Herbicide discovery in light of fast spreading resistance and ever increasing regulatory hurdles

GHRC 2017, Denver

May 16, 2017 / B. Peters & H. Strek
Agenda

- Challenges Weed Management
- Finding new Herbicides
- Sustainability
- Future
Weed Resistance

A long long time ago……
with the advent of Roundup Ready® crops farmers and industry dreamed the dream of weed-free fields.

But nature struck back…….
Today, weed resistance is a global problem.....

2017: 251 different resistant species to 23 of 26 known herbicide sides of action and to 162 herbicides — and the trend is continuing upwards!

- Black grass (Alopecurus myosuroides)
- Wild oat (Avena spp.)
- Loose silky-bent grass (Apera spica venti)
- Ryegrass (Lolium spp.)
- Brome grass (Bromus spp.)
- Amaranthus spp.,
- Common lambsquarter (Chenopodium album)
- Wild camomile (Matricaria chamomilla),
- Common poppy (Papaver rhoeas)

- Annual Ryegrass (Lolium rigidum)
- Wild Oat (Avena fatua)
- Brome grass (Bromus diandrus)
- Wild Radish (Raphanus raphanistrum)
- Barley grass (Hordeum murinum)
- Hairy fleabane (Conyza bonariensis)
- Echinochloa spp.
...beside other challenges for global food production

- limitation of farmland, competition for key resources
- changing consumer demands
- climate change
- demographic changes
- political and societal acceptance

Creating a pressing need for further innovation that addresses evolving societal and customer needs in a sustainable manner.
New herbicidal active ingredients are urgently needed!

Industry-wide sharp decrease in new herbicide patent applications

Loss of active ingredients e.g. due to increased regulatory hurdles

Most important herbicidal modes of action show major resistance issues

No introduction of new MoA for major markets in 30 y

- EPSPS
- ALS
- Auxins
- ACCase
- PSII
- VLCFA
- HPPD
Why is chemical crop protection so attractive?

Modern herbicides
- Convenient and cost-effective
- Flexible:
  - Before, during, or after seeding
  - After crop emergence until harvest
  - With soil residual or non-residual activity
- Products supported with labels and stewardship
- A fundamental contribution to modern agriculture:
  - Highly effective weed control, increases yields and farm revenues
  - Reduces pressure to cultivate un-cropped land
  - Safe, if handled and used correctly
  - Reducing soil erosion and CO₂ footprint
Challenges and drivers to providing new weed control solutions

**Challenges**

**Economic**
- high and rising R&D costs
- uncertainties and high risks for return on investment

**Biological efficacy**
- very high standards
- resistance-breaking
- finding new modes of action (MoA)

**Regulatory**
- safety (human, environmental, ecotox)
- hazard criteria
- political / public pressure

**Drivers**

**Economic**
- current low cost of weed control
- low and volatile commodity prices

**Resistance**
- increasing & multiple resistance
- need for resistance-breaking herbicides
- need for integrated solutions
- human psychology

**Convenience**
- flexibility of applications
- number of applications
- mixtures / sequences
Global societal trends and regulatory drivers

<table>
<thead>
<tr>
<th>EMEA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High and increasing regulatory requirements, cut-off and candidates for substitution</td>
<td></td>
</tr>
<tr>
<td>• Potential negative impact of EU decisions on trade flow and other regions</td>
<td></td>
</tr>
<tr>
<td>• Increasing impact of secondary legislation (CLP, water quality standards, etc.)</td>
<td></td>
</tr>
<tr>
<td>• Strong pressure by NGOs (risk-averse, anti-pesticide)</td>
<td></td>
</tr>
<tr>
<td>• High and increasing regulatory requirements</td>
<td></td>
</tr>
<tr>
<td>• Complex and sophisticated risk assessment, no cut-offs, impact of Endangered Species Act</td>
<td></td>
</tr>
<tr>
<td>• Export orientation requires global registration strategies</td>
<td></td>
</tr>
<tr>
<td>• Strong pressure by NGOs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LATAM</th>
<th>APAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increasing regulatory requirements in many countries (Brazil - cut-offs and environmental reviews, OLC – equivalence, ERA and ORE)</td>
<td></td>
</tr>
<tr>
<td>• Secondary standards continue to be important</td>
<td></td>
</tr>
<tr>
<td>• Low data protection in some countries, intellectual property legislations under discussion</td>
<td></td>
</tr>
<tr>
<td>• NGO influence and pressure increasing</td>
<td></td>
</tr>
<tr>
<td>• Very diverse standards across the region, risk-based assessment developing</td>
<td></td>
</tr>
<tr>
<td>• Standards increasing due to growing food safety and environmental concerns, aspiration towards international practices (i.e. China)</td>
<td></td>
</tr>
<tr>
<td>• High number of generic registrations</td>
<td></td>
</tr>
<tr>
<td>• Low data protection in many countries</td>
<td></td>
</tr>
</tbody>
</table>
Adapting the process to new needs: finding resistance-breaking herbicides

Early Research
- Ideation for new molecules using latest technologies
- Highly automated screening process
- Mode of action studies

Field Trials
- Testing under realistic conditions (including resistant populations)
- First formulations
- Safety studies

Optimization
- Improve efficacy and spectrum
- Crop selectivity (inherent, safeners, traits – GMO / non-GMO)
- Check activity on resistant weeds
- Primarily greenhouse testing

Launch
- Sales
- Active product stewardship

Development Project
- Development as commercial product
- Product concept testing
- Regulatory studies
- Registration
From Idea to Market – Developing a Crop Protection Product

PHASE 2
- Synthesis
- Process development
- Synthesis optimization
- Pilot plant production
- Formulation/packaging

PHASE 3
- Laboratory/greenhouse
- Profiling & positioning trials
- Efficacy trials for registration

SUBMISSION
- Production optimization
- Application optimization
- Production
- SALES

Active ingredient
- Chemistry
- Formulation
- Research
- Biology
- Development
- Biology
- Metabolism
- Environment
- Residues

Chemistry
- Synthesis
- Process development
- Synthesis optimization
- Pilot plant production
- Formulation/packaging

Toxicology
- Mammals
- Ecosystems
- Metabolism
- Environment
- Residues
- Synthesis
- Process development
- Synthesis optimization
- Pilot plant production
- Formulation/packaging

Environment
- Plants, animals, soil, water
- Soil, water, plants, animals, air
- Profiling & positioning trials
- Efficacy trials for registration
- Acute, sub-chronic, chronic toxicity
- Mutagenicity, carcinogenicity, teratogenicity, reproduction
- Algae, daphnia, fish, birds, microorganisms, bees, non-target organisms

After 12 (10 to 14) years and an average investment of about €250 million, one compound out of 160,000 substances reaches the market.
Target Safety Profile – Safety First already during Herbicide Discovery

License-to-Sell
Product authorization

- fulfillment of all regulatory requirements

License-to-Operate
Societal acceptance

- high level of safety & no relevant damage

Freedom-to-Operate
Competitiveness

- maximum flexibility for positioning & use of products

License-to-Sell

License-to-Operate

Freedom-to-Operate

- LEACHING
- SOIL
- MUTAGENICITY
- PERSISTENCE
- SOIL
- POLLINATOR
- SAFETY
- ACUTE
- TOXICITY
- AQUATIC
- TOXICOLOGY
- ENDOCRINE
- DISRUPTION
How do we sustain the efficacy of new molecules?

**Increasing Farmers’ Profitability**
- Optimize weed control cross rotation to sustain ROI
- Delay and/or minimize consequences of weed resistance
- Preserve the value of the land

**Preserving Farm Environment**
- Water protection – Application technology
- Soil Management
- Weed seed bank reduction

**Improving Farmers’ Livelihood**
- Education on weed control tactics
- Reduce Weed control complexity
- Worker protection: EASYFLOW
….and in future

Robots

Weed Resistance

Digital farming
Thank you!

GHRC Denver, 2017