Resisting resistance: Incorporation and preservation of SDHI fungicides for disease management

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February 2, 2017
# SDHI Fungicides: A Brief History

<table>
<thead>
<tr>
<th>Target site/code</th>
<th>Group name</th>
<th>Chemical Group</th>
<th>Common Name</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>C2: complex II:</td>
<td>SDHI (Succinate dehydrogenase inhibitors)</td>
<td>phenyl-benzamides</td>
<td>benodani, fluotolanil, mepronil</td>
<td>Resistance known for several fungal species in field populations and lab mutants. Target site mutations in sdh gene, e.g. H/Y (or H/L) at 257, 267, 272 or P225L, dependent on fungal species. Resistance management required. See FRAC SDHI Guidelines for resistance management.</td>
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<td>phenyl-oxo-ethyl thiophene amide</td>
<td>isofetamid</td>
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<td>pyridinyl-ethyl-benzamides</td>
<td>fluopyram</td>
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<td>furan-carboxamides</td>
<td>fenfuram</td>
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<td>oxathiin-carboxamides</td>
<td>carboxin, oxycarboxin</td>
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<td>thiazole carboxamides</td>
<td>thifluzamide</td>
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<td>pyrazole-4-carboxamides</td>
<td>bensovindiflupyrbixafen, fluxapyroxad, furametpyr, isopyrazam, penfluven, penthopyrad, sedaxane</td>
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<td>N-methoxy-(phenyl-ethyl)-pyrazole-carboxamides</td>
<td>pydfluometofen</td>
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<td>pyridine-carboxamides</td>
<td>boscald</td>
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SDHI Fungicides: A Brief History

• 50 years ago: First SDHI product (carboxin) released for seed treatments
  – Very limited m.o.a (mushrooms and smuts)

• 1971-1997: 6 additional SDHI fungicides
  – Still very narrow spectrum

• 2003: Boscalid hits the market
  – Endura, Pristine (+ pyraclostrobin)
  – Broad spectrum, foliar disease
SDHI Fungicide Overview

• “Next generation” Succinate Dehydrogenase Inhibitor fungicides
  – New spin on an old chemistry

• FRAC 7
  – 9 chemical groups
  – Standalone and pre-mix products for tree fruit disease control
  – Extremely broad spectrum (no oomycetes yet)

- Pristine
  - boscalid

- Merivan
  - fluxapyroxad

- Aprovia
  - benzovindiflupyr

- DuPont Fontellis
  - pentaerythrpyrad

- Luna SENSATION
- Luna TRANQUILITY

- ISK
  - isofetamid

- fluopyram
SDHI Fungicide Overview

- **SDHI fungicides**: Respiration inhibitors: Target succinate dehydrogenase reductase enzyme
  - 4 subunits

QoI fungicides

Intermembrane space

Mitochondrial matrix

NADH $\rightarrow$ NAD$^+$

$\text{O}_2 \rightarrow H_2O$

AOX

Qo

$Q_i$

$\text{O}_2 \rightarrow H_2O$

ADP+Pi $\rightarrow$ ATP

SDHC

SDHD

SDHB

SDHA
• Multiple opportunities for mutation
  – Many SDHI fungicide interactions within binding pocket
SDHI Fungicide Overview

- Complete or partial resistance?
  - SDHI fungicide or chemical group
  - Mutation location & substituting residue: Fitness cost
  - # of mutations
  - Pathogen species

SDHC and SDHD: Very different across different fungi

- H134R
- T90I
- S135R
- H133R/P/T
- D123E
- T28A
- H272Y/R/L
- P225L/F/T
- N230I
Questions Surrounding the SDHIs

- Are all similarly effective against specific tree fruit pathogens?
- What growth stage should we be targeting?
  - Protectant/germination? Curative/mycelial growth inhibition?
- Is there cross-sensitivity between SDHI fungicides?

*In vitro studies (completed in lab with Venturia inaequalis)*

- How do SDHI fungicides perform with fungal populations resistant to other single-site fungicide classes (i.e. QoI, DMI)
- What is the risk of resistance development among the SDHI fungicides?
Question 1: Efficacy of SDHI Fungicides

Lesion wash-dislodge conidia

10^3-10^4 conidia/ml

7 days

SDHI fungicide

PDA ++

% Rel. Inhibition

SDHI fungicide &

SDHI fungicide

PDA ++
Baseline Fungicide Sensitivity: Apple Scab

- Conidial germ tube growth inhibition assay
  - Protective mode-targets conidial germination/germ tube elongation
- 2012-2014: 105 (70) baseline V. inaequalis isolates collected

<table>
<thead>
<tr>
<th>Round 1 (n = 35)</th>
<th>Round 2 (n = 35)</th>
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<tr>
<td>Penthio pyrad (Fontelis)</td>
<td>Benzovindiflupyr (Aprovia)</td>
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<td>Fluopyram (Luna)</td>
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- EC$_{50}$ values using 11 SDHI fungicide concentrations (0.0001 to 10 µg ml$^{-1}$)
SDHI Baseline Sensitivity: Conidial Inhibition

- Benzovindiflupyr (Aprovia) demonstrated highest level of activity during initial growth stages
  - Enhanced interaction with A.A. residues inside binding pocket?
SDHI Baseline Sensitivity: Conidial Inhibition

- Similar and significant levels of cross-sensitivity observed between penthiopyrad or benzovindiflupyr and fluopyram = Cross resistance between fungicides?

- Role of mutations within different subunits in SDHI sensitivity?
  - *A. alternata, D. bryoniae, C. cassicola, and P. xanthii*
SDHI Baseline Sensitivity: Mycelial Inhibition

- Mycelial growth inhibition assay
  - Curative/kick-back mode
  - Benzovindiflupyr & fluopyram only
- 2012-2014: 105 (35) baseline V. inaequalis isolates collected
  - measured biweekly for 6 weeks

\[
\text{EC}_{50} \text{ values benzovindiflupyr (µg ml}^{-1}\) \\
0.00 \quad 0.05 \quad 0.10 \quad 0.15 \quad 0.20 \\
0.0 \quad 0.5 \quad 1.0 \quad 1.5 \quad 2.0 \quad 2.5 \quad 3.0
\]

\[
\text{EC}_{50} \text{ values fluopyram (µg ml}^{-1}\) \\
0.00 \quad 0.05 \quad 0.10 \quad 0.15 \quad 0.20 \\
0.0 \quad 1.0 \quad 2.0 \quad 3.0 \quad 4.0 \quad 5.0
\]

week 2
- \( r = 0.48 \)
- \( P = 0.004 \)

week 6
- \( r = 0.93 \)
- \( P < 0.0001 \)
SDHI Baseline Sensitivity Summary

SDHI fungicides can inhibit both conidial germ tube growth and mycelial growth however greater efficacy during early growth stages

- Benzovindiflupyr EC\textsubscript{50}: 0.002 vs. 0.043 µg/ml
- Fluopyram EC\textsubscript{50}: 0.176 vs. 2.02 µg/ml

Higher energy requirements during different growth stages?

Greatest control when applied in protective mode?

Cross-sensitivity observed across SDHI chemical groups, but more apparent during later stage mycelial growth
Questions Surrounding the SDHIs

- Are all similarly effective against specific tree fruit pathogens?
- What stage of growth should we be targeting?
  - Protectant/germination? Curative/mycelial growth inhibition?
- Is there cross-sensitivity between SDHI fungicides?

How do SDHI fungicides perform with fungal populations resistant to other single-site fungicide classes (i.e. QoI, DMI)?

What is the risk of development for resistance among the SDHI fungicides?
2015 SDHI Efficacy Trial

- Mature orchard site of paired ‘Empire’ and ‘Jonagold’ trees on M.9/M.111 interstem
- *V. inaequalis* population resistant to DMIs (2010) and QoIs (2011); no confirmed SDHI resistance
  - Applied dilute to run-off w/handgun sprayer (200psi)
  - Dodine, DMIs, QoIs, SDHIs, protectants
Primary apple scab infections still occurring mid- late June: high incidence in general

SDHI/QoI premix products: lower incidence of apple scab on leaf terminals
SDHI Efficacy Trials: Apple Scab

SDHI fungicide efficacy: Mature fruit

- No difference in apple scab incidence on fruit between stand alone SDHI and SDHI/QoI premix
  - Aprovia (benzovindiflupyr) exception
• Aprovia: Best for apple scab, among worst against powdery mildew
SDHI Efficacy Trials: *Colletotrichum* spp.

- Cabrio (Pyraclostrobin, Group 11) and Merivon provided greater control against fruit rot caused by *Colletotrichum* at harvest and post-harvest compared to Sercadis (fluxapyroxad, Group 7)
Questions Surrounding the SDHIs

- Are all similarly effective against specific tree fruit pathogens?
- What stage of growth should we be targeting?
  - Protectant/germination? Curative/mycelial growth inhibition?
- Is there cross-sensitivity between SDHI fungicides?

How do SDHI fungicides perform with fungal populations resistant to other single-site fungicide classes (i.e. QoI, DMI)

- What is the risk of development for resistance among the SDHI fungicides?
Mitigating SDHI Resistance: What We Know

• Mutation #, location, and SDHI active ingredient can all affect resistance level (partial resistance vs. complete)

• Cross-resistance has been observed across some SDHIs and not others
  • Depends on where mutation is: Mutation in SDHC subunit may result in cross-resistance between 2 SDHI fungicides, but mutation in SDHB may only confer resistance to one of those fungicides:
  • Pre-selection and multiple applications
Mitigating SDHI Resistance

• Apply fungicides when fungal population numbers are low-apply before infection when possible

OR

• Use highest legal rates of fungicide

• Get complete coverage of host, make sure sprayer is calibrated, avoid ARM
Mitigating SDHI Resistance

• Apply fungicides in tank mixture with effective, unrelated fungicides
  – i.e. Mancozeb + Fontelis: Mancozeb should “clean up” any resistant “survivors”
Mitigating SDHI Resistance

• Use correct SDHI fungicide for target pathogen
  • Be aware that SDHI fungicide may not be efficacious against other major pathogens (Aprovia: apple scab and powdery mildew)

• Rotate and be careful of promoting pre-mix partner resistance (QoI)
Acknowledgements and Questions?

• State, federal, and institutional funds appropriated to the Cornell NYSAES and to NCSU, NYSAES

• Agrichemical company support through product testing
  – Bayer, BASF, Syngenta, DuPont

• Summer Crew