The Dawn of Agrochemistry:
- 2000 BC: elemental sulfur employed as pesticide in ancient Sumer
- 15th century: farmers treat crops with arsenic, mercury, and lead to kill pests
- 17th century: farmers use nicotine sulfate as an insecticide
- 1815: Humphry Davy publishes "Elements of Agricultural Chemistry"
- 1816: Mount Tambora erupts causing the "year without a Summer" famine.
- 1840: Justus von Liebig publishes "Chemistry in its application to agriculture..."
- Justus von Liebig develops first nitrogen-based fertilizers
- 19th century: more natural pesticides introduced: pyrethrum and rotenone
- 1940's: DDT and other organochlorines introduced
- 1970's: organochlorines were replaced by organophosphates and carbamates
- Today: pyrethrin compounds are preferred

Top Agrochemical Companies*:
- Bayer CropScience
- Syngenta
- Monsanto
- BASF
- Dow AgroScience
- DuPont
- Makhteshim
- Sumitomo
- FMC

Pesticide R&D:
- pesticides must pass up to 120 EPA health and environmental tests prior to approval and registration
- These tests (comparable to the clinical phase in drug discovery) take an average of 9 years
- Average costs for development are $180 million (vs. ~18 for clinical trials)
- only 1 in 139,000 compounds make it to market (vs. ~10,000 in med. chem.)

Pros
- In the last 50 years, food production increased 2-3 fold without increasing land used for production
- Successfully supported world population and sustained food surpluses in industrialized countries
- Preserved billions of acres of world's forests and grasslands
- Countries that use pesticides spent less money on food and have access to more fruits and vegetables leading to better health
- Prevented spread of some diseases

Cons
- Contaminated the environment and harmed other wildlife (off target activity)
- Could harm farmers and people ingesting treated food
- Caused increased resilience and resistance in pests
- Killed the would-be food supply for natural predators that can help in crop production

Unsettling facts:
- World population will peak at ~10 billion and then likely decline
- We reach this peak around the middle of this century
- There are 13 billion hectares of land on earth and much is unarable
- 1.5 billion hectares used for food production currently (would be ~4.0 if no pesticides)

Agrochemistry Topics not covered:
- Xenobiotics (animals)
- Genetic modification of food
- Food chemistry - flavor
- Food chemistry - color
- Food chemistry - texture
- Fertilizers/Soil enhancement

See: "New Discoveries in Agrochemicals" in ACS symposium series (2004), v. 892 pp. 2-16

Initial basic considerations when developing agrochemicals:
1) Where will the pesticide be applied? (seeds, soil, foliage)
2) What insect is being targeted and how? (contact vs. oral activity)
3) What are that particular insect's feeding habits? (leaf, inside leaf, stem, root, flower)

Penetration into the leaf: necessary for compounds with limited photostability (i.e. imidacloprid) to target insects that feed inside the leaf. Generally logP= -4 to 5.5 at pH 7 ex: spinosad and abamectin

Translaminar Systemicity: necessary for insects that feed on the ventral surface of the leaf when pesticide is applied to the dorsal surface. Need a slightly lower logP (~ 4) or higher vapor pressure ex: carbosulfan and fipronil

Xylem Systemicity: compounds need to be absorbed at root where water is taken up and therefore have lower logP of usually <2.5

Phloem Systemicity: compounds need to have a logP similar to or less than glucose (logP= 2.92 at pH 7) or high vapor pressure to translocate from one leaf to another. Additionally, the phloem is slightly basic and attracts weak acids ex: benfenthrin and metominostrobin

Factors: 1) logP 2) Vapor Pressure 3) Acidity

Xylem: vascular system that transports water and water soluble nutrients from the roots to other parts of the plant
Phloem: vascular system that transports organic nutrients, mainly glucose, from the leaves to other parts of the plant

Other considerations - Plant Metabolism:

\[
\begin{align*}
\text{[O]} & \rightarrow \text{[OH]} & \text{Me} & \rightarrow \text{[OH]} \\
\text{CO}_2\text{Me} & \rightarrow \text{CO}_2\text{H} & \text{Me} & \rightarrow \text{OH} \\
\text{OMe} & \rightarrow \text{OH} & \text{OH} & \rightarrow \text{O}_2\text{Sug}
\end{align*}
\]
**What does "Organic" really mean?**

The government created the Organic Foods Production Act in 1990 which contains two lists: "National list of allowed synthetic substances" and "National list of prohibited non-synthetic substances." If a SYNTHETIC substance is not on the first list, it cannot be used and if a NON-SYNTHETIC substance is not on the second list, it can be used. The following is a summary of the substances for crop production only (not livestock).

**Allowed synthetic substances:**

\((\text{NH}_4)_2\text{CO}_3\)  \(\text{B(OH)}_3\)  \(\text{S} \text{ (elemental)}\)  \(\text{K}_2\text{O}_3\text{Si} \text{ (aqueous)}\)  \(\text{CuSO}_4\)

**Calcium Polysulfide** (\(\text{CaS}_n\))  \(\text{Soap (sodium lauryl sulfate)}\)

**Sucrose Octanoate Esters:**

\[
\text{HO}^{\cdot} \text{O}^{\cdot} \text{OR}^{\cdot} \text{OR}'^{\cdot} \text{OH}^{\cdot} \text{OH}^{\cdot} \text{OH}^{\cdot} \text{OH}^{\cdot} \\
\text{OR}=\text{CO(CH}_2)_7\text{CH}_3 \\
\text{OR}'=\text{H or CO(CH}_2)_7\text{CH}_3
\]

**Prohibited non-synthetic substances:**

As, \(\text{CaCl}_2\), Lead Salts, \(\text{KCl}\), \(\text{Na}_3\text{AlF}_6\), \(\text{NaNO}_3\)

**Styronine:**

\[
\text{N} \text{H}^{\cdot} \text{H}^{\cdot} \text{SO}_4^{2-}
\]

**Nicotine Sulfate:**

See: Cherney 2009 GM "L. N. Mander"

**Approved Pesticides: Natural Products**

- **spinosyn A** (\(R=\text{H}\))
- **spinosyn D** (\(R=\text{Me}\))
- **giberellic acid**
- **rotenone**
- **toosendanin**
- **volkensin**
- **annoin I**

See: Shenvi 2004 GM "Ryanodol"

See: Renata 2011 GM "Limonoids"
Agrochemistry: Insecticides

Approved Pesticides: Natural Products Cont'd

tetranactin
nikkomycin X
milbemectin (and other milbemycins/avermectins)
haedoxan
rocaaglamine
menthol
citronellal
thiangelzone
thiangelzone
thiangelzone
capsaicin
DL-phosphinothricin
glyphosate
Pyrethrin I
codelmone
stroilurin A

diabroticin A
pyrofumatin
methylanthranilate
tebufenozide
Section 1: Total Syntheses of Natural Product Pesticides

**Spinosyn A**

Spinosyn A and D are the active ingredients in Spinosad (an insecticide produced by Dow). These two natural products were isolated from soil samples collected from an abandoned rum still by an employee vacationing in the Caribbean in 1982.

*Paquette et al., JACS (1998) v. 120, pp. 2543-2562.*

1. **Total Synthesis of Spinosyn A**
   - **Steps:**
     1. PivCl, pyr.
     2. TBAF
     3. PCC, AlCl₃
     4. K₂CO₃, MeOH
   - **Yield:** 54%

2. **Total Synthesis of Spinosyn D**
   - **Steps:**
     1. HMDMS, Comin's
     2. (P₃H)₃Pd, LiCl
     3. Me₃SnSnMe₃
   - **Yield:** 48%

3. **Yamaguchi Lactonization 2x Glycosylation**
   - **Yield:** 83%

4. **Tandem HWE-DA**
   - **Yield:** 75%

5. **Final Steps**
   - **Yield:** 88%
   - **Me₃P (8 eq) t-amyl alcohol (0.005 M)**

**Spinosyn A**

**Baran Group Meeting**

**Agrochemistry: Insecticides**

**Emily Cherney**

---

**4-deguelin**

Sames *et al*, *Org. Lett.* *(2003)* v. 5, pp. 4053-4055

---


---

**Section 2: From Natural Products to Synthetic Pesticides**

1. *Pyrethrin*

   - Natural Product
   - Commerical Insecticide

---

Indigenous tribes in French Guiana smashed jicama roots containing rotenone to use while fishing. The rotenone poisoned the fish causing them to rise to the surface of the water. The fish were still edible since rotenone is poorly absorbed by the GI tract in humans. Today it is also used in aquatic research to collect cryptic fish.
1-pyrethrin (cont’d.)
Syngenta process route to cyhalothrin: formulated in and marketed under the names “Karate” “Kung-fu” and “Matador”

![Chemical structure of cyhalothrin]

Recrystallization

Sorry for the vague procedures here, but to quote the patent: “The reaction can be carried out in a solvent or in a mixture of a water immiscible solvent or an aqueous solution of the source of cyanide or in the absence of a solvent”

Additionally... “the acid chloride and 3-phenoxybenzaldehyde can be added sequentially or simultaneously to the source of cyanide in the presence of the solvent or the solvent mixture, optionally in the presence of an organic base or an ionium salt.”

More vagueness continues on like this for about a dozen more paragraphs...

Analogs based on pyrethrin:

2-nicotine
Natural Product

![Chemical structure of nicotine]

Commercial Insecticide

A Synthesis of Thiamethoxam: US Patent No: 6861522 (B2)
1) MeNH2, NaOH, H2O, EtOH
2) Aq. CH2O, 80 °C, pH 8-9


Other Commercial Products:
- clothianidine
- acetamiprid
- nitenpyram
3-organophosphates
Natural Product

![Structure of glyphosate and acephate]

Making various Phosphates:

<table>
<thead>
<tr>
<th>reagents</th>
<th>product</th>
<th>target</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCl3, MeOH, NaOH, PhMe</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>- P2S5, MeOH then Cl2</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>- P(O)(OMe)2, Lawsson's then SO2Cl2</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Phosphorous, Sulfur, Silicon and Related Elements (2010) 347)</td>
<td>(R= Nu')</td>
<td></td>
</tr>
<tr>
<td>P2S5, MeOH, PhH</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Nongyao (2001) 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO- P'O Me, NH2OH, DCM</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Phosphorous, Sulfur, Silicon and Related Elements (2010) 347)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO- P'O Me, SO2Me2</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Phosphorous, Sulfur, Silicon and Related Elements (2010) 347)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSCl3, 2 eq RMgBr</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Phosphorous, Sulfur, Silicon and Related Elements (2010) 347)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POCl3, 1 eq EtOH, Et3N</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Huazhong Nongye Daxue Zuebao 2000 339)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POCl3, 1 eq EtOH, Et3N then 1 eq ArOH</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>(Tetrahedron 1995 7981)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-organophosphates (cont'd.)

A Synthesis of Methidathion: (Nongyao (2001) 13)

A Synthesis of Pyrimiphos-Methyl: (Huaxue Shiji 2010) 845

(Agrochemistry: Insecticides)
Agrochemistry: Insecticides

4- Carbamates

- Natural Product: physostigmine
- Commercial Insecticide: xylolcarb

Other Commercial Carbamates:
- Aldicarb
- Bendiocarb
- Carbaryl
- Fenobucarb
- Methomyl

Section 3: Totally Synthetic Pesticides

1-organochlorides

\[
\text{C}_6\text{H}_5 + \text{Cl}_2\text{C}_6\text{H}_4\text{Cl}_2 \xrightarrow{\text{Diels - Alder}} \text{Aldrin}
\]

Similarly:
- Chlorodane
- Endrin
- Endosulfan

Kepone and Mirex:

\[
\begin{align*}
\text{OC} & \quad \text{OC} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\text{MeO} \quad \text{MeCl} \quad \text{MeCl}
\]

DDT etc.:

\[
\text{H}_2\text{SO}_4 \quad \text{(cat.)}
\]

- Dichlorodiphenyl trichloroethane (DDT)
- Methoxychlor
dichlorodiphenyl dichloroethane

DDT was discovered by a Paul Müller in 1940. It was first brought to market in 1944 and was used during the second half of WWII to prevent the spread of malaria and typhus. Paul Müller won the Nobel Prize in Physiology and Medicine for the discovery in 1948. It was later used as an insecticide, however it was found to be harmful to wildlife, particularly birds including the bald eagle, and was banned from use in the US in 1972.

* Almost all organochlorides have been banned globally.

2- fun transformations from the agrochemistry literature!


\[
\begin{align*}
\text{RO}_2\text{C} & \quad \text{C}_6\text{H}_5 \quad \text{NH}_2 \quad \text{C}_6\text{H}_5 \quad \text{O}_{2}\text{C}
\end{align*}
\]

1) NaOH

2) ClCO_2Me

\[
\begin{align*}
\text{MeNHNNH}_2 & \quad \text{MeNHNNH}_2
\end{align*}
\]
2-Fun transformations from the agrochemistry literature! (cont'd)


