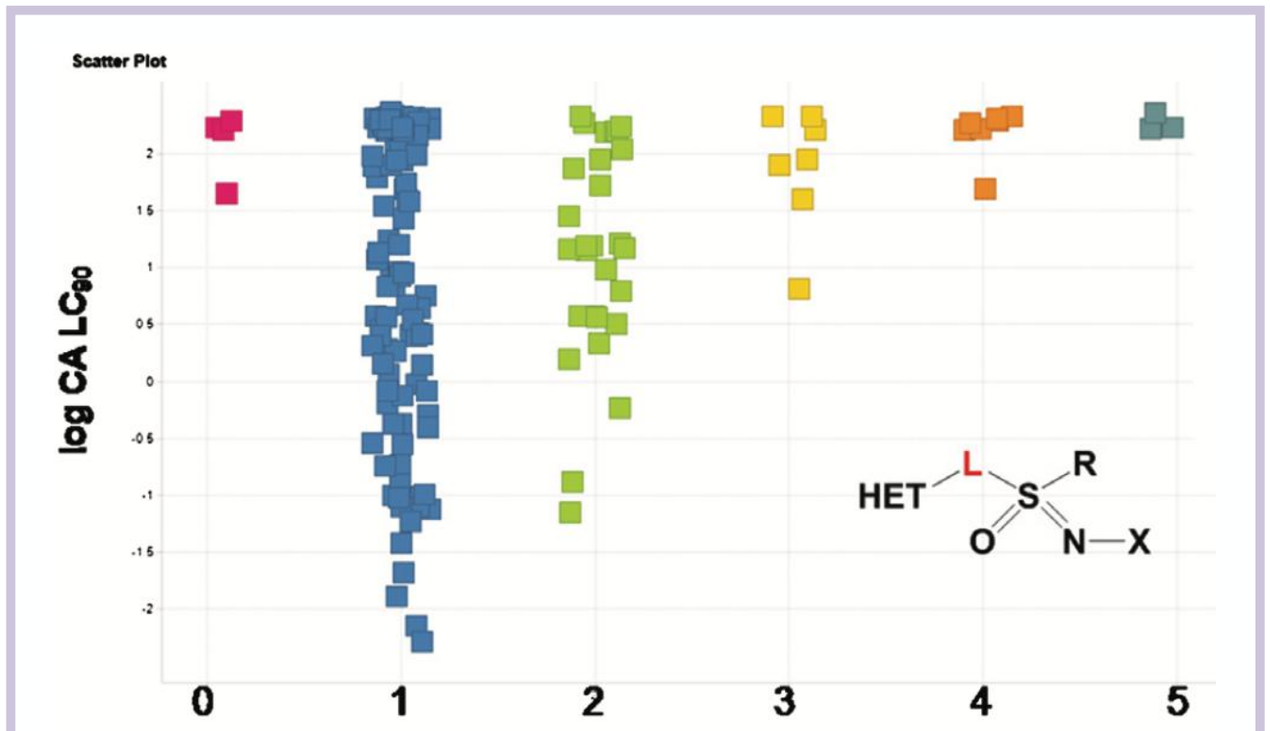
library synthesis



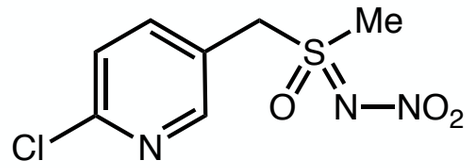
targeted for fungicidal motif



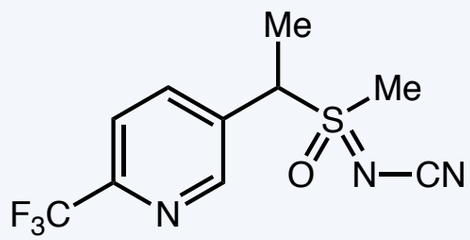
targeted for intrigue



initial hit



M. persicae LC_{50} = 20 ppm



Sulfoxaflor 2

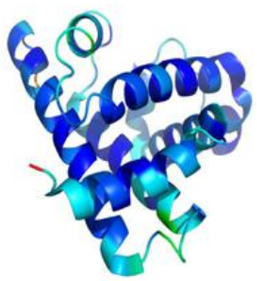
insecticide

nAChR agonist, novel MOA discovered

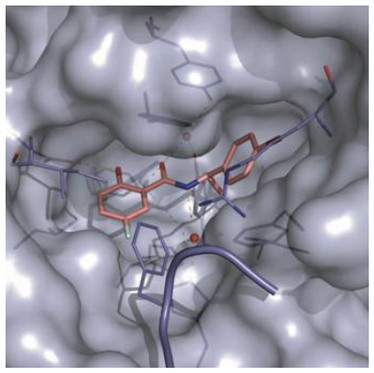
Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Structure-Based Approach to Pesticide Discovery

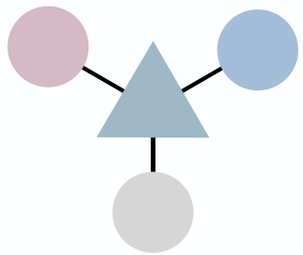
Structure-Based Approach



candidate protein



crystal structure obtained



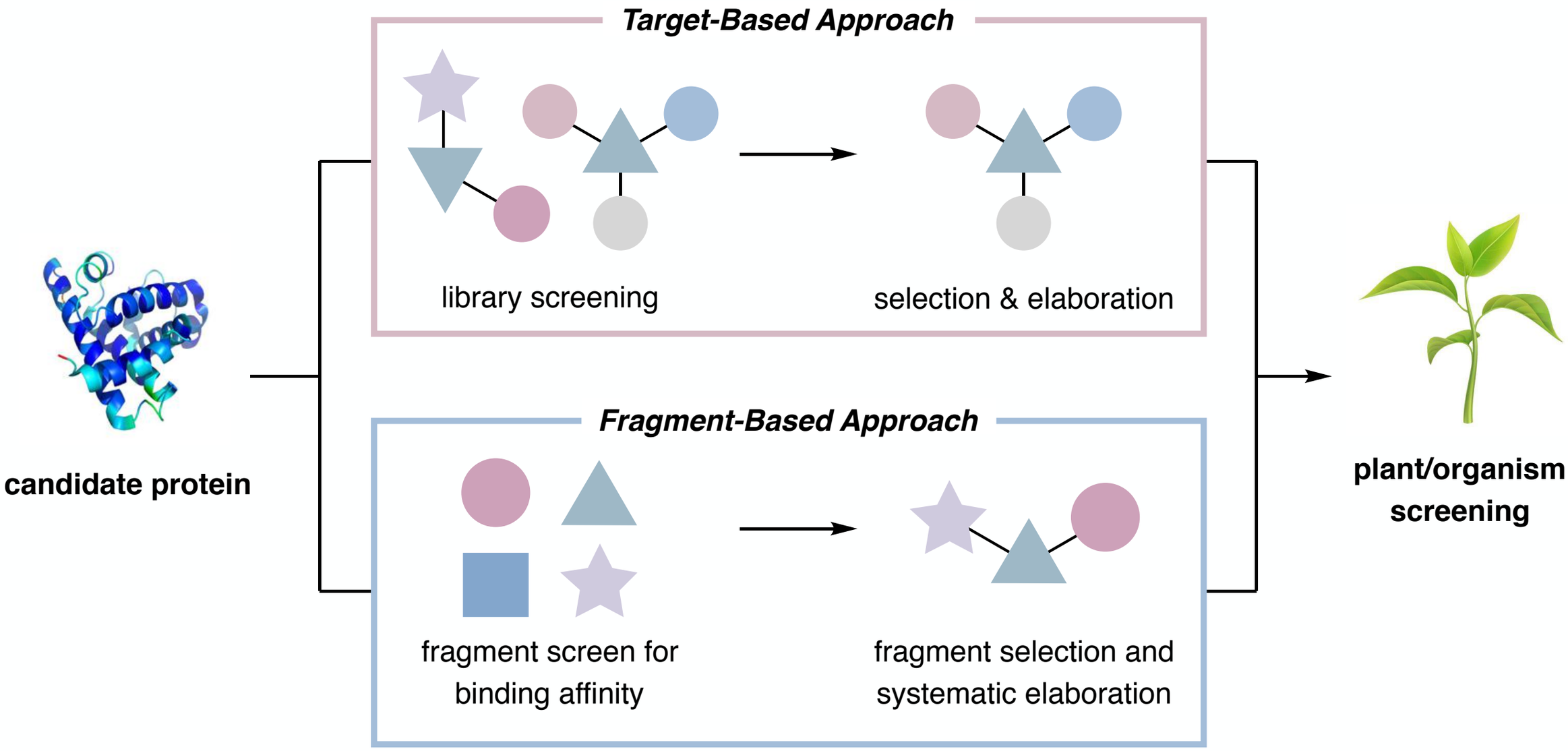
rational ligand design & optimization

plant/organism screening

relatively new strategy, no current marketed pesticides developed through this approach

Lamberth, C.; Jeanmart, S.; Luksch, T.; Plant, A. *Science* **2013**, *341*, 742–746.

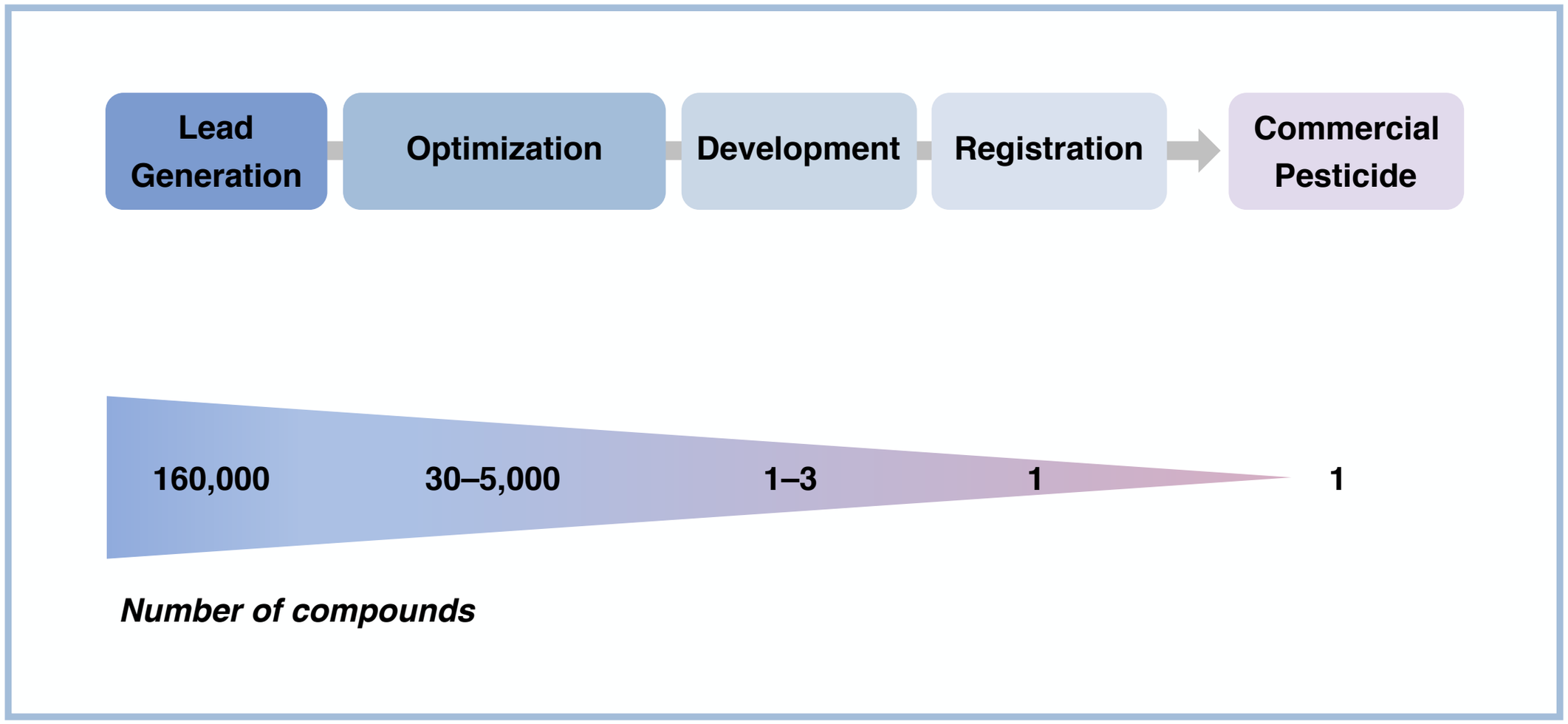
Target-Based Approach to Pesticide Discovery



very little success of *in vitro* hit translation to *in vivo;* Ag-like hits with translatable properties rare

Loso, M. R.; Garizi, N.; Hegde, V. B.; Hunter, J. E.; Sparks, T. C. *Pest. Manag. Sci.* **2017**, *73*, 678–685.

Agrochemical Discovery Process

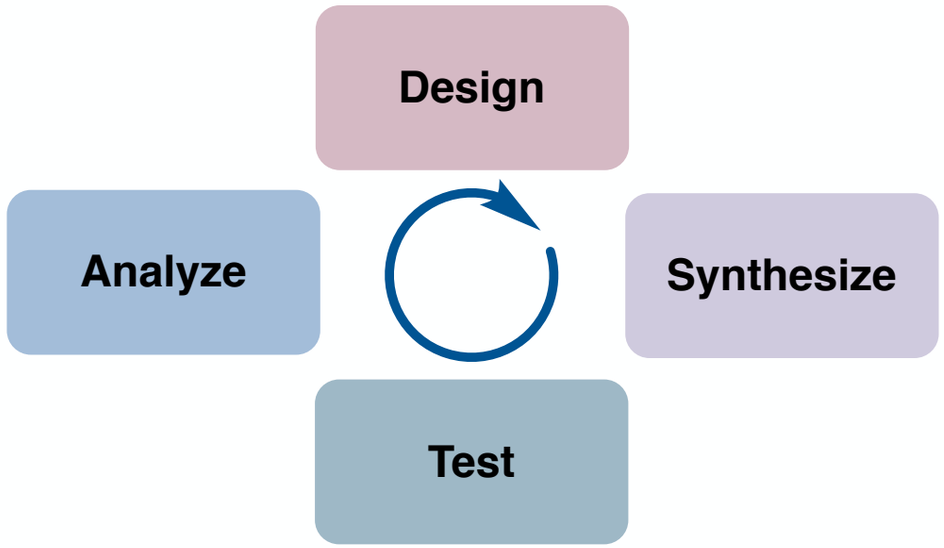


Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

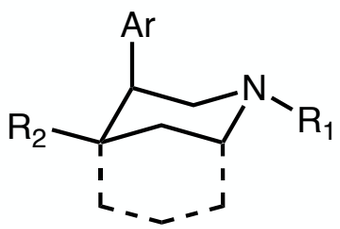
Optimization of Lead Candidates

iterative process to improve pesticide properties

- increasing level of potency
- selectivity for desired target
- optimize physical properties (e.g. bioavailability)



QSAR Data Modeling



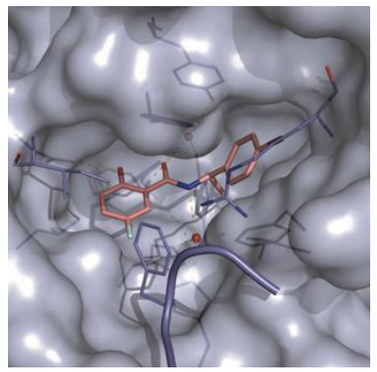
data &

linear regression

predicted activity

- quantitative structure-activity relationships
- data-driven technique

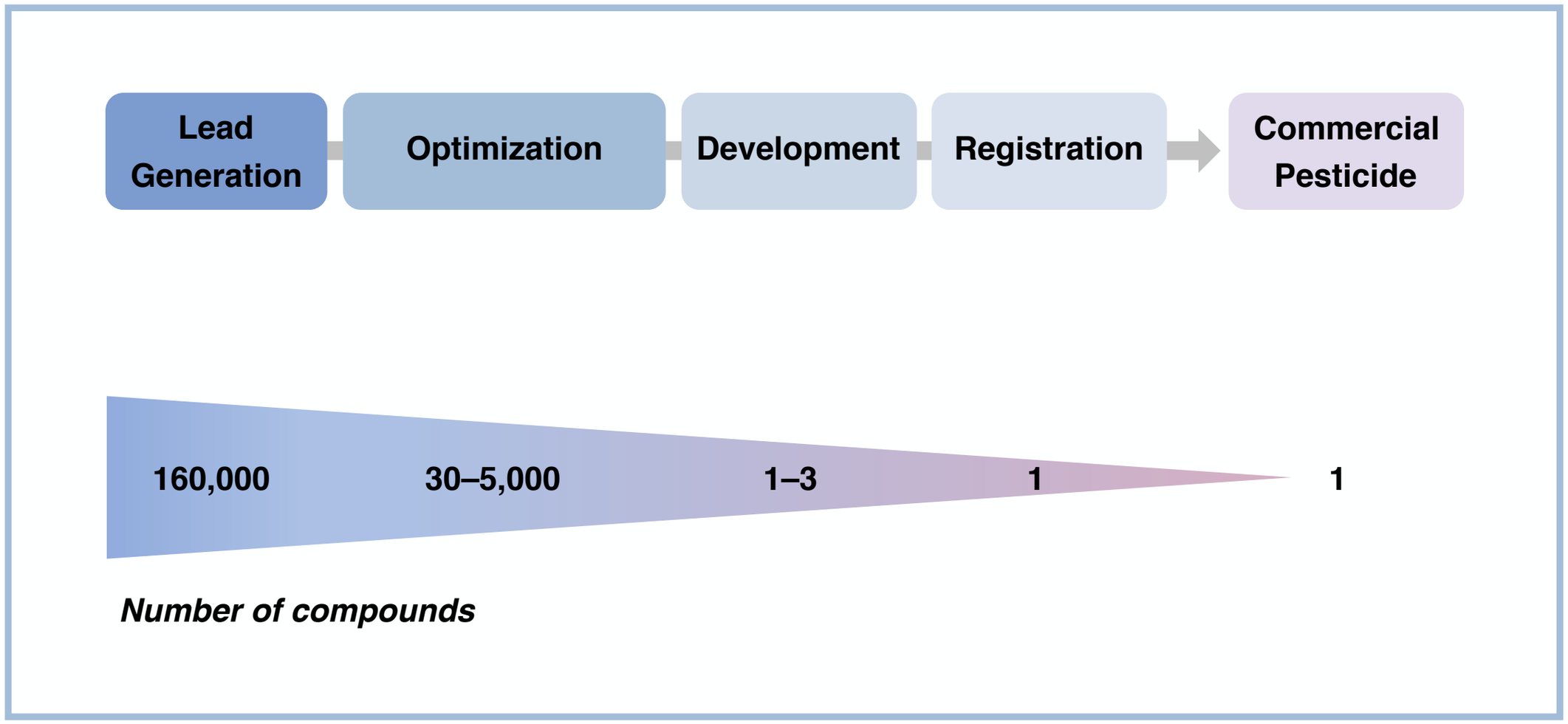
In Silico Modeling



- modern computational tool for rapid 3D modeling
- requires structural information of protein

Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Agrochemical Discovery Process



Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Development of Lead Candidates

Questions in pesticide development phase:

1. Does it work?

at this point, formulation method is optimized

for stability, application, and plant uptake

glasshouse tests

plants well cared for, no other pests

field trials

more realistic conditions (pests & weather)

Source: Syngenta’s Introduction to Agrochemicals and Modern Agronomy course

Development of Lead Candidates

Questions in pesticide development phase:

1. Does it work?
2. Can it be made on scale?

similar to pharmaceutical process chemistry,

but larger scale and cheaper syntheses required

10 – 100 mg

glasshouse screening

discovery chemistry

10 g – 1 kg

field trials

1 – 100 kg

toxicological &

environmental studies

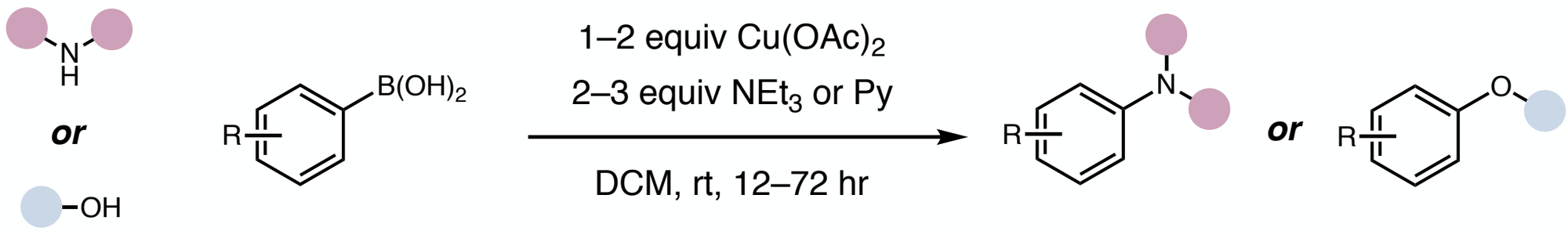
1000+ tons

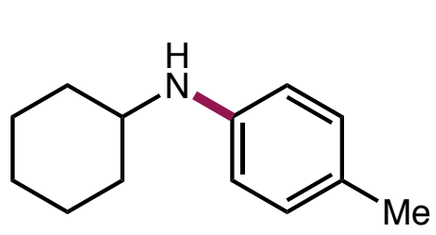
manufacturing & sales

pesticide discovery & development process

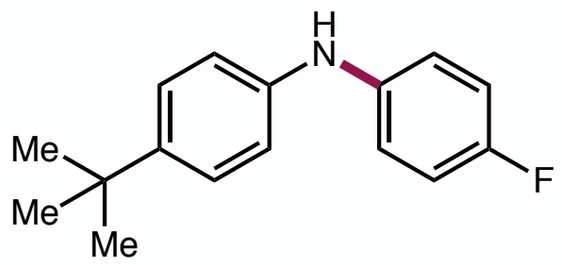
Source: Syngenta's Introduction to Agrochemicals and Modern Agronomy course

Chan–Lam Coupling: Discovered at DuPont Agricultural Products

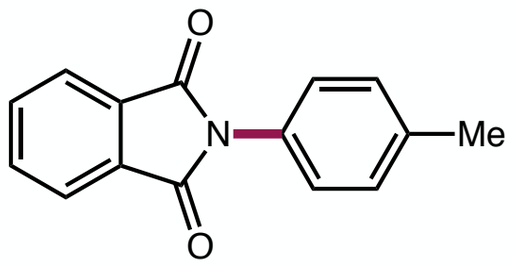




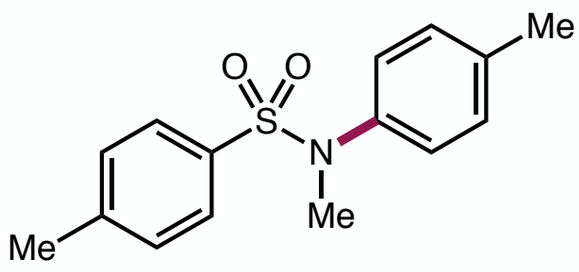
63% yield



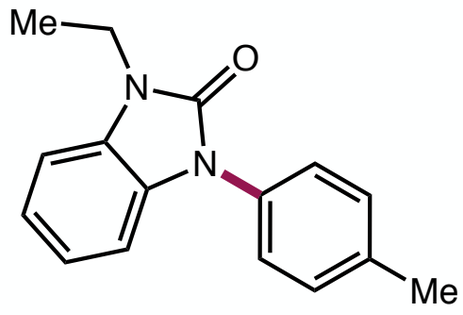
93% yield



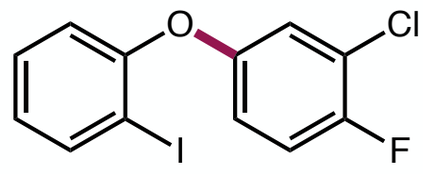
92% yield



72% yield



96% yield



78% yield

Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tet. Lett.* **1998**, *39*, 2933–2936.

Development of Lead Candidates

Questions in pesticide development phase:

1. Does it work?
2. Can it be made on scale?
3. Is it safe?

environmental health

where does pesticide go?

what does it decompose to?

effect on non-target organisms?

human health

how hazardous is it?

how much is retained in food?

how much exposure during application?

more than 100 regulatory tests conducted before pesticide can be registered

Canturk, B.; Johnson, P.; Taylor, J.; Kister, J.; Balcer, J. *Org. Process Res. Dev.* **2019**, *23*, 2234–2242.

The Use of Radiolabeled Pesticides in R&D

^{14}C

Carbon

^{3}H

Tritium

commonly used radioisotopes in agrochem

^{14}C preferred due to enhanced metabolic stability

several metabolic studies employ radiolabels

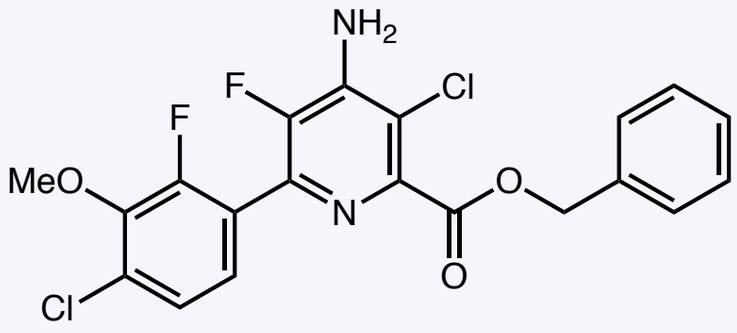
- Aqueous hydrolysis and photolysis products
- Metabolism in various crop species
- Metabolic fate in livestock (cattle, goats, chicken)
- ADME studies in rats

"The purpose for conducting metabolism studies is to determine the qualitative metabolic fate of the active ingredient… To obtain this information, the pesticide is labelled with a radioactive atom"

–United States Environmental Protection Agency

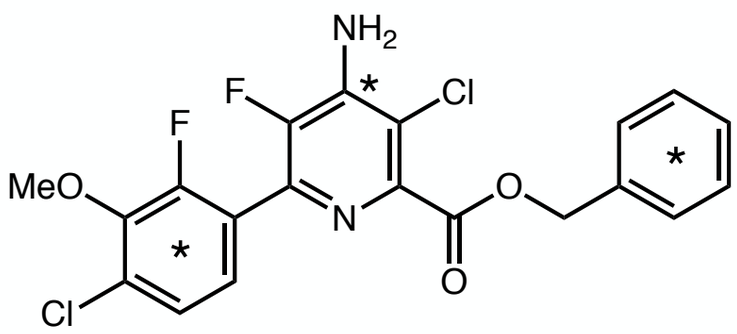
Information from http://www.selcia.com/sites/default/files/Selcia_RadioLabelledPesticides15%28i%29.pdf

Case Study of Carbon-14 Labeling for Agrochemical Registration



Rinskor™
selective herbicide

- low application rate (7.5–30 g/ha vs. 280–2240 g/ha)
  - ACS 2018 Green Chemistry Challenge Award



3 different radiolabeled molecules prepared with unique carbon-14 incorporation

Canturk, B.; Johnson, P.; Taylor, J.; Kister, J.; Balcer, J. *Org. Process Res. Dev.* **2019**, *23*, 2234–2242.

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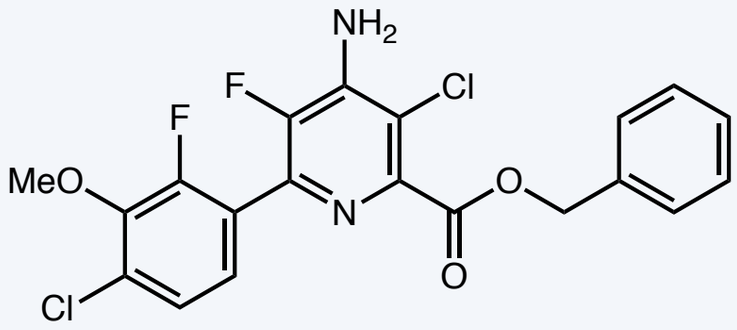

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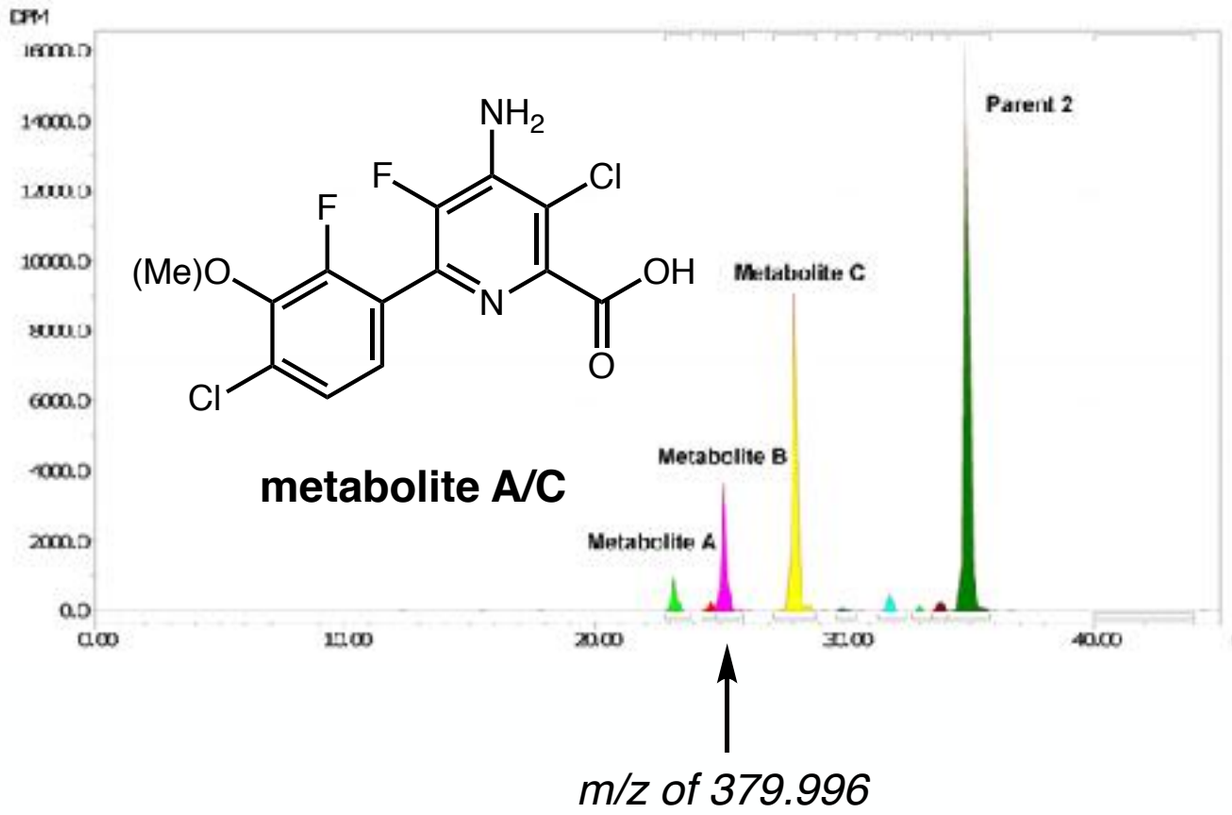
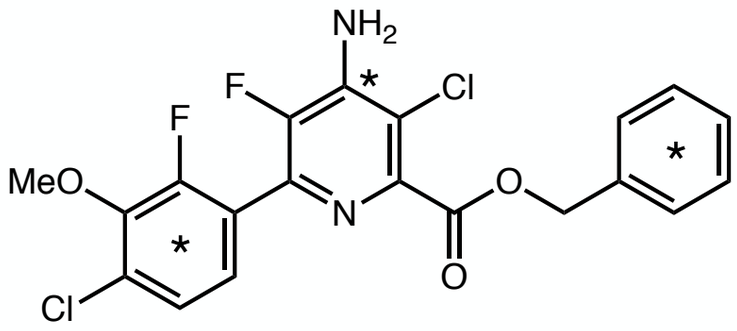
selective herbicide





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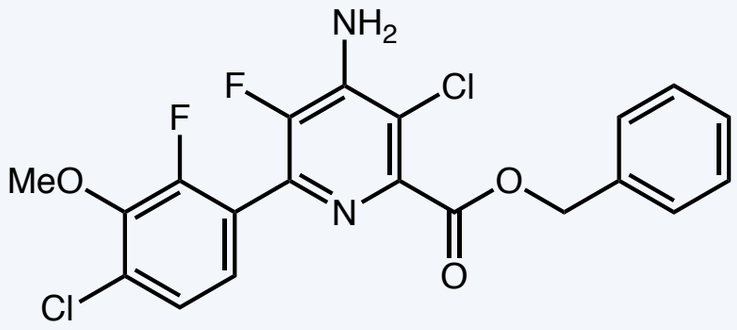

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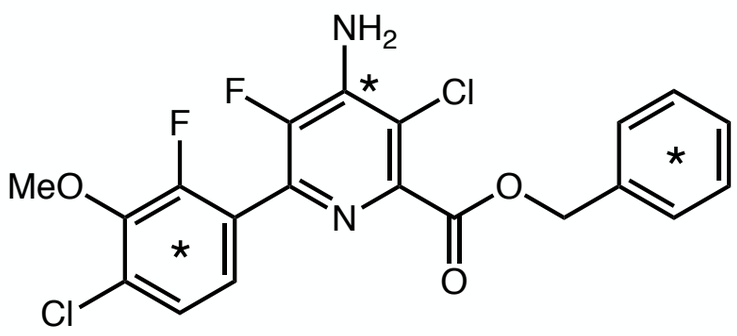
selective herbicide



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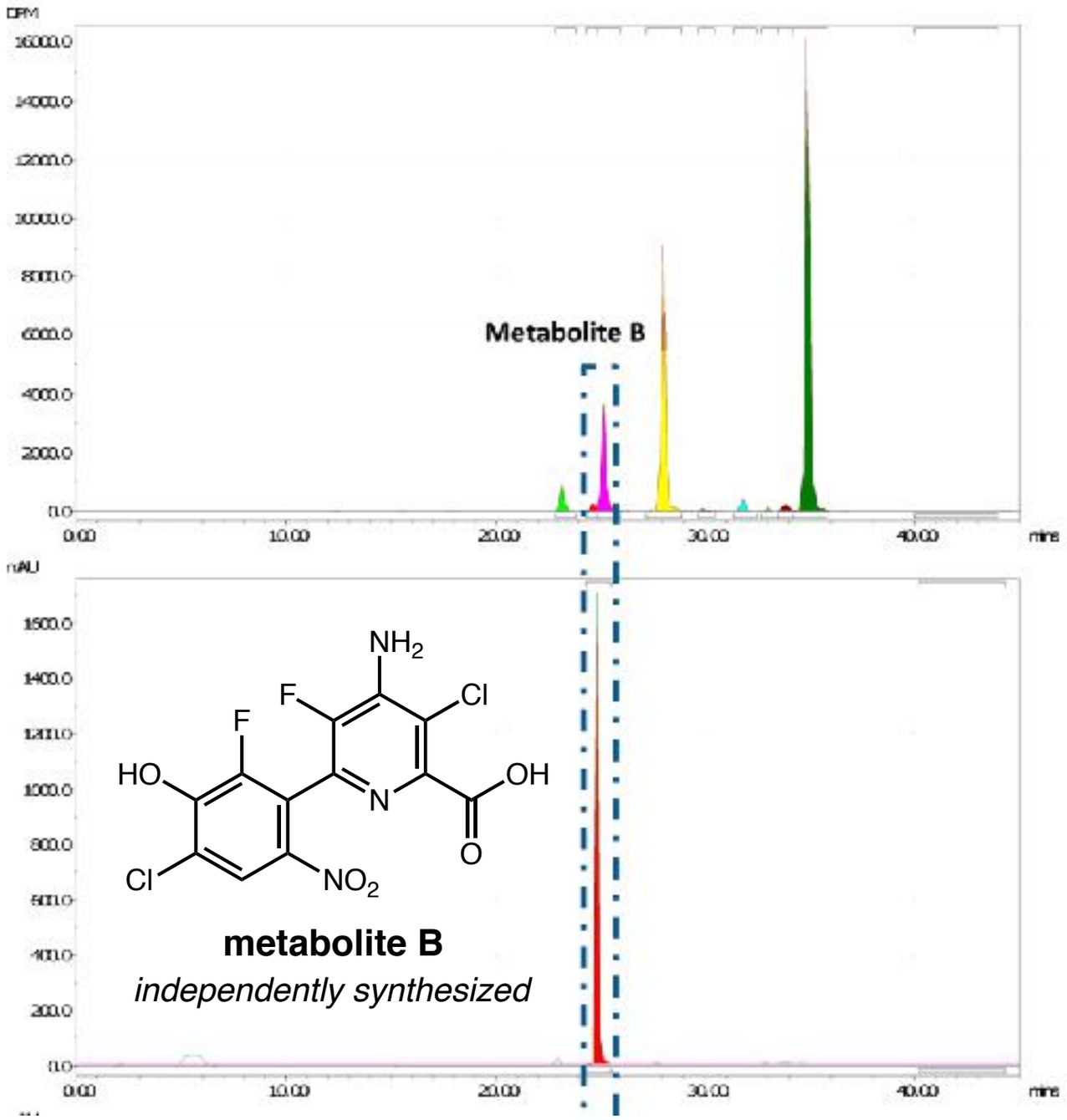
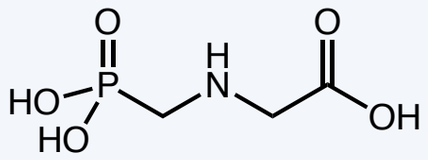


Canturk, B.; Johnson, P.; Taylor, J.; Kister, J.; Balcer, J. *Org. Process Res. Dev.* **2019**, *23*, 2234–2242.

Pesticides in Agrochemical Research & Development

- **Background of Agrochemical Industry**
  - Factors shaping industry
  - Landscape of agrochemical companies
- **Methods for Research & Development**
  - Plant biology & ag-like properties
  - Discovery process
  - Development process
  - Utility of radiolabeled pesticides
- **Pesticides of Note**
  - Glyphosate
  - DDT
- **Outlook on Pesticide Development**

Pesticides of Note: Glyphosate



glyphosate

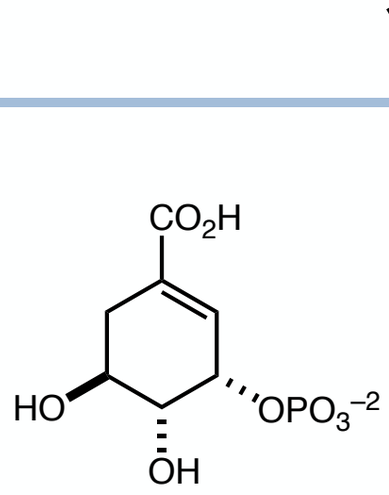
non-selective herbicide

Developed in 1974 by Monsanto

main component of *Roundup*

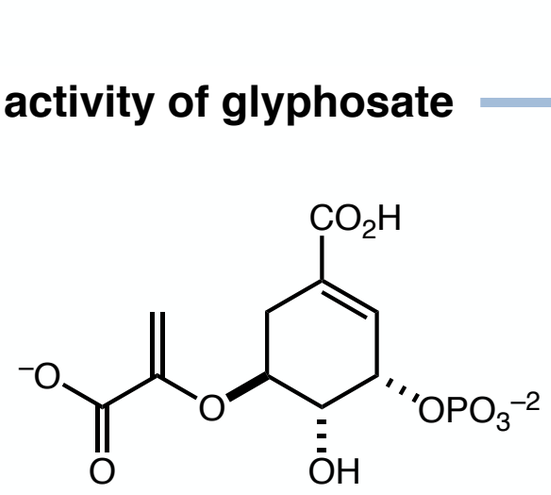
Roundup Ready soybeans developed 1996

herbicidal activity of glyphosate



shikimic acid-3-phosphate

EPSP synthase



5-enolpyruvyl shikimic acid-3-phosphate

phenylalanine

tyrosine

tryptophan

insufficient biosynthesis of amino acids kills plant

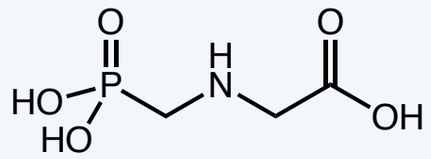
Agrobacterium CP4 EPSP synthase

Roundup Ready

GMO crops with enzyme insensitive to glyphosate

Van Bruggen, A. H. C.; He, M. M.; Shin, K.; Mai, V.; Jeong, K. C.; Finckh, M. R.; Morris, J. G. Jr. *Sci. Total Environ.* **2017**, 616, 255–268.

Pesticides of Note: Glyphosate



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Developed in 1974 by Monsanto

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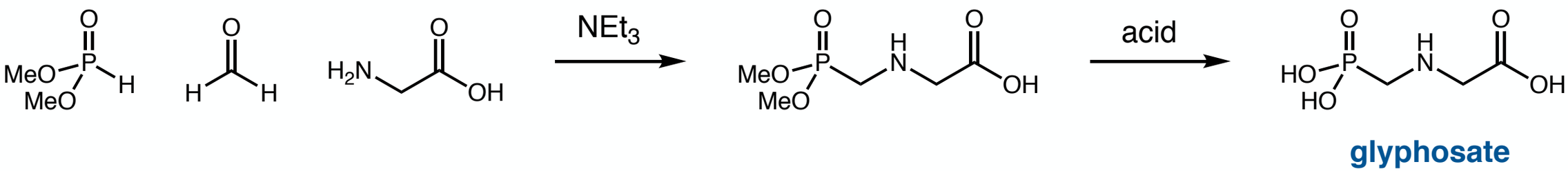
Roundup Ready soybeans developed 1996

original process scale synthesis of glyphosate



glyphosate

- more recent methods avoid using triethylamine

Van Bruggen, A. H. C.; He, M. M.; Shin, K.; Mai, V.; Jeong, K. C.; Finckh, M. R.; Morris, J. G. Jr. *Sci. Total Environ.* **2017**, 616, 255–268.

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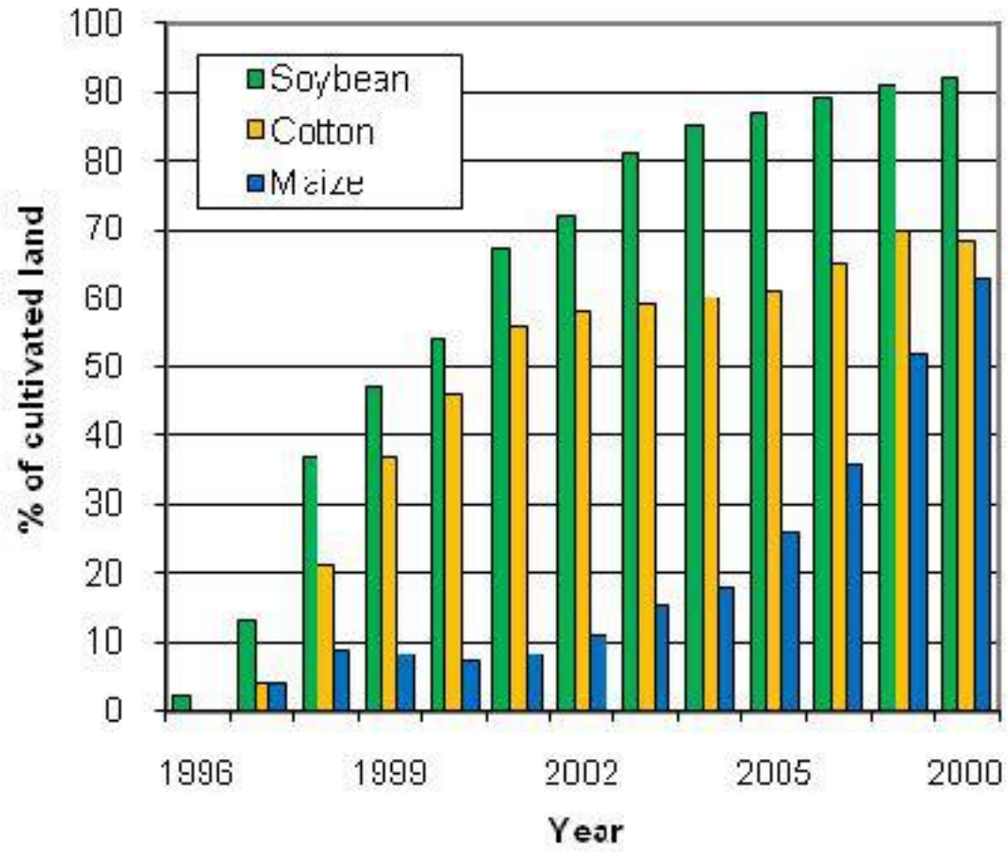


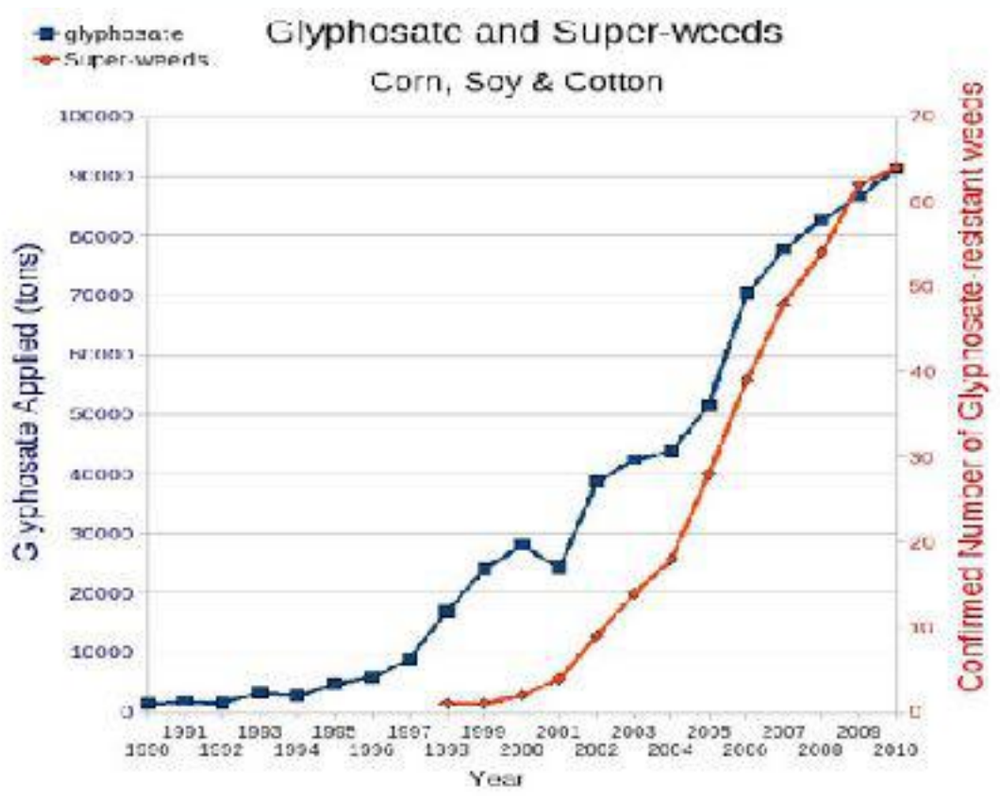
In 2015, 89% of corn, 94% of soybeans,

and 89% of cotton produced in the US

derived from herbicide-resistant GMO crops

growing resistance of weeds to glyphosate

has led to increase in glyphosate usage



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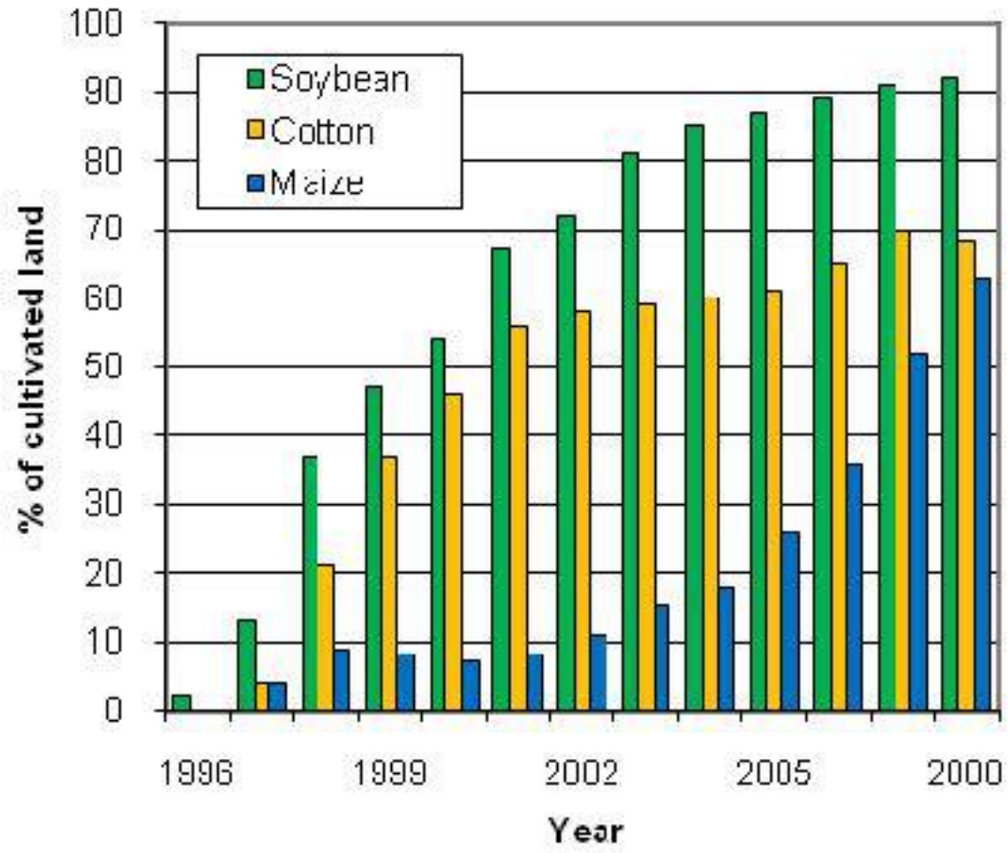

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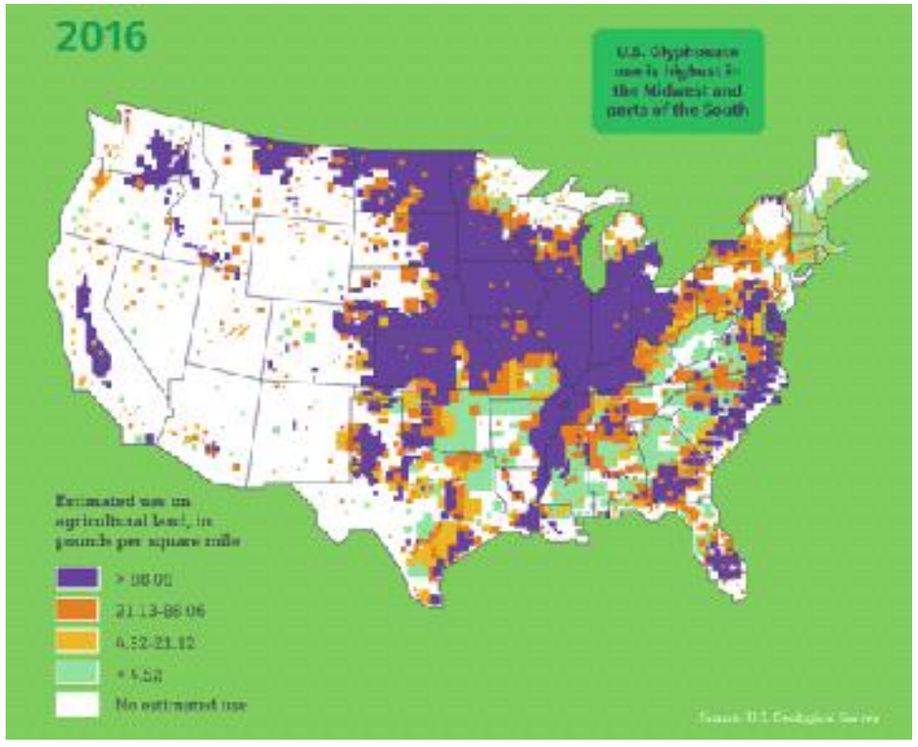
In 2012, 127,000 tons glyphosate used in USA,

700,000 tons worldwide

residues of glyphosate found in 60–80% of the US general public



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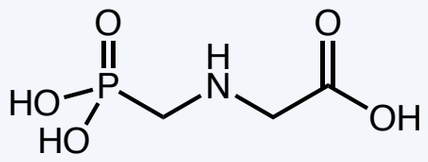


glyphosate

non-selective herbicide

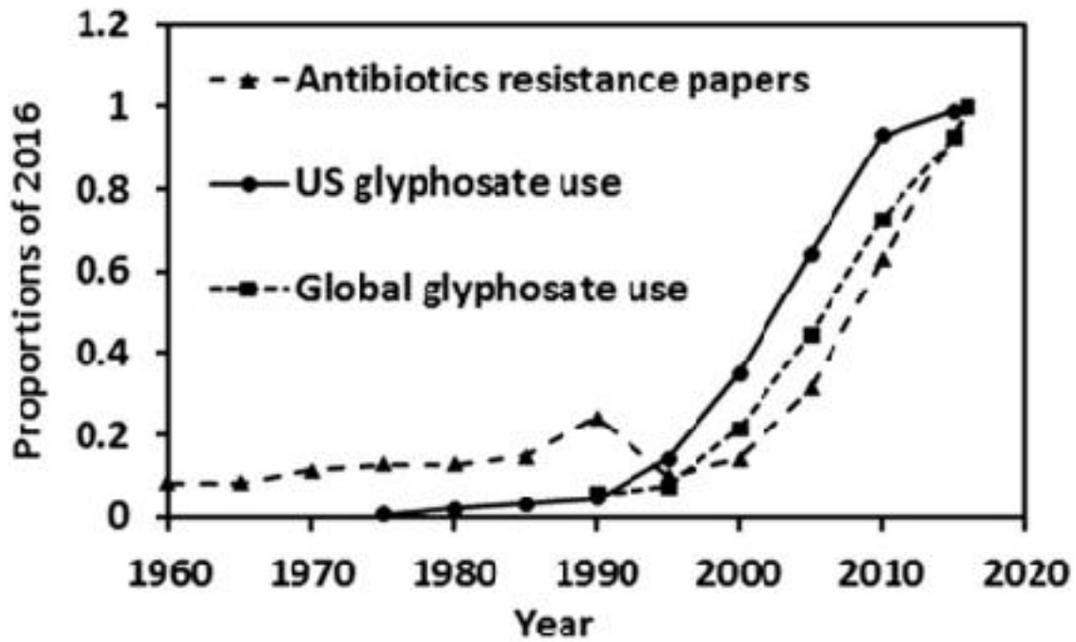
glyphosate not only used for agricultural purposes

- urban areas for weed control in streets/parks
- waterways to eliminate aquatic plants

based on recent reports, WHO reclassified glyphosate as probably carcinogenic to humans in 2015

shifts in microbial compositions due to glyphosate

increases in antibiotic resistance



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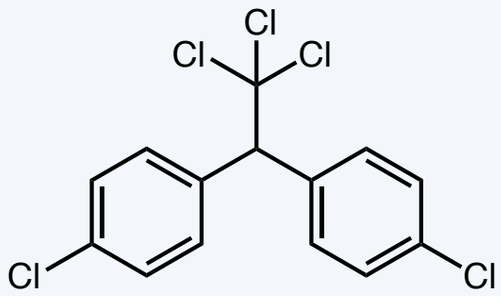
Pesticides of Note: DDT



DDT

first modern insecticide

Paul Müller – 1948 Nobel Laureate

"for his discovery of the high efficiency of DDT as a contact poison against several arthropods."

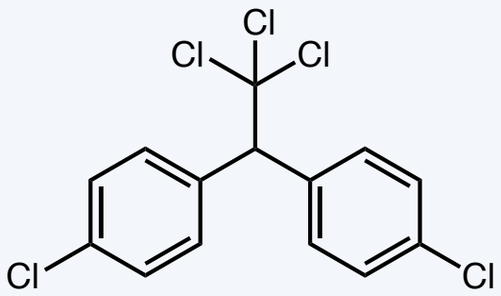
U.S. soldier sprayed for typhus-carrying lice

DDT broadly employed 1945–1972 for:

- Agricultural tool
- WHO anti-malaria campaign
- Treating typhus and malaria in WWII

Turusov, V.; Rakitsky, V.; Tomatis, L. *Environ. Health Perspec.* **2002**, *110*, 125–128.

Pesticides of Note: DDT



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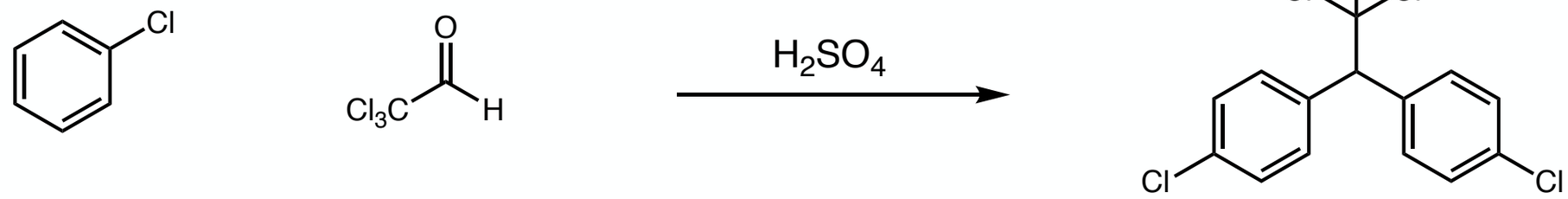
DDT synthesis: nearly ideal organic synthesis



chlorobenzene chloral

DDT

+25% other regioisomers

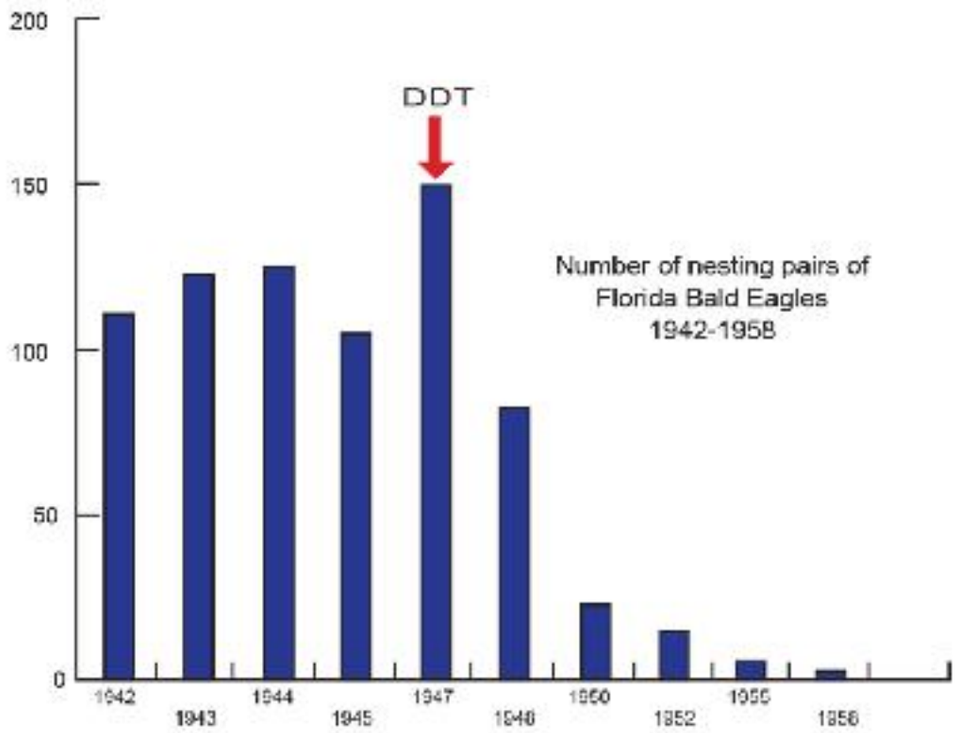
Turusov, V.; Rakitsky, V.; Tomatis, L. *Environ. Health Perspec.* **2002**, *110*, 125–128.

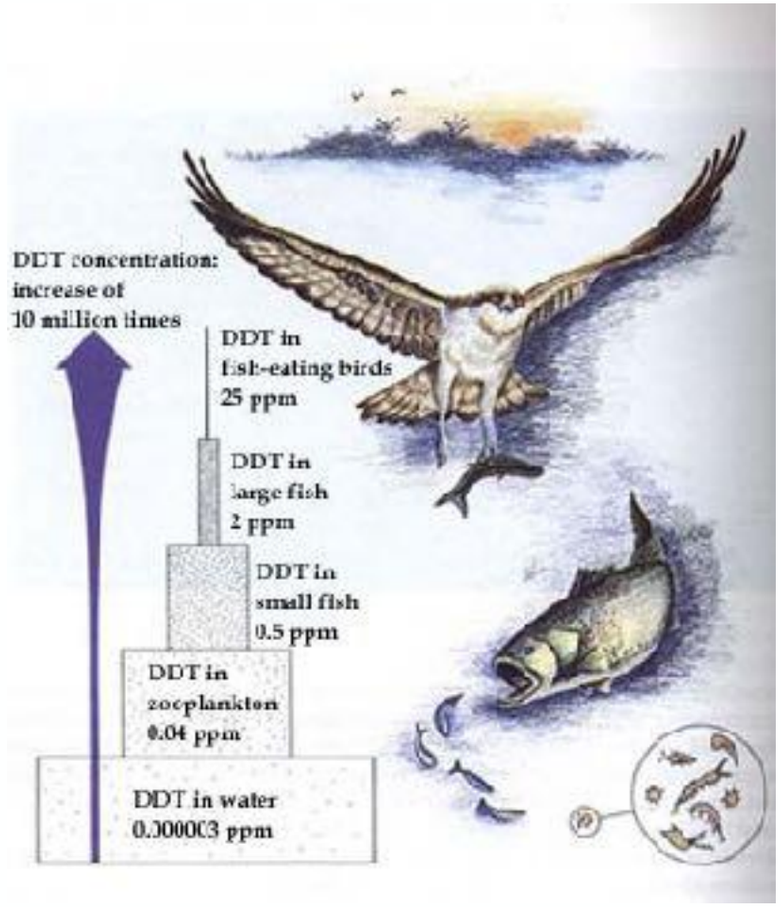
Pesticides of Note: DDT

Silent Spring, 1962 – Rachel Carson

- book documenting adverse environmental effects of DDT & other indiscriminate pesticides
- accuses chemical industry of spreading disinformation
- seminal event for the environmental movement

DDT contributed to bald eagle endangerment:





Carson, R., Darling, L., & Darling, L. (1962). *Silent Spring*. Boston : Cambridge, Mass.: Houghton Mifflin.

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US ban on DDT use in 1972, followed by worldwide ban on agricultural use under Stockholm Convention

Image obtained from American Eagle Foundation

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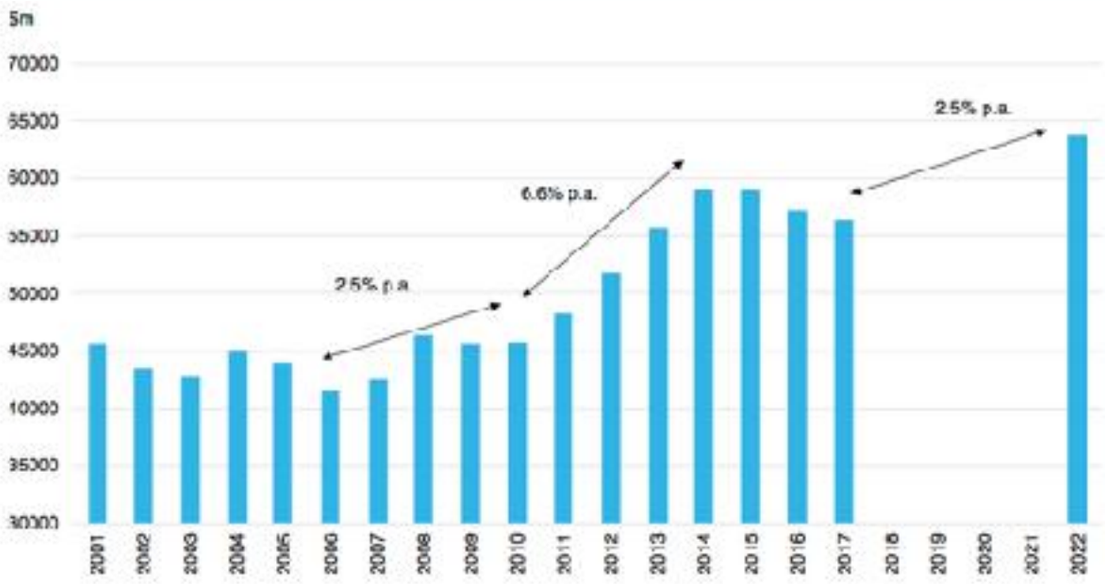
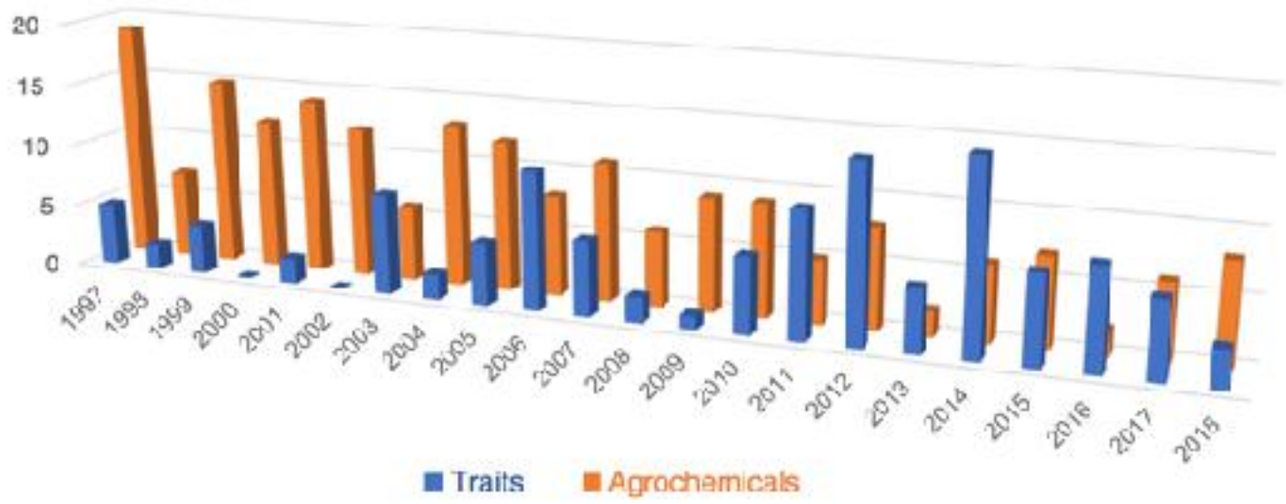
Outlook on Pesticide Development



- agrochemical industry projected to continue growing
  - while pesticide development has slowed, development of GMO traits has increased



Phillips, M. W. A. *Pest Manag. Sci.* **2019**, DOI: 10.1002/ps.5728.