All you need to grow – from planting to harvest

Past present and future of Chemical control of late blight

Albert Schirring
GILB 3rd International Conference Beijing 2008
## Major Trends and Challenges in Agriculture

<table>
<thead>
<tr>
<th>Growing world population</th>
<th>Need for alternative energy feedstocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>- increasing food &amp; energy demand</td>
<td></td>
</tr>
<tr>
<td>- decreasing farmland per capita</td>
<td></td>
</tr>
<tr>
<td>- increasing demand for renewable energy and biofuel</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Climate change</th>
<th>Growing wealth</th>
</tr>
</thead>
<tbody>
<tr>
<td>- yield losses through adverse weather conditions</td>
<td></td>
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<tr>
<td>- new diseases will appear</td>
<td></td>
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<tr>
<td>- driving shifting disease epidemics</td>
<td></td>
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<tr>
<td>- increasing meat consumption and need for feed</td>
<td></td>
</tr>
<tr>
<td>- decreasing stocks to use</td>
<td></td>
</tr>
</tbody>
</table>
Presentation topics

- Phytophthora infestans impact on yield
- Phytophthora infestans
- Fungicide development: short history
  - contact fungicides
  - penetrant fungicides
  - penetrant / systemic
- The ideal fungicide
- Challenges in fungicide research
- Research methods
- New chemistry future outlook
- Experiences INFINITO Europe 2007: UK + NL
Crop Protection is Vital – Classical Situation

Major crops analyzed: rice, wheat, barley, corn, potatoes, soybeans, cotton and coffee

- Yield without crop protection
- Actual yield with crop protection
- Attainable yield without pests

Without crop protection nearly half of the current harvest would be lost.
Further opportunities will open with productivity increase in agriculture.

Source: Oerke et al., Crop Production and Crop Protection, Elsevier, Amsterdam.
EUROPEAN AGRICULTURE OF THE FUTURE: THE ROLE OF PLANT PROTECTION PRODUCTS (PPPs)

Press Conference
Brussels, 24 January 2008
Nomisma: impact reduced package crop protection products on the yield of potatoes

The impacts of the new regulation: case studies

Reduced availability of PPPs in EU-27 could generate impacts over long term (2020)
New regulation effects + availability of new PPPs due to R&D activity of PPP Industry

Static evaluation

<table>
<thead>
<tr>
<th>Crop</th>
<th>0%</th>
<th>-10%</th>
<th>-20%</th>
<th>-30%</th>
<th>-40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat</td>
<td>-29%</td>
<td>-30%</td>
<td>-20%</td>
<td>-10%</td>
<td>0%</td>
</tr>
<tr>
<td>Potato</td>
<td>-33%</td>
<td>-40%</td>
<td>-30%</td>
<td>-20%</td>
<td>0%</td>
</tr>
<tr>
<td>Wine grape</td>
<td>0%</td>
<td>-10%</td>
<td>-20%</td>
<td>-30%</td>
<td>-40%</td>
</tr>
<tr>
<td>Cereals</td>
<td>0%</td>
<td>-10%</td>
<td>-20%</td>
<td>-30%</td>
<td>-40%</td>
</tr>
</tbody>
</table>

yield reduction
Phytophthora infestans continuous adaptation...
First symptoms are slight lesions on the leaves, however when Late Blight gets a hold, destruction is rapid and total.

Despite existing solutions in the market today’s economic damage through potato yield loss is estimated > $3 billion.

Yield loss per ha ranging from 20 – 100% (GILB 2008)
Phytophthora life cycle: where to interfere?

Phytophthora
Asexual life cycle

Systemic action
(mycelium growth, sporulation)

Penetrant action
(post infection)

Contact action
(spore germination)
<table>
<thead>
<tr>
<th>Year</th>
<th>Product Class &amp; Compound(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1885</td>
<td>Bordeaux mixture (Copper + lime)</td>
</tr>
<tr>
<td>1900</td>
<td>Copper (copper oxides, copperoxychloride)</td>
</tr>
<tr>
<td>1943</td>
<td>Dithiocarbamates (mancozeb, maneb)</td>
</tr>
<tr>
<td>1955</td>
<td>Triphenyl tin (fentin hydroxide and fentin acetate)</td>
</tr>
<tr>
<td>1955</td>
<td>Phthalimides (folpet and captafol)</td>
</tr>
<tr>
<td>1960</td>
<td>Phthalonitriles (chlorothalonil)</td>
</tr>
<tr>
<td>1964</td>
<td>Propineb (propineb)</td>
</tr>
<tr>
<td>1991</td>
<td>Pyridineamines (fluazinam)</td>
</tr>
<tr>
<td>2001</td>
<td>Sulfonylimidazole (cyazofamid, amisulbrom)</td>
</tr>
<tr>
<td>2003</td>
<td>Tubulin polymerisation (zoxamide, ethaboxam)</td>
</tr>
</tbody>
</table>
Classical contact fungicides: multi-site fungicides

How multi-site fungicides can affect cell metabolism in fungal pathogens
Site of action of propineb

- Inhibition of protein biosynthesis
- Interference with membrane function
- Inhibition of biosynthesis of e.g. coenzyme A
- Inhibition of cellular respiration

Cell wall
Amino acids
Ribosomes
Proteins
Golgi apparatus
Endoplasmic reticulum
Cell membrane
Nucleus
Cytoplasm
Mitochondrion

Presentation • 08 May 2008 • Slide 11
Contact fungicides features

Activity is based upon contact: sporicide
Full protection achieved through prophylactic repeated application at relative
Short intervals to ensure protection of new growth
Fungicidal activity: non specific limitation on plant compatibility (eg Copper)
Mode of action: non-specific reaction with thiol groups (enzymes)
High and non specific biological activity (multi site activity) framed by strict regulation (reduction of dose rate and number of applications)
Multi site activity: a valuable feature as part of resistance management
Recent contact fungicides with specific MOA

1885  Bordeaux mixture (Copper + lime)
1900  Copper (copper oxides, copperoxychloride)
1940  Dithiocarbamates (mancozeb, maneb)
1955  Tripehyl tin (fentin hydroxide and fentin acetate)
1955  Phthalimides (folpet and captafol)
1960  Phthalonitriles (chlorothalonil)
1991  Uncoupler respiration (fluazinam)
2001  Respiration complex III (Qil) (cyazofamid, amisulbrom)
2003  Tubulin polymerisation (zoxamide, ethaboxam)
Historic milestones contact + penetrant fungicides

Contact fungicides with penetrant properties

1992  Cinnamic Acid derivatives (CAA chemistry)
       (**dimethomorph**, iprovalicarb, benthiovalicarb (05),
       mandipropamid (07), flumorph (07), valiphenal (8))

2001  Respiration complex III (QoI) (famoxadone, **fenamidone**)

2006  Spectrin like proteins (**fluopicolide**)
Features: contact + penetrant fungicides

Activity based upon contact and specific mode of action:
sporicide, germination, suppression of sporulation (mycelium growth)

Full protection achieved by repeated application.
Penetration of the fungicide in plant tissue offers options for more flexibility to control the disease

Mode of action: specific target sites
Regulatory profile favourable
Resistance management required to ensure sustainable activity
### Historic milestones: penetrant and systemic

#### “Internal therapy of plants”

<table>
<thead>
<tr>
<th>Year</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978</td>
<td>Cyanoacetamide-oximes</td>
<td><strong>cymoxanil</strong>&lt;br&gt;(RNA synthesize)</td>
</tr>
<tr>
<td>1980</td>
<td>Phehylamides</td>
<td><strong>metalaxyl</strong>, oxydixyl, benalaxyl, ofurace&lt;br&gt;(RNA polymerase)</td>
</tr>
<tr>
<td>1994</td>
<td>Carbamates</td>
<td><strong>propamocarb HCl</strong>&lt;br&gt;(unknown probably non specific phospholipid synthesis)</td>
</tr>
</tbody>
</table>
Features: penetrant + systemic fungicides

- Activity based upon contact and specific mode of action:
  - metalaxyl – germination, sporulation, mycelium growth
  - cymoxanil – germination
  - propamocarb – germination, sporulation, mycelium growth
- Protection achieved through uptake of the fungicide in the leaf tissue
- Full systemic activity: metalaxyl rapid movement into the canopy
- Mode of action: specific target sites
- Regulatory profile favourable
- Specific mode of action requires resistance management strategies
### INFINITO: inbuild two different modes of action

<table>
<thead>
<tr>
<th>Mode of action (FRAC)</th>
<th>Chemical group</th>
<th>Fungicide</th>
<th>Tradename</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncouplers</td>
<td>2,6-Dinitro-Aniline</td>
<td>fluazinam</td>
<td>Shirlan</td>
</tr>
<tr>
<td><strong>Carbamate</strong></td>
<td><strong>carbamates</strong></td>
<td><strong>propamocarb</strong></td>
<td><strong>INFINITO</strong></td>
</tr>
<tr>
<td>Cellwall synthesis</td>
<td>cinnamic acid</td>
<td>dimethomorph</td>
<td>Acrobat (+M)</td>
</tr>
<tr>
<td></td>
<td>cinnamic acid</td>
<td>benthiovalicarb</td>
<td>Valbon (+M)</td>
</tr>
<tr>
<td></td>
<td>Mandelamide</td>
<td>mandipropamid</td>
<td>Revis</td>
</tr>
<tr>
<td></td>
<td>cinnamic acid</td>
<td>flumorph</td>
<td>Flumorph (+M)</td>
</tr>
<tr>
<td>Unknown</td>
<td>Cyanoacetamide-oximes</td>
<td>cymoxanil</td>
<td>Curzate (+M)</td>
</tr>
<tr>
<td>Respiration (Qil)</td>
<td>Cyanoimidazole</td>
<td>cyazofamid</td>
<td>Ranman</td>
</tr>
<tr>
<td>RNA polymerase</td>
<td>Acylalanine</td>
<td>metalaxyl</td>
<td>Ridomil MZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>metalaxyl R</td>
<td>Ridomil Gold</td>
</tr>
<tr>
<td>Respiration (QoI)</td>
<td>Oxazolidindione</td>
<td>famoxadone</td>
<td>Equation Pro (+M)</td>
</tr>
<tr>
<td></td>
<td>Imidazolinone</td>
<td>fenamidone</td>
<td>Sereno (+M)</td>
</tr>
<tr>
<td>Spectrin interaction</td>
<td>Acylpicolide</td>
<td>fluopicolide</td>
<td><strong>INFINITO</strong></td>
</tr>
</tbody>
</table>
Sustainable Crop Protection
Modern crop protection products: high demands

**Efficacy**
- high reliable biological control
- high selectivity
- Quick onset of activity
- Subsequent distribution in the plant
- Optimal duration of activity
- Good Crop tolerance
- Low risk of resistance

**Environmental safety**
- Low toxicity to beneficial insects
- Good environmental degradability
- Low soil mobility
- No significant residues in food and animal feed

**User friendly**
- Low rate of application
- Low acute toxicity
- Low toxicity on long term exposure
- Safe packaging
- Good formulation properties
- Problem free application
- Long storage stability

**Economic viability**
- Favourable cost/benefit ratio to the user
- Suitable for use in integrated crop management systems (ICM)
- Broad range of applications
- Innovative product characteristics
- Competitiveness
- Patentability
Blue sky chemistry to identify a new late blight fungicide....
Research concepts for new AI identification

- Lead Optimisation of Random Screening Hits
- Solid Phase Combi. Chem.
- Library Synthesis Robot Runs
- Follow up Ideas from Literature
- “Me Too” Chemistry Patent Busting
- Mix and Match
- “Agrophore” Approach
- “Blue Sky” Chemistry
- “Spin Off” from other Indications
Developing a New Active Ingredient

200,000 different molecules

Active ingredients

<4 5 >10

1 - 2

Project Discovery  Project Realization  Business Realization

Total cost > €150mio.
R&D activities demand 10 years till market introduction
### Profile of a new Late blight fungicide

<table>
<thead>
<tr>
<th>Excellent activity</th>
<th>Excellent selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protection of leaves and stems</td>
<td>Formulation easy to handle</td>
</tr>
<tr>
<td>Tuber protection</td>
<td>Compatible by tankmixing</td>
</tr>
<tr>
<td>Preventative</td>
<td>Safe tox profile</td>
</tr>
<tr>
<td>Quick activity</td>
<td>Good environmental profile</td>
</tr>
<tr>
<td>Long lasting protection</td>
<td>Compatible with sustainable production</td>
</tr>
<tr>
<td>Protection of new growth</td>
<td>Low dose rates</td>
</tr>
<tr>
<td>Yield enhancing</td>
<td>Low residues</td>
</tr>
<tr>
<td>Reliable performance (consistency)</td>
<td>Profile fit within ICM</td>
</tr>
<tr>
<td>Temperature independent activity</td>
<td></td>
</tr>
<tr>
<td>Rainfast</td>
<td>Foodchain friendly</td>
</tr>
<tr>
<td>New mode of action</td>
<td></td>
</tr>
<tr>
<td>Low risk on resistance development</td>
<td></td>
</tr>
<tr>
<td>No cross resistance with other MOA</td>
<td></td>
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</tbody>
</table>
New chemistry outlook

- Plant Health
- Climate change
- Biofuel
- CO₂
- New Fungicides
- Fungal diseases

- Quality
- Bioenergy plants
- Soil life
- Phloem
- Xylem
Conclusions

- Potato yield increase essential to meet millennium goals and beyond

- Fungicides are essential tools to safeguard yield potential when embedded in integrated crop management

- Multisite fungicides (contact) are an essential part of effective resistance management

- Hurdles for development of fungicides are extremely challenging

- A small number of new fungicides with low use rates and attractive environmental profile are expected to arrive at mid term
Thank you for your attention