Some Aspects of Weed Management and Herbicide Safeners

Hans-Joachim Santel
Fall Line Capital Meeting
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1. Introductory comments
2. Integrated Weed Management
3. Dose – Response
4. Herbicide Safening Technology
Topics

1. Introductory comments
2. Integrated Weed Management
3. Dose – Response
4. Herbicide Safening Technology
Different Characteristics in Crops and Weeds

<table>
<thead>
<tr>
<th></th>
<th><strong>Weeds</strong></th>
<th><strong>Crops</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development</strong></td>
<td>• Moderate to rapid growth</td>
<td>• Rapid growth</td>
</tr>
<tr>
<td></td>
<td>• Adapted to <strong>solitary</strong> development</td>
<td>• Adapted to development in dense crop stand (tolerate “crowding”)</td>
</tr>
<tr>
<td></td>
<td>• Highly adaptive to a <strong>wide range</strong> of environmental conditions</td>
<td>• Adapted to <strong>specific</strong> regional environmental conditions (local varieties)</td>
</tr>
<tr>
<td><strong>Reproduction &amp;</strong></td>
<td>• Mature throughout growth period</td>
<td>• Synchronous maturity</td>
</tr>
<tr>
<td><strong>Propagation</strong></td>
<td>• <strong>Variable</strong> seed production</td>
<td>• <strong>Predictable</strong> seed output</td>
</tr>
<tr>
<td></td>
<td>• Germination over <strong>extend time</strong> period</td>
<td>• <strong>Synchronous</strong> germination</td>
</tr>
<tr>
<td></td>
<td>• Extended dormancy</td>
<td>• No dormancy</td>
</tr>
<tr>
<td><strong>Direction of</strong></td>
<td>• Selected by “<strong>nature</strong>” for survival, reproduction and propagation even under extreme natural conditions</td>
<td>• Bred, selected and grown by “<strong>man</strong>” for yield under predictable and often artificially adjusted conditions (fertilization, irrigation, crop protection…)</td>
</tr>
<tr>
<td><strong>selection</strong></td>
<td>• Strive for <strong>survival</strong></td>
<td>• Strive for <strong>yield and uniformity</strong></td>
</tr>
<tr>
<td><strong>“Purpose of life”</strong></td>
<td>• Reproduction</td>
<td>• <strong>Production</strong></td>
</tr>
</tbody>
</table>

Life cycles and development patterns of evolved under almost opposite conditions resulting in different requirements for growth, yield formation and reproduction.
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What is Integrated Weed Management?

The use of all measures, techniques, methods, treatments…. discovered, developed and adopted by mankind since the start of agriculture > 10 000 years ago to successfully deal with weeds infesting crops.
**What is Integrated Weed Management?**

Integrated Weed Management
Principal weed control program that uses a range of integrated control techniques
- physical, chemical, biological
- without reliance on one method only

<table>
<thead>
<tr>
<th>Objectives of IWM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of weed growth</td>
<td>reduce weed pressure&lt;br&gt;decrease competitiveness of weeds&lt;br&gt;maintain weed population below economic threshold</td>
</tr>
<tr>
<td>Prevention or suppression of weed seed production</td>
<td>limit weed spread&lt;br&gt;reduce soil weed seed bank</td>
</tr>
<tr>
<td>Reduction of weed seed reserves in the soil</td>
<td>prevent and manage herbicide-resistant weeds</td>
</tr>
<tr>
<td>Prevention or reduction of weed spread</td>
<td></td>
</tr>
</tbody>
</table>
2 Alternative Approaches

Chemical weed control (straight)

Integrated weed control (wide)

The integrated approach to weed control gives you more options for success.
Important Tactics in Integrated Weed Management

<table>
<thead>
<tr>
<th>Preventive (indirect) approach</th>
<th>Corrective (direct) approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weed control by agronomic measures</td>
<td>Mechanical weed control using tillage equipment</td>
</tr>
<tr>
<td>- soil tillage</td>
<td>- Chemical weed control with (selective) herbicides (maintain diversity)</td>
</tr>
<tr>
<td>- crop rotation</td>
<td></td>
</tr>
<tr>
<td>- seeding date</td>
<td></td>
</tr>
<tr>
<td>- field hygiene</td>
<td></td>
</tr>
<tr>
<td>- other</td>
<td></td>
</tr>
</tbody>
</table>

Integrated Weed Control = Weed Control Triathlon
Steps to Weed Management

- Diagnosis of weed problems (accurate weed ID)
- Decide on weed control measure
- Implementation of weed control program
- Measuring weed control success
Trends in Weed Control

“Pre herbicide era < 1950

Mechanical

Herbicide

Cultural

Current

Herbicide

Mechanical

Cultural

Future

Herbicide

Mechanical

Cultural


Hans-Joachim Santel
Integrated Weed Management
3 Approaches – 7 Ways to Control

- Agronomic weed control (indirect)
  → Change condition for weed development from good to bad

- Non chemical (mechanical) weed control (direct)
  → Rip out and desiccate weeds
  → Cut weeds in pieces
  → Bury weeds under soil

- Chemical weed control (direct)
  → Inhibit one reaction and starve weeds to death
  → Disrupt regulation of development so weeds “grow to death”
  → Trigger formation of aggressive molecules so weeds “commit suicide”
Options for Chemical Weed Control

Number of available active substances is limited
- approx. 300 (292 in 2010) different molecules
- 21 different modes of action
- 23 Bn $ business in 2015
Synergism of cultural practices with suppression of weed biomass in maize and sunflowers

Source: Andersen 2007
Herbicide Selection Checklist

1. Crop → Species, Variety, planned following crop
2. Development stage of crop
3. Soil type
4. Condition / accessibility of field (too wet?)
5. Herbicide history of field
6. Resistance situation
7. Weed flora and development stages present
8. Required weed control spectrum of herbicide
   (→ single product or tank mixture or weed control program)
9. Potential product interactions
10. Selectivity and rotational restrictions of herbicide
11. Weather during 72 h prior to herbicide application and forecast
12. Estimated yield potential
13. Cost / return on investment
Rewards of Integrated Weed Management

Technical
- Sustainable productivity
  - maintain long term fertility of land
  - keep “clean island” without of resistance problems

Financial
- Sustainable profitability
  - keep production cost at optimum over several seasons
  - maintain land value (asset and rental value)
  - avoid devaluation by problem built up

Emotional
- Be a good steward of a property
  - avoid exploitation of resources
Opportunity and Risk

What you can maintain

Herbicide performance in soybeans protected by Integrated Weed Management and Proactive Resistance Management

What you must avoid

Herbicide resistant weed infestation of soybeans to be tackled with Reactive Resistance Management
Maintain diversity
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Dose response of herbicides

What you can control

→ Dose of herbicide in spray tank and on field area

Understanding is needed

What you have to achieve

→ Reach and maintain correct dose at molecular target inside the cells of weeds
### Dose Transfer
From the Spray Tank to the Cellular Target

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Influenced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray droplet formation</td>
<td>Spraying equipment</td>
</tr>
<tr>
<td>Retention</td>
<td>Leaf surface, droplet speed, angle</td>
</tr>
<tr>
<td>Spray deposit &amp; coverage</td>
<td>Leaf surface, formulation, physicochemical properties of herbicide</td>
</tr>
<tr>
<td>Penetration of leaf</td>
<td>Cuticle, waxes, hydration of cell wall, physicochemical properties of herbicide</td>
</tr>
<tr>
<td>Translocation to the cellular target</td>
<td>Xylem &amp; phloem streams, plant metabolism, chemistry of herbicide</td>
</tr>
</tbody>
</table>
Typical Sigmoid Dose Response Curve

Idealistic view of dose response – only valid for one plant at one location at one point in time
Real-Life Situation

- Different weed populations
- Different weed biotypes
- Different weed development stages
- Different crop varieties
- Different locations
- Different conditions (soil, weather, climate…)
- Different agronomic practices (seed bed, planting depth, spraying accuracy, water rate, application timing, plant stages, etc.)
- Difference from year to year

**Result:**

→ Multiple dose/response curves
Real-Life Dose Responses of Populations (= Multiple Individuals)

Result:
Multiple dose-response curves form a dose response range
Simplified Dose-Response Representation

The dose-response curve is a simplification of reality-averaging multiple situations.

Efficacy:
- Over countries
- Conditions
- Multiple populations
- Multiple years

Herbicide supplier → complex view
- high dose recommended

Grower → simple view
- one year
- one field
- one set of conditions
- best dose within label?

Hans Joachim Santel
Never forget on dose rate

- Always observe the principles of Good Agricultural Practice GAP
- Non compliance with product label may
  - eliminate supplier’s product liability
  - result in legal infringements
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Basic Equation of Selective Weed Control

Efficacy on Weeds
+ Crop Tolerance
= Selective Weed Control

Efficacy → Determined by chemical structure of active ingredient(s)
Crop tolerance → Determined by herbicide
Increased by safener

Both parameters can be modulated by formulation (uptake, translocation)
What are Safeners?

Definition
Safeners (also known as antidotes) are synthetic chemicals used worldwide to protect plants from herbicide injury without reducing weed control.

(Hatzios and Hoagland 1989)

- Maintain subtoxic herbicide levels at target site(s) inside crop plants at all times
- It is an „enabling technology“ for herbicides
Commercial Relevance of Safeners

Herbicide world market 16.6 Bn $
Value of safened herbicides 2.1 Bn $

Year: 2012
2.1 Bn $

Crops
- corn 1.3 Bn $
- cereals 0.7 Bn $
- rice 0.1 Bn $

Companies
- Bayer 1.1 Bn $
- Syngenta 0.8 Bn €
- other 0.2 Bn $

Safers, Crops and Companies
Crops Accepting Safeners

- **Cereals**
  - Wheat
  - Barley
  - Rye
  - Triticale
- **Corn**
- **Sorghum**
- **Rice**

- There is no known safener for dicotyledonous crops
**Safener structures**

<table>
<thead>
<tr>
<th>Safener</th>
<th>Crop</th>
<th>Herbicide</th>
<th>Application method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benxanor (CGA 154281)</td>
<td>Maize</td>
<td>Metolachlor</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Cloquintocet-mexyl (CGA 184927)</td>
<td>Wheat</td>
<td>Clodinafop-propyl</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Cymethrin (CGA 45089)</td>
<td>Sorghum</td>
<td>Metolachlor</td>
<td>Seed-treatment</td>
</tr>
<tr>
<td>Dichlorid (DDCA, R25788)</td>
<td>Maize</td>
<td>EPTC, butylate, vernolate</td>
<td>Pre-plant incorporated with herbicide</td>
</tr>
<tr>
<td>Fenchloroazol-ethyl (HOE 70542)</td>
<td>Wheat</td>
<td>Fenoxaprop-ethyl</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Fenclorim (CGA 123407)</td>
<td>Rice</td>
<td>Pretilachlor</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Flurazole (MON 4606)</td>
<td>Sorghum</td>
<td>Atachlor</td>
<td>Seed-treatment</td>
</tr>
<tr>
<td>Flurofuran (CGA 133205)</td>
<td>Sorghum</td>
<td>Metolachlor</td>
<td>Seed-treatment</td>
</tr>
<tr>
<td>Flumazin (MON 13900)</td>
<td>Cereals</td>
<td>Halosulfuron-methyl</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Mefenapry-diethyl</td>
<td>Wheat, rye, triticale, barley</td>
<td>Fenoxaprop-ethyl</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>MG 191</td>
<td>Maize</td>
<td>Thiocarbamates</td>
<td>Spray as mixture with herbicide</td>
</tr>
<tr>
<td>Naphthalic anhydride (NA)</td>
<td>Maize</td>
<td>EPTC, butylate, vernolate</td>
<td>Seed-treatment</td>
</tr>
<tr>
<td>Oxabenztrinil (CGA 92194)</td>
<td>Sorghum</td>
<td>Metolachlor</td>
<td>Seed-treatment</td>
</tr>
</tbody>
</table>

13 safeners
7 different crops
# Examples of Important Safener/Herbicide Combinations

<table>
<thead>
<tr>
<th>Herbicide</th>
<th>Safener</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodinafop</td>
<td>Cloquintocetmexyl</td>
</tr>
<tr>
<td>Fenoxaprop</td>
<td>Mefenpyr</td>
</tr>
<tr>
<td>Foramsulfuron / Iodosufuron</td>
<td>Isoxadifen or cyprosulfamide</td>
</tr>
<tr>
<td>Iodosulfuron</td>
<td>Mefenpyr</td>
</tr>
<tr>
<td>Isoxaflutole</td>
<td>Cyprosulfamide</td>
</tr>
<tr>
<td>Mesosulfuron</td>
<td>Mefenpyr</td>
</tr>
<tr>
<td>Pretilachlor</td>
<td>Fenclorim</td>
</tr>
<tr>
<td>Pyrasulfotole</td>
<td>Mefenpyr</td>
</tr>
<tr>
<td>S-Metolachlor</td>
<td>Benoxacor</td>
</tr>
<tr>
<td>Tembotrione</td>
<td>Isoxadifen</td>
</tr>
<tr>
<td>Thiencarbazole</td>
<td>Cyprosulfamide or mefenpyr</td>
</tr>
</tbody>
</table>
Effect of Safener on Cellular Herbicide Concentration

Safeners limit herbicide to safe concentration in cell

Herbicide concentration in plant cell

Concentration limit for crop damage

No safener – crop safety not assured

With safener – full crop safety

Herbicide application

Time
Three Hypotheses for Safening

- Pre-requisite: Safeners must enter the plant

1. Safeners act as herbicide antagonists at the site of action (no evidence found)

2. Safeners interfere with uptake and translocation of herbicides to the site of action in the cell (no evidence found)

3. Safeners induce herbicide metabolism (strongly supported by evidence)
Herbicide Binding to Cell Components

Degradation = Crop safety

Storage (sequestration)

Vacuole

Target

Herbicide Activity = Weed control Crop Damage

Bound to other cell components

Desired for crop safety, enhanced by safeners

Herbicide Activity = Weed control Crop Damage

Degradation enzyme

Binding

non-target
Safeners act as **signals** to stimulate the activity of the herbicide metabolizing systems, **not as reaction partners** in herbicide metabolism.

- No stoichiometric safener herbicide/relationship
- Safening may continue without safener presence
Herbicide Safener Action: Safeners Boost Metabolism

**Safeners:**
- Must be taken up in the plant to be effective
- Are used for soil and foliar herbicides
- Act as inductors and activators of herbicide degradation enzymes in crop plants
- Are unique chemicals that cause the plant to produce more degradation enzymes
Herbicide Safener Action: Safeners Trigger Biochemical Pathways

- **Important safener-activated enzyme systems include:**
  - **Cytochrome P 450 mixed functional oxygenases (P450 system)**
    - introduces oxygen atoms into herbicide metabolites as receptor points, for example for sugar resulting in herbicide inactivation.
  - **Glutathion-S-transferases (GSH system)**
    - inactivates herbicides by the attachment of the tripeptid glutathion to the herbicide molecules before the complexes are cleaved into next-order metabolites.
  - **UDP-dependent glycosyl transferases**
    - attach glucose to metabolites
  - **Transmembrane carriers**
    - move metabolites into the vacuole
Biotransformation of Herbicides Resulting in Inactivation Scheme 1

- **Conversion**
  - Removal of substituents
  - Cleavage of complex systems

- **Conjugation(s)**
  - Attachment of GSH, amino acids, sugars...

- **Compartmentation**
  - Removal to vacuole, cell wall, lignin...
  - NER

- **Vacuole**

- **Conjugation with other cell components**

- **P 450 - Oxidations**
  - Reductions
  - Hydrolyses

- All three steps are stimulated by safeners
Possible Chain of Events

Safener

Unknown signaling chain (oxylipins, jasmonic acids) \(\downarrow\) Gene activation (promotor/repressor interaction?)

Induction of gene expression

Herbicide metabolism

Herbicide detoxification

Herbicide tolerance

Source: Riechers et al 2010 modified by Santel
# Application of Safeners

<table>
<thead>
<tr>
<th>Application</th>
<th>Safener product</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Seed treatment               | Single product                 | *Naphthalic anhydride*  
|                              |                                | *Fluoxofenim*                   |
| Pre-emergence spray          | Co-formulation with herbicide  | *Benoxacor*  
|                              |                                | *Cyprosulfamide*                |
| Post-emergence spray         |                                | *Mefenpyr*  
|                              |                                | *Isoxadifen*  
|                              |                                | *Cloquintocet*  
|                              |                                | *Cyprosulfamide*                |
Extension of Safening Activity to Tank-Mix Partner in Corn

Dicamba + other bleacher, no safener

Corn leaves are rolled and stand upright

Dicamba WG + LAUDIS, safener included

Perfect crop tolerance – no damage symptoms
Safening: Pre-Emergence Application

Safening of corn on light soil after a pre-emergence herbicide application

Including safener:
IFT + safener CSA
+ atrazine
(100 + 1000 g ai/ha)

No safener:
IFT + atrazine
(100 + 1000 g ai/ha)
Safening: Post-Emergence Application

Safening of corn after a post-emergence herbicide application

Unsafened Thiencarbazone

Thiencarbazone + Cyprosulfamide
Key Points from Herbicide Safening

• **Safeners:**
  - Protect crops from herbicide damage by boosting herbicide metabolism
    - more application flexibility \(\rightarrow\) wider usage window
    - safe on variable soils
    - safening may extend to tank-mix partners and result in “cross-safening”
      - may add more crops to selectivity list
  - May broaden the herbicide choice in a crop
  - May ensure selectivity of highly active herbicides
  - Increase probability of success in search for new herbicides
Potential for More

- Safeners stimulate metabolic systems developed by nature to manage/mitigate chemical stress from xenobiotics

  → anecdotal reports of positive impact under environmental stress conditions
  → evidence of activation of genes outside detoxification pathways
Physiological Effects of Cyprosulfamide

Presently 42 different sites of activity of CSA are identified in the cells of the target crop maize.

- Approx. 2/3 are related to herbicide metabolism → securing crop tolerance
- Approx. 1/3 are related to other metabolic pathways → further beneficial effects

Realization of yield & Securing of yield
Further Remarks on Safeners

• Require full regulatory package/development investment → added (double) cost

• Only added if herbicide alone is not sufficiently selective → crop tolerance risk

• Risk of separation of safener and herbicide after application → insufficient safener performance
The Opposite

• Safeners,

there is also the opposite. Molecules that block or reduce the breakdown of herbicides in plants.

→ Synergists
Modulation of Herbicide Activity

Herbicide → Metabolising enzymes → Herbicide metabolites → No crop damage

Safeners

Synergists

Weed control
Simplistic Total Picture

Safeners contribute to mitigation of
→ herbicide & other chemical stress
→ potentially of other forms of stress

Synergists maintain herbicide stress