Fungicide resistance theory: how best to preserve the longevity of our fungicide classes

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Questions

- Are there FRAC groups where resistance develops more quickly (e.g. 2,3,7, & 9)?
- If we have resistance/decreased efficacy to FRAC group 11 or 9, is it ok to include these for other diseases?
- Should we take a year off from using a certain FRAC group if the population is resistant or shifting towards resistance?
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Do some FRAC groups where develop resistance more quickly?

- Higher risk: single target-site genes & SNPs in the binding site that confer resistance
- Final code list: www.frac.info. lists relative risks
- High risk 11 (QoI) & Medium High 2 (iprodione) and 7 (SDHI) – single mutations
- Medium risk 3 & 9 (DMI & AP) – Multiple or Unknown
- Low to medium: 12 (fludioxonil) & 17 (fenhexamid)

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C3 complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site *(cyt b gene)*	**QoI**-fungicides (**Q**uinone **o**utside **I**nhibitors)	methoxy-acrylates	azoxystrobin coumoxystrobin enoxastrobin flufenoxystrobin picoxystrobin pyraoxystrobin	Resistance known in various fungal species. Target site mutations in cyt b gene (G143A, F129L) and additional mechanisms. Cross resistance shown between all members of the QoI group. **High risk.** **See FRAC QoI Guidelines for resistance management.**	11
		methoxy-acetamide	mandestrobin		
		methoxy-carbamates	pyraclostrobin pyrametostrobin triclopyricarb		
		oximino-acetates	kresoxim-methyl trifloxystrobin		
		oximino-acetamides	dimoxystrobin fenaminstrobin metominostrobin orysastrobin		
		oxazolidine-diones	famoxadone		
		dihydro-dioxazines	fluoxastrobin		
		Imidazolinones	fenamidone		
		benzyl-carbamates	pyribencarb		

Do some FRAC groups where develop resistance more quickly?

- Medium -site genes & e that confer re

MOA	TARGET SITE AND CODE	GROUP NAME	CHEMICAL GROUP	COMMON NAME	COMMENTS	FRAC CODE
Sterol biosynthesis in membranes	G1 C14- demethylase in sterol biosynthesis *(erg11/cyp51)*	**DMI**-fungicides (**DeM**ethylation **I**nhibitors) (SBI: Class I)	piperazines	triforine	There are big differences in the activity spectra of DMI fungicides. Resistance is known in various fungal species. Several resistance mechanisms are known incl. target site mutations in cyp51 (erg 11) gene, e.g. V136A, Y137F, A379G, I381V; cyp51 promotor; ABC transporters and others. Generally wise to accept that cross resistance is present between DMI fungicides active against the same fungus. DMI fungicides are Sterol Biosynthesis Inhibitors (SBIs), but show no cross resistance to other SBI classes. **Medium risk.** **See FRAC SBI Guidelines for resistance management.**	3
			pyridines	pyrifenox pyrisoxazole		
			pyrimidines	fenarimol nuarimol		
			imidazoles	imazalil oxpoconazole pefurazoate prochloraz triflumizole		
			triazoles	azaconazole bitertanol bromuconazole cyproconazole difenoconazole diniconazole epoxiconazole etaconazole fenbuconazole fluquinconazole flusilazole flutriafol hexaconazole imibenconazole ipconazole metconazole myclobutanil penconazole propiconazole simeconazole tebuconazole tetraconazole triadimefon triadimenol triticonazole		
			triazolinthiones	prothioconazole		

Do some FRAC groups where develop resistance more quickly?

- Lower risk: unknown target-site genes & potential multiple gene/mutations needed

synthesis	**D1** methionine biosynthesis (proposed) *(cgs gene)*	**AP -** fungicides (**A**nilino-**P**yrimidines)	anilino-pyrimidines	cyprodinil mepanipyrim pyrimethanil	Resistance known in *Botrytis* and *Venturia*, sporadically in *Oculimacula*. **Medium risk.** **See FRAC Anilinopyrimidine Guidelines for resistance management.**	**9**

E2 MAP/Histidine-Kinase in osmotic signal transduction *(os-2, HOG1)*	**PP**-fungicides (**P**henyl**P**yrroles)	phenylpyrroles	fenpiclonil fludioxonil	Resistance found sporadically, mechanism speculative. Low to medium risk. Resistance management required.	**12**

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- **Cross-resistance** – resistance to multiple fungicides that share the same biochemical mode of action or target site
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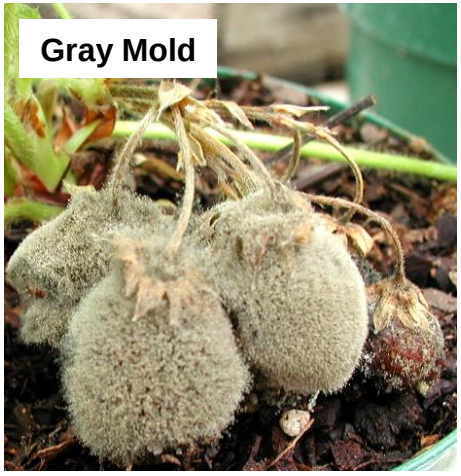
Apple Scab

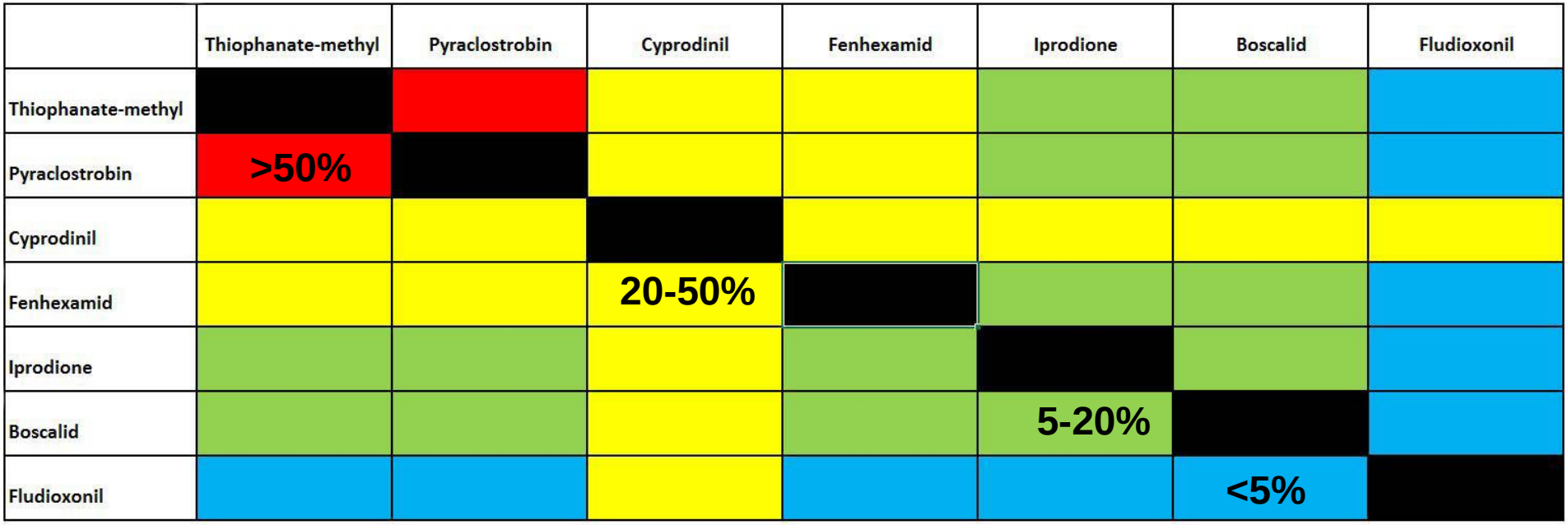

Gray Mold

Multiple fungicide resistance *Botrytis cinerea* on strawberry

- 213 commercial strawberry field 11 Eastern US states (2011 to 2104)
- Growers subscribed to fungicide resistance testing service & followed resistance management recommends over four seasons
- Frequency of MFR isolates increased after 4 seasons
- Frequency of isolates with resistance to 3 – 7 classes of fungicides increased

Selection by Association

Logistic Regression Analysis of 2130 *Botrytis* isolates from Eastern US



Hu, Cox, and Schnabel, Phytopathology 106:1513-1520

Selection by Association

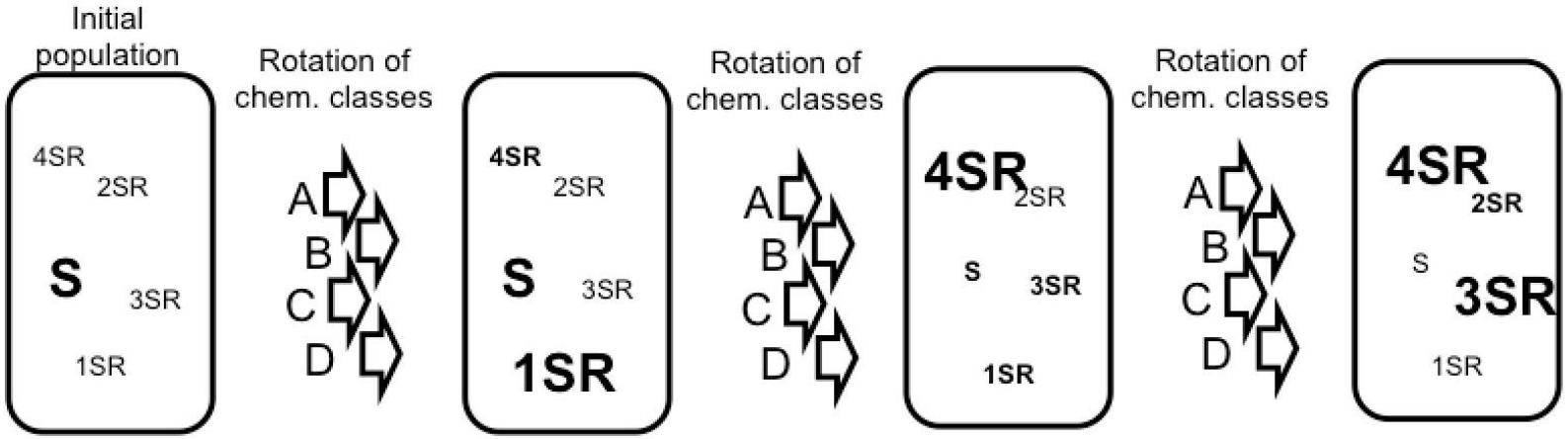


Figure x. Simplified model of 'Selection by Association'. The model assumes that 1SR to 4SR isolates are already present at low frequencies in the initial population. The rotation of fungicides belonging to chemical classes A, B, C, or D would most strongly select for 4SR isolates. Font 12 not bold = very low frequency; Font 12 bold = low frequency; Font 18 bold = significant proportion of the population; Font 24 bold = main proportion of the population.

Hu, Cox, and Schnabel, Phytopathology 106:1513-1520

Resistance to FRAC 11 & 9 is less effective in SLB; ok to use for other diseases?

- What should we do about *Botrytis* or *SLB*?
- Do not use Group 1 (benzimidazoles) & minimize Group 11 (QoI) fungicides use (2x)
- Use fenhexamid (Elevate) and group 9 (AP) (Scala) sparingly (3x)
- Consider iprodione (Rovral), new group 7 SDHIs (Secardis over boscalid) & Fludioxonil (Switch)

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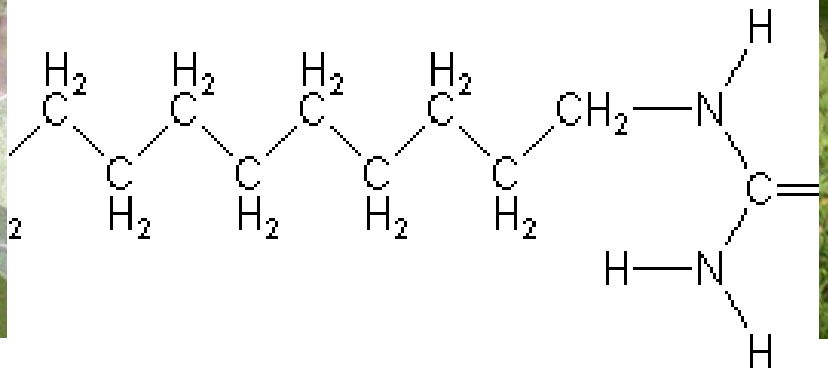
Should we take a year off from a FRAC group if it is gone or shifting?

- Single-site fungicide: FRAC Code: U12
  - Dodine: guanidines (1957)
  - Activity against certain fungi (e.g. apple scab & cherry leaf spot
  - **Mode of action**: Cell disruption (proposed)


Apple Scab

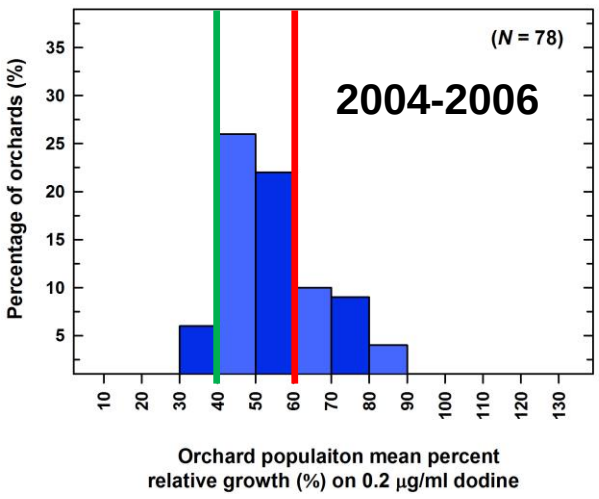


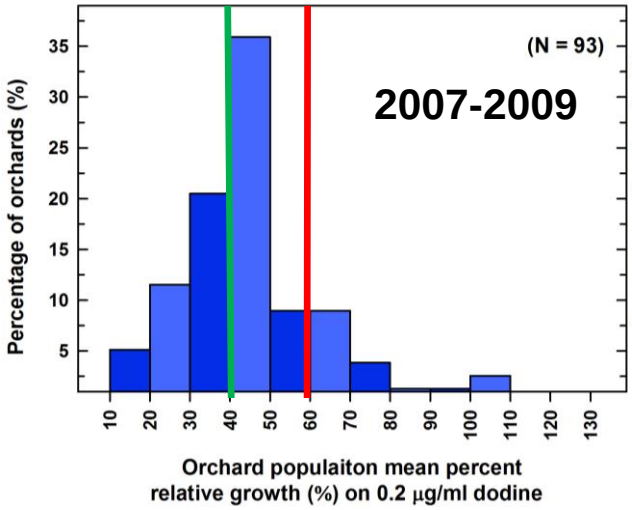

Cherry Leafspot

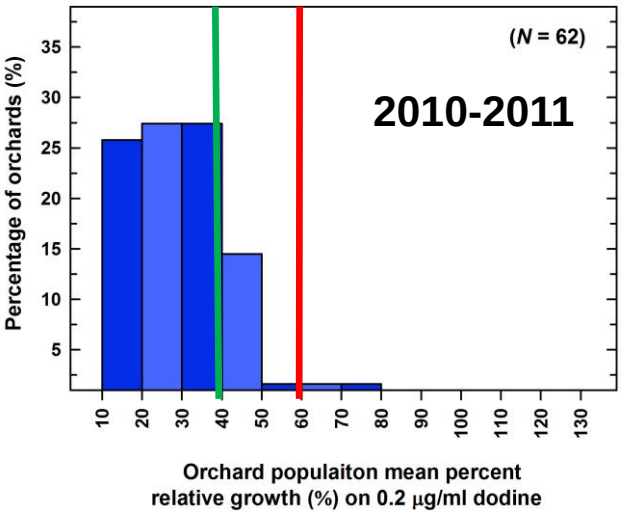
Should we take a year off from a FRAC group if it is gone or shifting?

- History of dodine resistance
  - Mechanism of resistance (quantitati
  - 1969 reported for apple scab (*Vent* *inaequalis*) – widespread in 1970s (
  - 2000 NY and MI – spot checking/still R


Cherry Leafspot







Should we take a year off from a FRAC group if it is gone or shifting?

- What about SLB and Group 11 or 9
  - Dodine quantitative: slow selection slow recovery?
  - Group 9 (APs) Scala – give it 20 years
  - QoI's qualitative – whole population complete resistance quickly
  - Group 1 (benzimidazoles) qualitative (point mutation). Resistance stable > 30 years with no use w/ apples in Geneva
  - **Catch it before whole population resistant**

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Is it better to rotate after one week or after two sequential sprays?

- Changes seem to happen on seasonal or multi year time scale
  - Rotating every week – may not see differences

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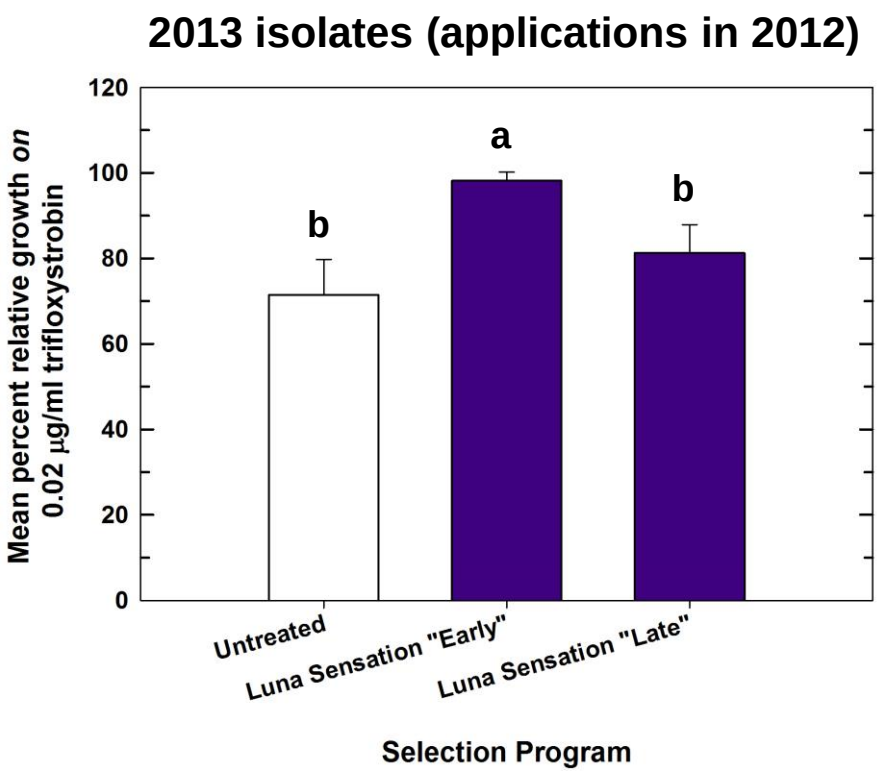
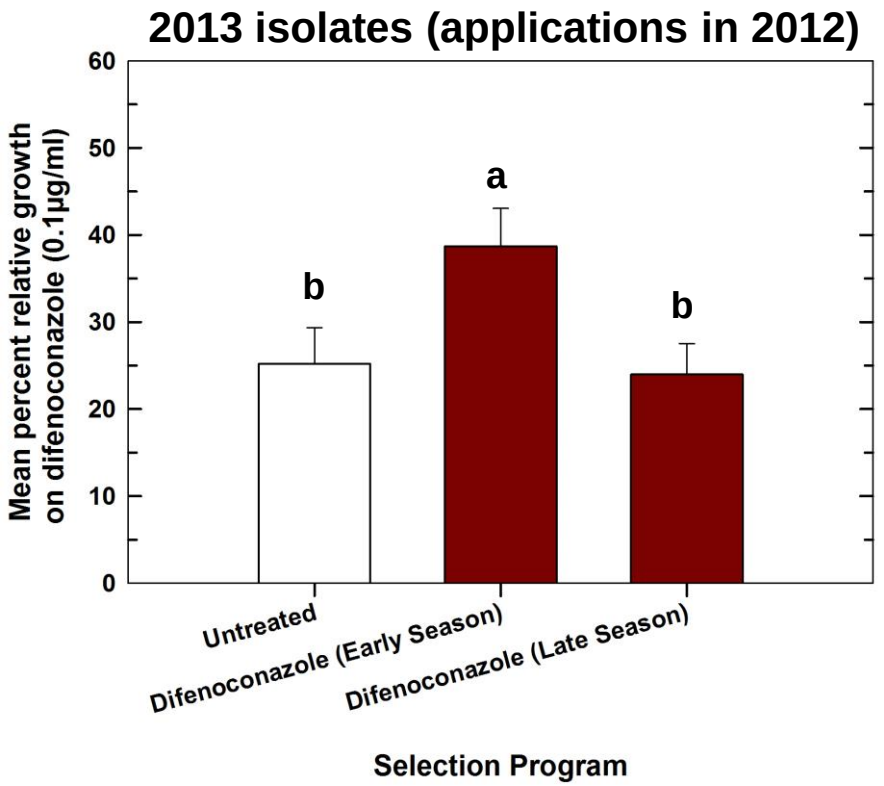
- Applications during high disease pressure period > greater selection?





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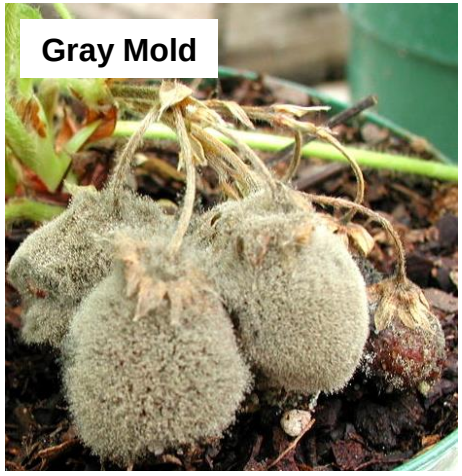

Gray Mold

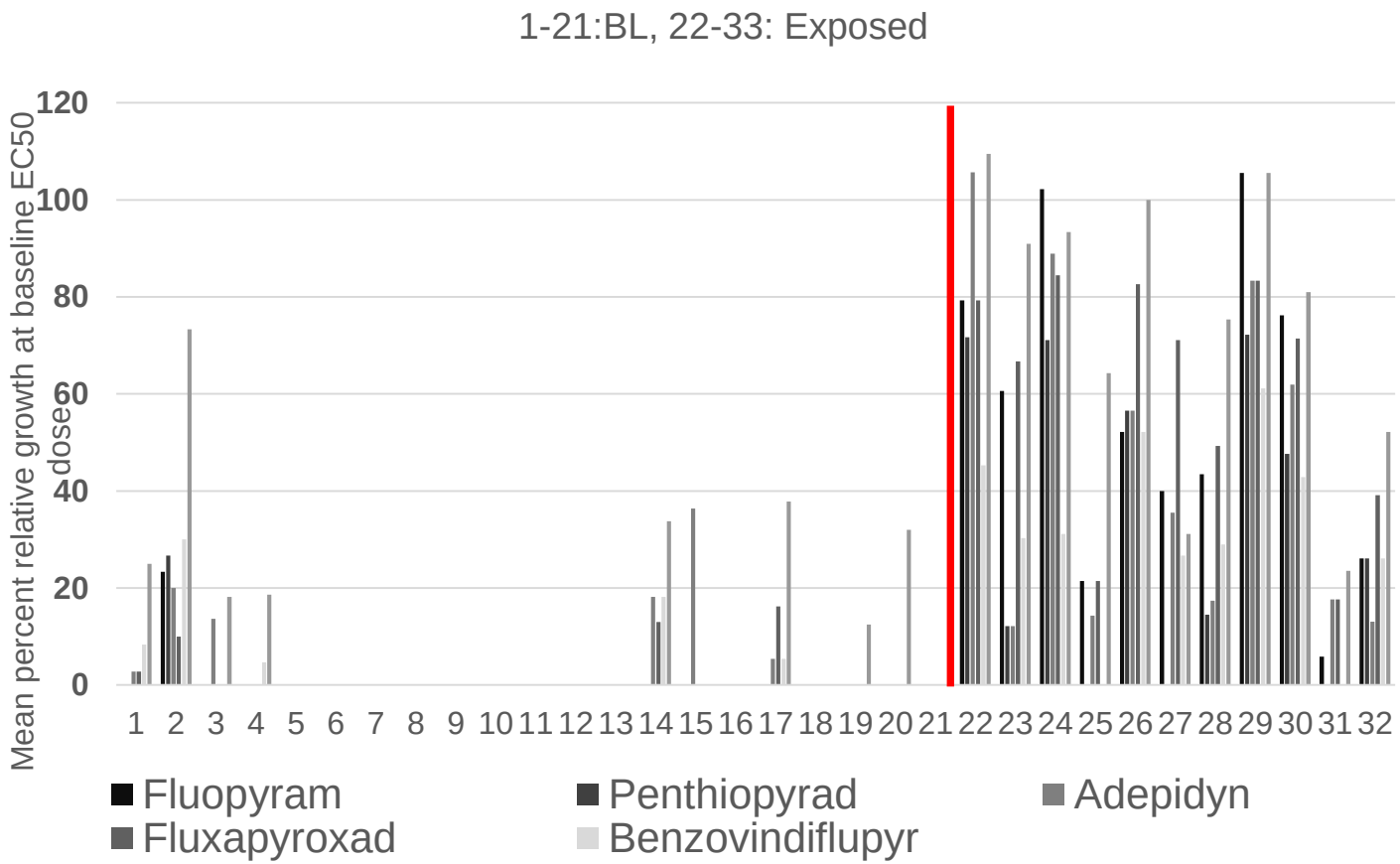
What is the risk of cross-resistance in FRAC group 7 fungicides?

- Common mode of action > cross-resistance is assured, but each fungicide > different affinity for the target site

- Baseline of group 7 fungicides in *V. inaequalis* > germinating conidia vs mycelium
  - Penthiopyrad EC50: 0.086 vs. 0.66 µg/ml
  - Adepidyn EC50: 0.0037 vs. 0.062 µg/ml
  - Benzovindiflupyr EC50: 0.002 vs. 0.057 µg/ml
  - Fluxapyroxad EC50: 0.028 vs. 0.228 µg/ml
  - Fluopyram EC50: 0.176 vs. 2.02 µg/ml

Cross-sensitivity in FRAC group 7 fungicides?

Exposed isolates have higher RGs than baseline > multi-drug efflux pumps (MDEPs)?



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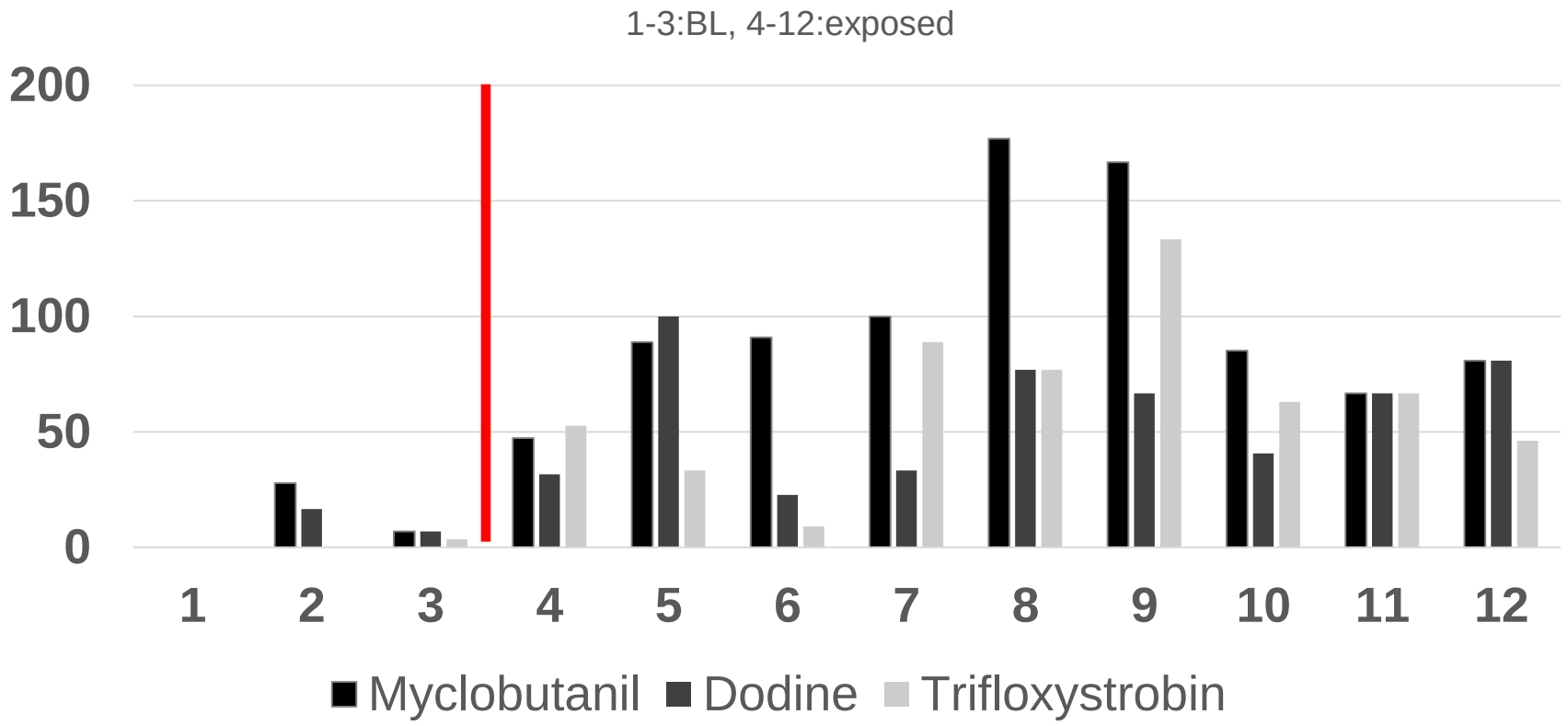
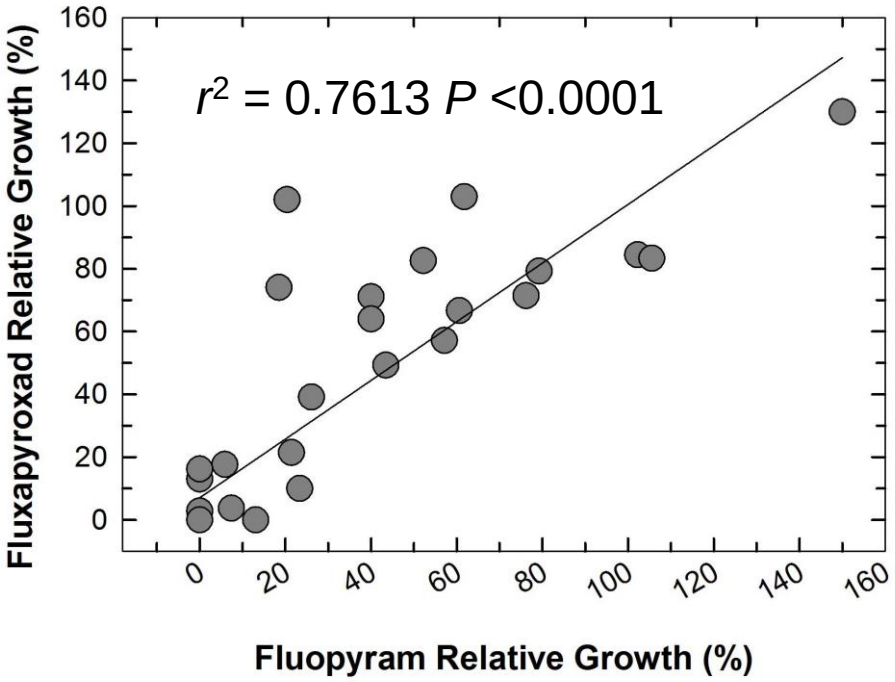
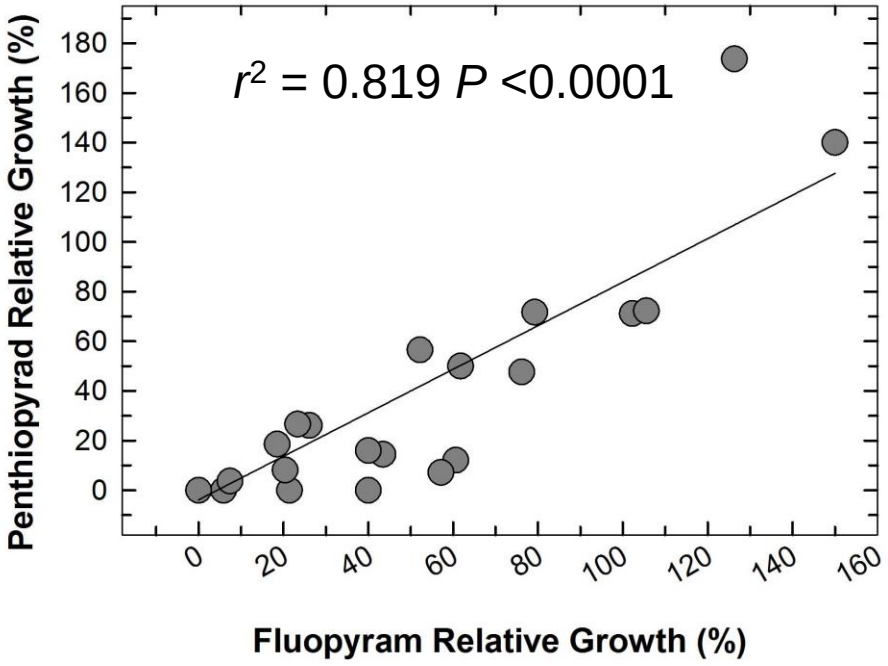


Cross-sensitivity in FRAC group 7 fungicides?

As insensitivity goes up to one group 7, it is mirrored in another





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Are lower or higher rates and mixtures better for resistance management?

- **Treatments**
  - **Control** (no fungicides)
  - **SDHI low dose** (Sercadis®: fluxapyroxad 26g a.i./A)
  - **SDHI high dose** (Sercadis®: fluxapyroxad 54g a.i./A)
  - **SDHI & single-site** (Merivon®: fluxapyroxad 26g a.i./A + pyraclostrobin 26g a.i./A)
  - **SDHI & multi-site** (Sercadis®: fluxapyroxad 26g a.i./A & Mancozeb 75 - 1kg a.i./A)

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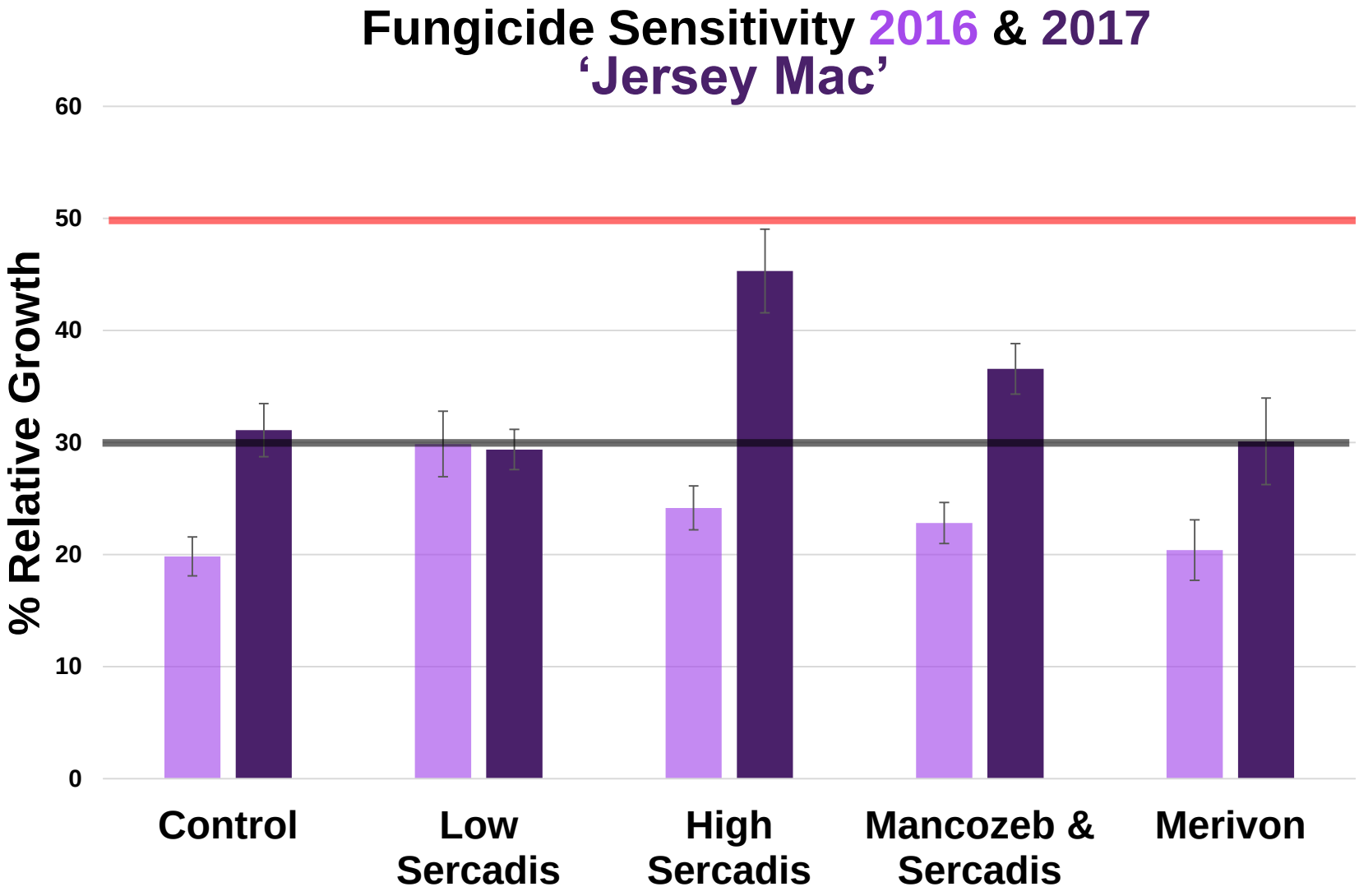

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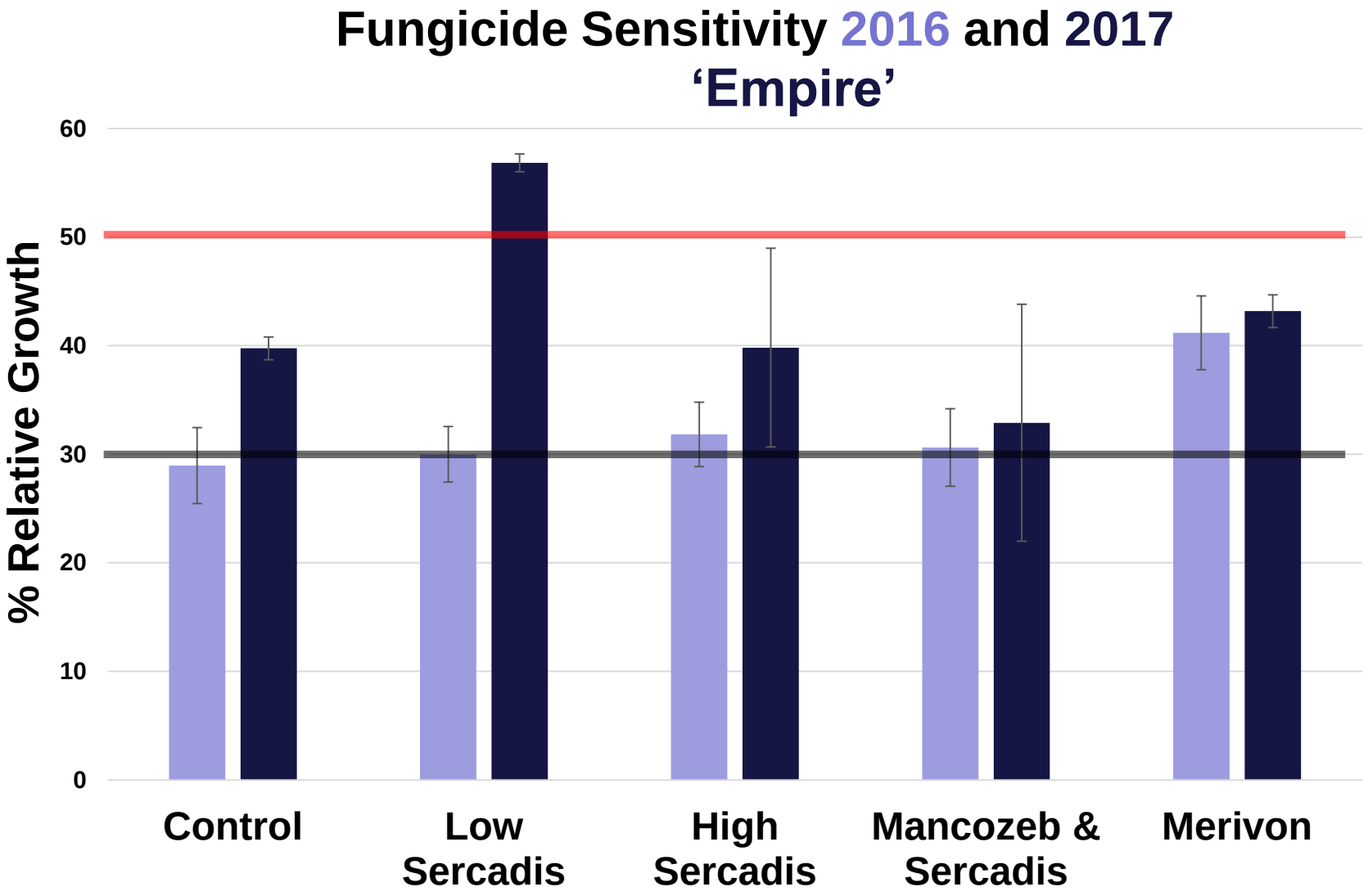

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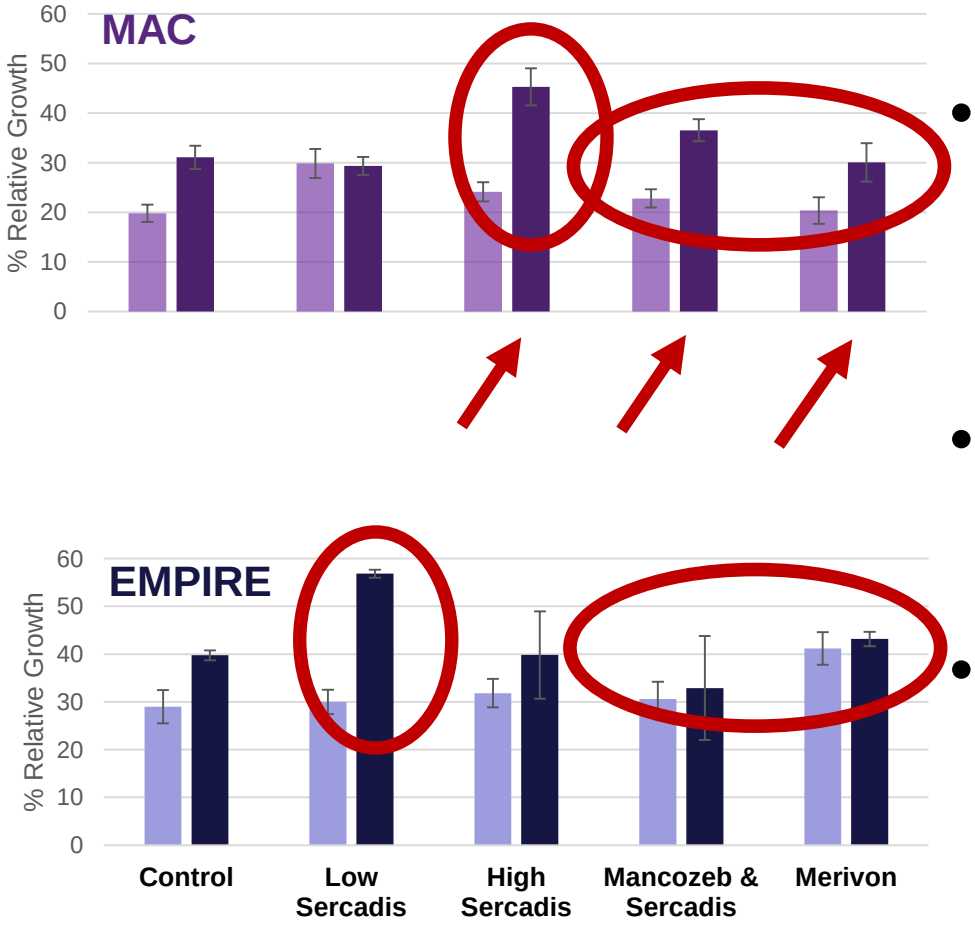
To Do: Repeat for 3rd - 4th year



- RG increases between 2016 & 2017: weather & pressure
- SDHIs alone: Dose independent?
- Importance of mixing w/single vs multi site

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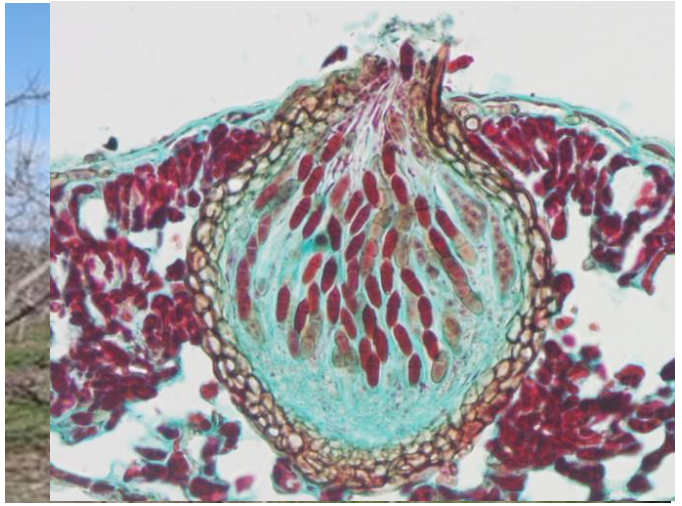
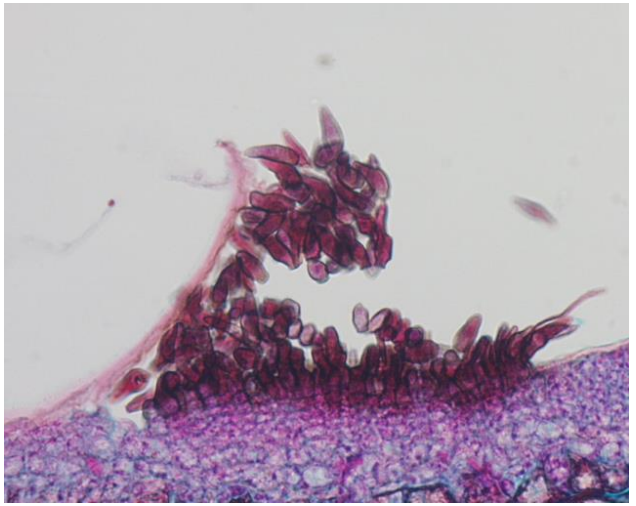
Does it matter what my neighbor is spraying?

- Overwinters: infected leaf litter
- Infection: ascospores from leaf litter
- Secondary spores on infected leaves spread infection to other leaves
- Spread is local & management is site-specific



Pseudothecium of ***Venturia inaequalis***



Acervulis of ***Venturia inaequalis***

Acknowledgements

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Questions