METABOLISM-BASED HERBICIDE RESISTANCE: WHY SHOULD WE BE AFRAID?

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MORE THAN MEETS THE I

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Indiana Certified Crop Adviser Conference
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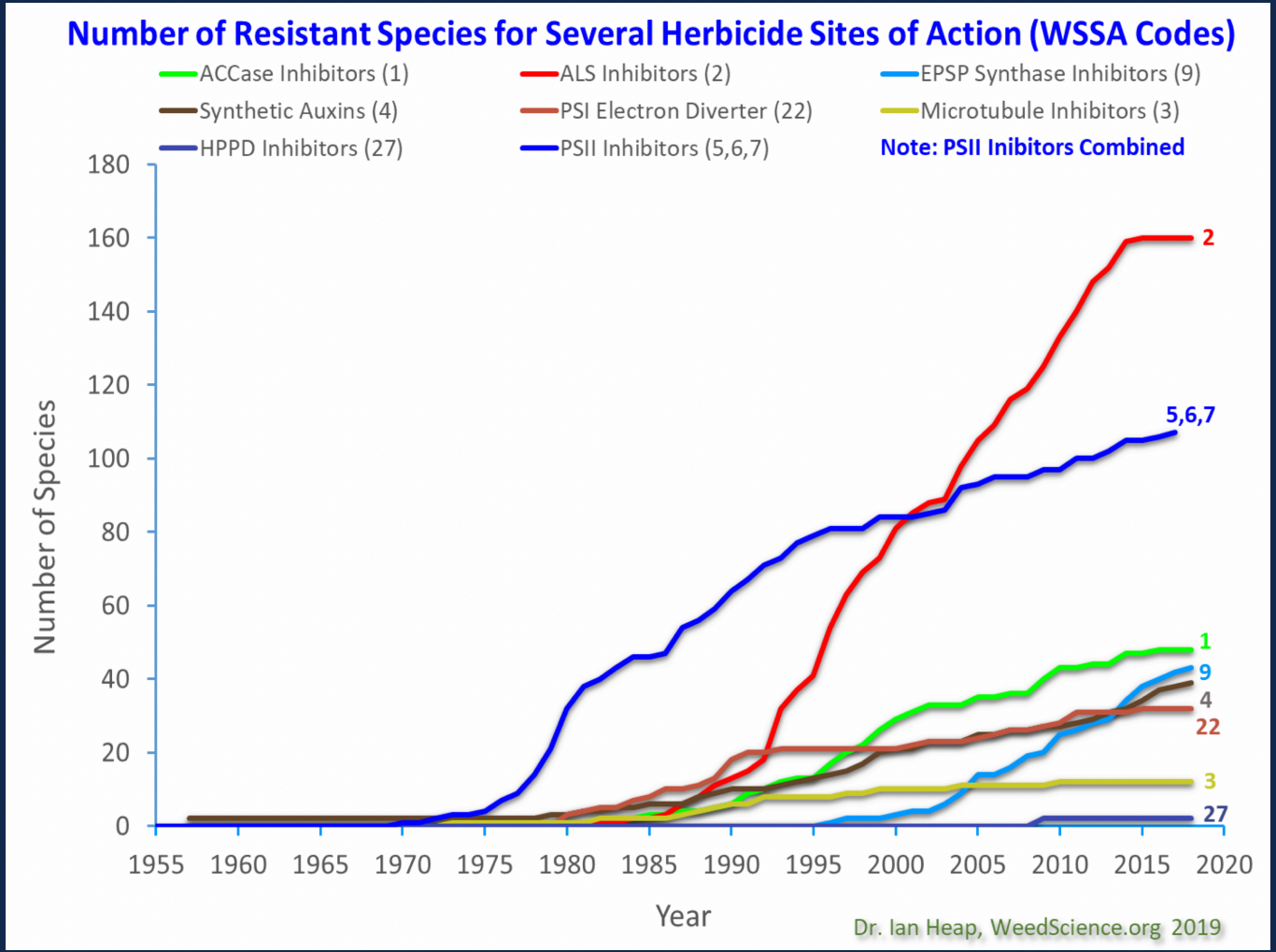
Outline

- Herbicide resistance
- The familiar: Target-site resistance
- The unfamiliar: Non-target-site resistance
- Management implications

First… some definitions

- Herbicide resistance: A decrease in the herbicide sensitivity of a population due to evolution
- Cross resistance: When evolution of resistance to one herbicide results in resistance to another herbicide
- Multiple resistance: When a plant (or population) possesses more than one resistance mechanism

Cases of resistant weeds are numerous and increasing



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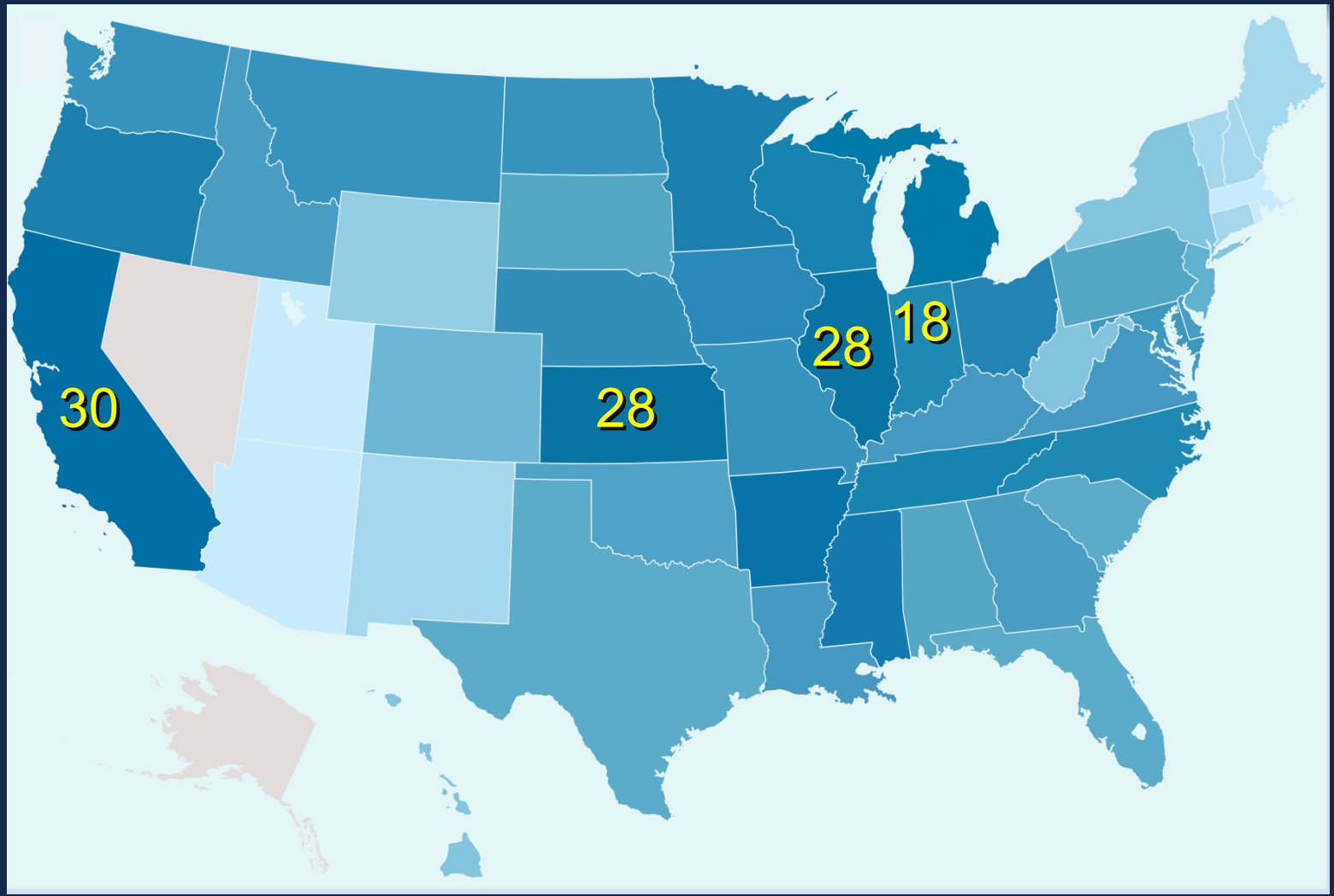
30
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18

Illinois / Indiana top 5 resistant weeds

Waterhemp

PSII (5)
ALS (2)
PPO (14)
Glyphosate (9)
HPPD (27)
Auxins (4)
VLCFA (15)

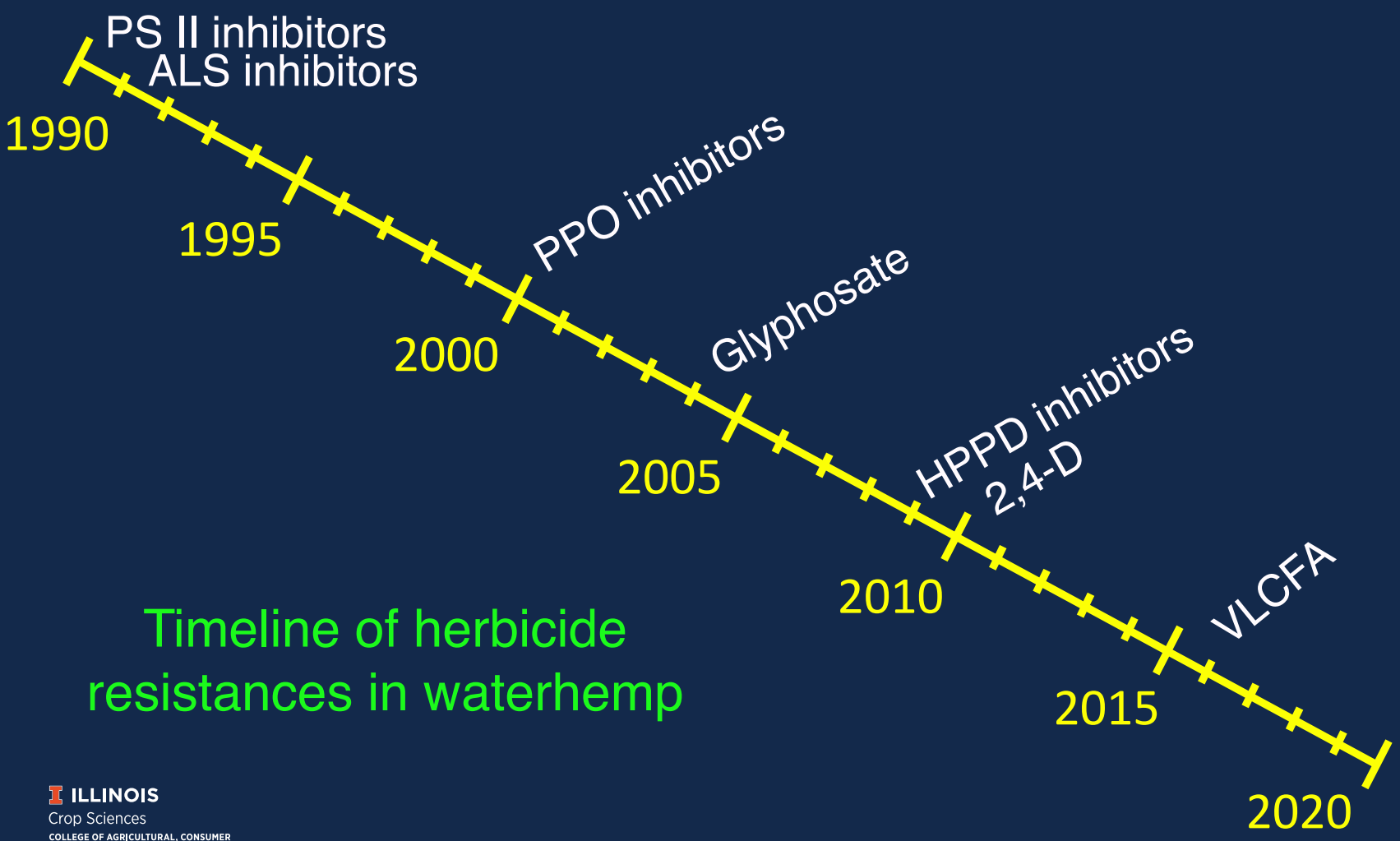
Palmer amaranth

ALS (2)
PPO (14)
Glyphosate (9)

Horseweed

ALS (2)
Glyphosate (9)

Giant, Common ragweed



Timeline of herbicide resistances in waterhemp

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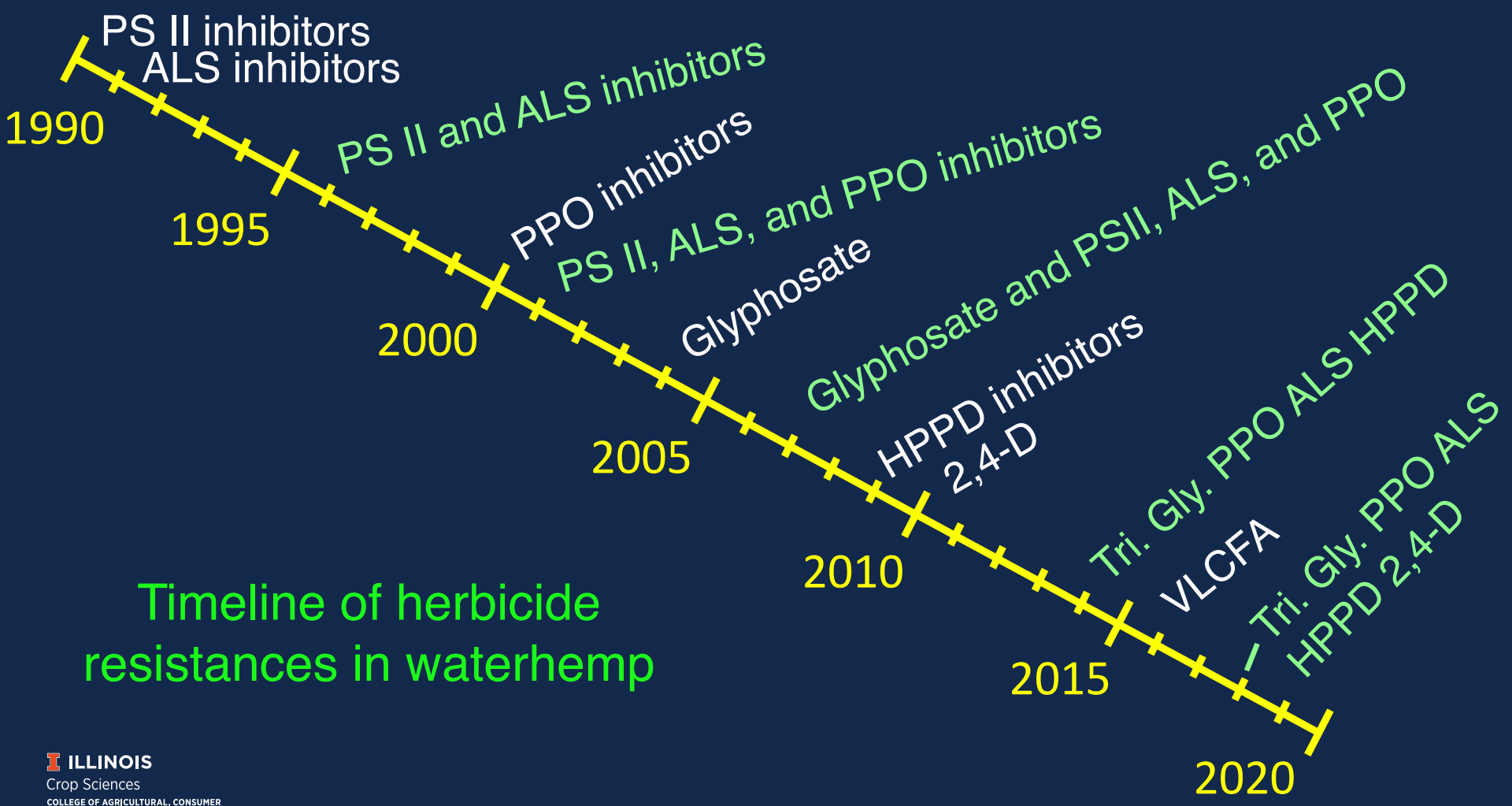

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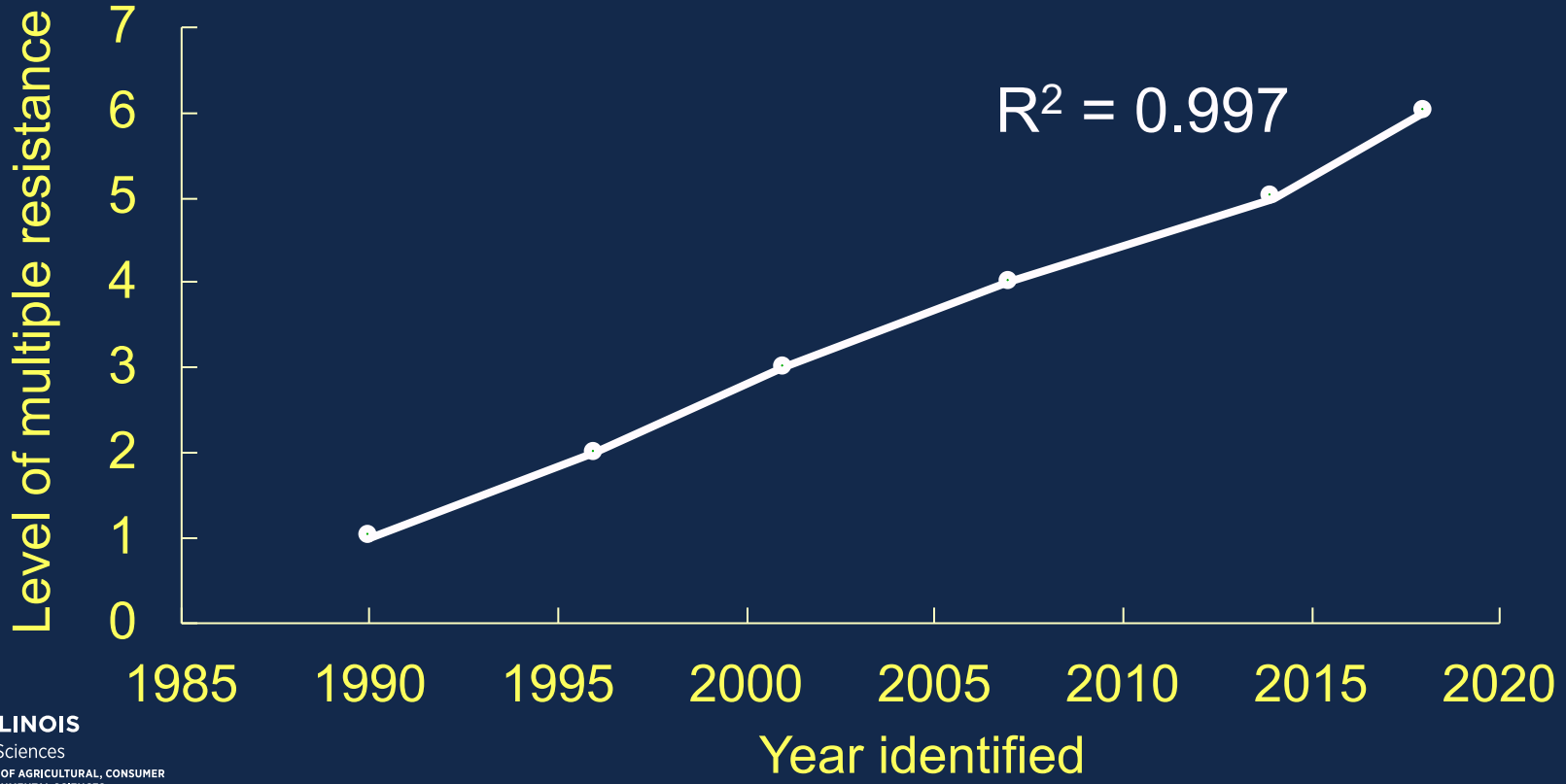
Multiple resistance in waterhemp: Is there a trend?



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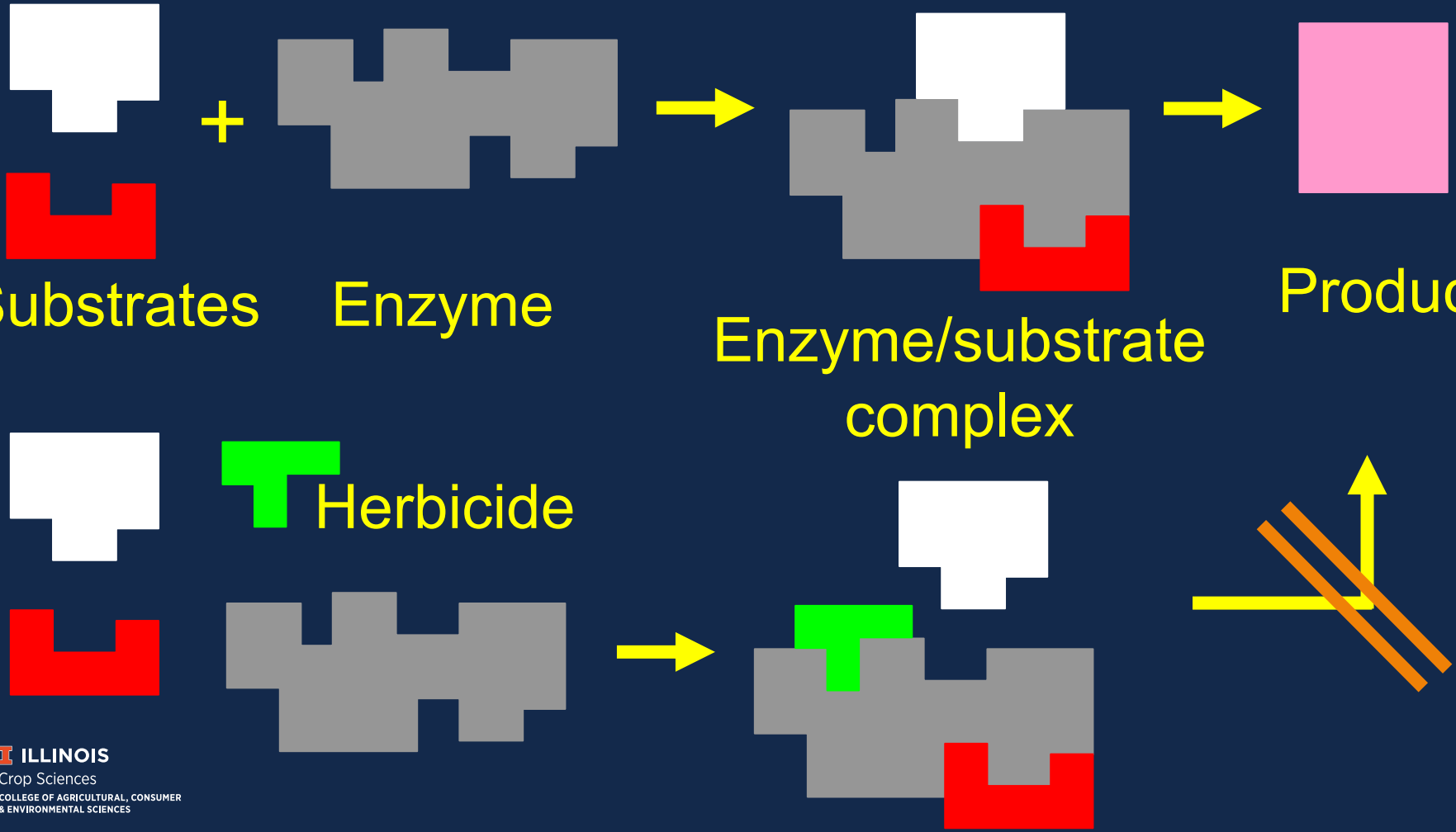
- Management implications

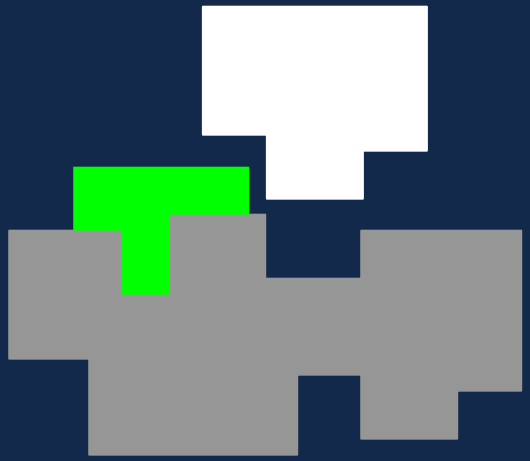
- Herbicide resistance: A decrease in the herbicide sensitivity of a population due to evolution

A common way in which this occurs:

1. A mutation occurs in gene encoding herbicide target site
2. Individual carrying that mutation survives herbicide and reproduces
3. Over time, the % of individuals in the population carrying that mutation increases


Substrates
Enzyme
Enzyme/substrate complex
Product
Herbicide

Target-site resistance



Sensitive enzyme

Resistant enzyme

Herbicides with known target site resistance in weeds

- Photosystem II inhibitors (5-7) (1983)
- Acetolactate synthase inhibitors (2) (1992)
- Dinitroanilines (3) (1998)
- ACCase inhibitors (1) (2001)
- Glyphosate (9) (2002)
- Phytoene desaturase inhibitors (12) (2004)
- PPO inhibitors (14) (2006)
- glufosinate (10) (2012)
- Auxinics (4) (2018)

Practical implications of TS resistance

- It usually occurs due to a simple mutation in a single gene
  - It is easy to diagnose
  - It is easy to predict and model

Practical implications of TS resistance (cont.)

- It only affects herbicides with the same SOA
  - If my weed population only has TS resistance to group 2 herbicides, what other herbicides can I use?
  - TS resistance can be effectively mitigated by mixing herbicides with two different SOAs

Mitigating TS resistance

- Probability of TS resistance to herbicide “A” = 10^{-6}
- Probability of TS resistance to herbicide “B” = 10^{-6}
- Probability that a single plant will possess resistance to both “A” and “B” = $10^{-6} \times 10^{-6} = 10^{-12}$

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What is NTSR?

- Anything other than a TS change that confers resistance
  - Decreased uptake
  - Altered translocation
  - Increased detoxification (metabolism)

Glyphosate resistance in horseweed

In most cases, why do herbicides not injury the crop?

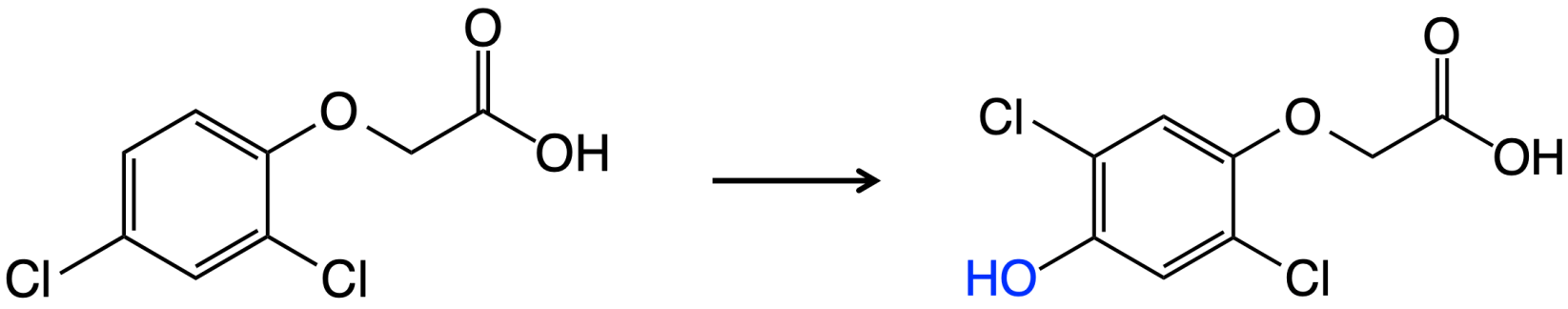
Herbicide metabolism

- Multi-step process
- Plant enzymes convert the “parent” molecule into “metabolites”
- In general, metabolites have decreasing toxicity and increasing water solubility

Herbicide metabolism – four phases

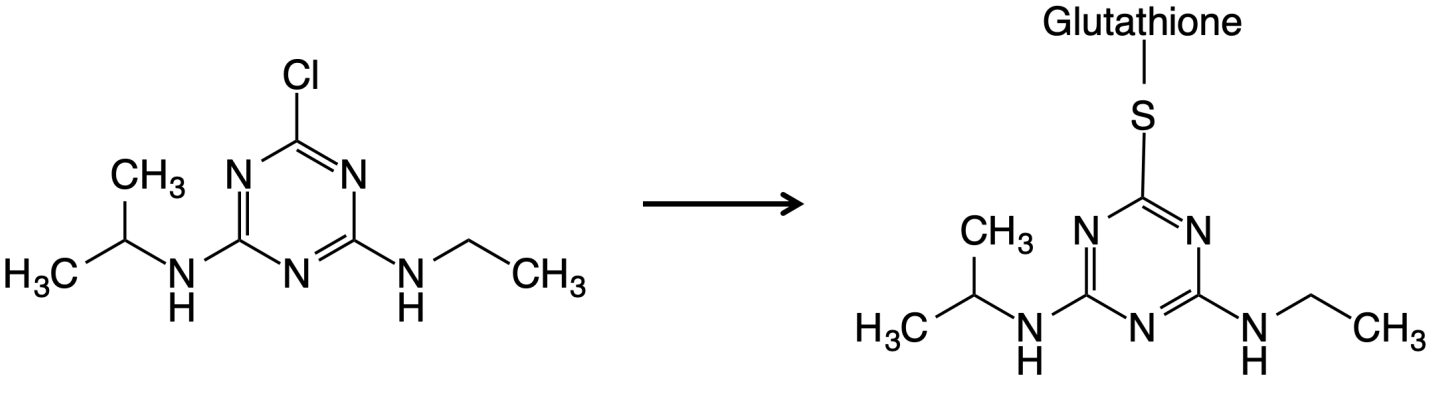
- Phase I – initial reactions
  - Oxidation, hydrolysis, reduction
- Phase II – conjugation
- Phase III – transport to vacuole
- Phase IV – subsequent metabolism

Herbicide metabolism – Phase I example



Aromatic hydroxylation of 2,4-D

Herbicide metabolism – Phase II example



GST-mediated conjugation of atrazine

Herbicide metabolism – many players

- Herbicide metabolism occurs by enzymes that normally have other functions
  - Primary or secondary biochemical processes
  - Responding to environmental stresses
  - Detoxification of naturally occurring “foreign” chemicals (xenobiotics)
- Sometimes, these same enzymes also are able to work on herbicide molecules

Herbicide metabolism – many players

- Cytochrome P450s
- Glycosyl transferases
- Glutathione-S-transferases
- Transporter proteins

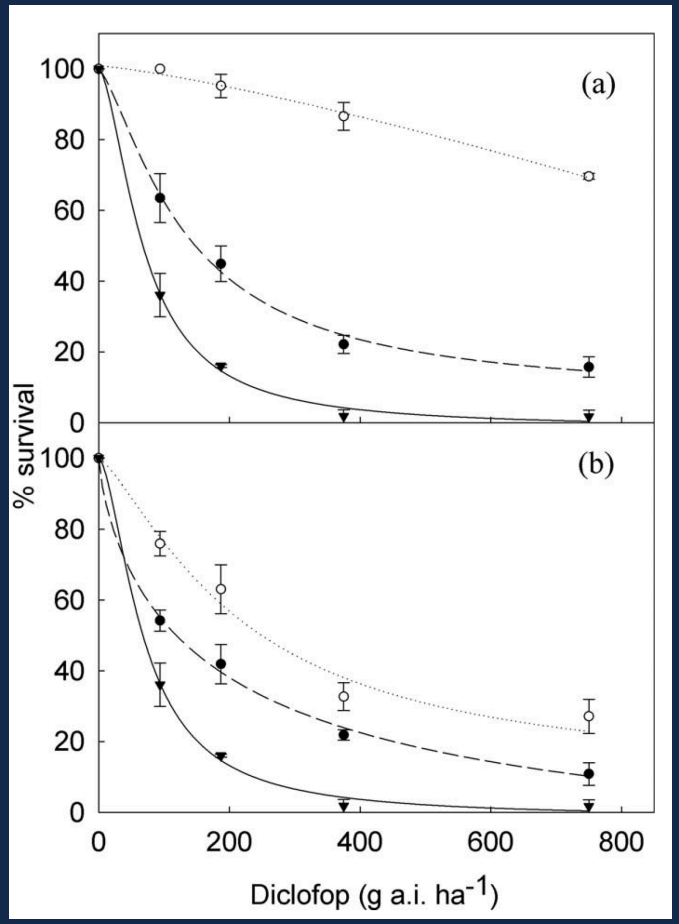
Herbicide metabolism – many players

- Cytochrome P450s – 246
- Glycosyl transferases – 146
- Glutathione-S-transferases – 56
- Transporter proteins – 939

Metabolic resistance

- Metabolic resistance occurs when a weed population evolves the ability to metabolize a herbicide (or metabolize it faster)
- Examples:
  - Increased expression of a P450
  - Mutation in a GST allowing it to recognize the herbicide
  - Combining multiple genes that each contribute to metabolism of the herbicide

Metabolic resistance can be a quantitative trait

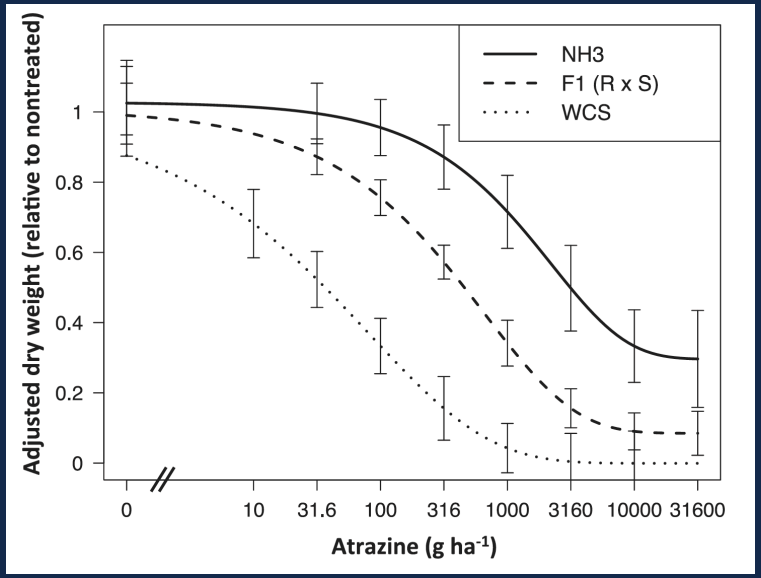


Decrease in diclofop sensitivity after two generations of low-dose selection

Manalil et al. Weed Sci. 59 (2011)

Or a qualitative trait

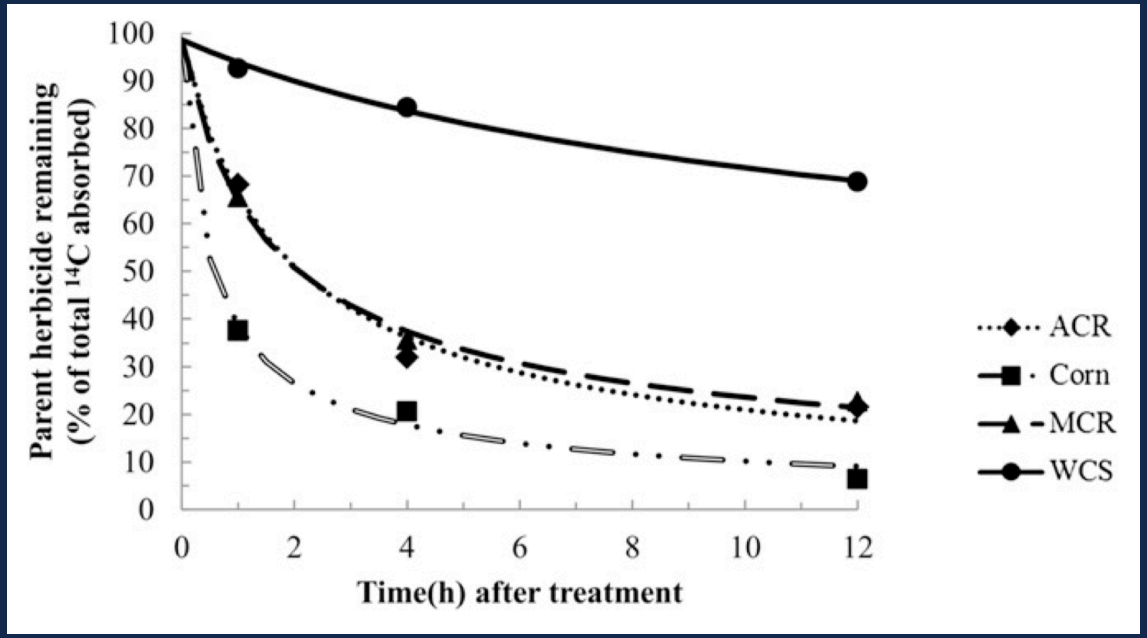
- Single metabolism gene also can confer a high level resistance on its own



Atrazine resistance in waterhemp due to a GST

Huffman et al. Weed Sci. 63 (2015)

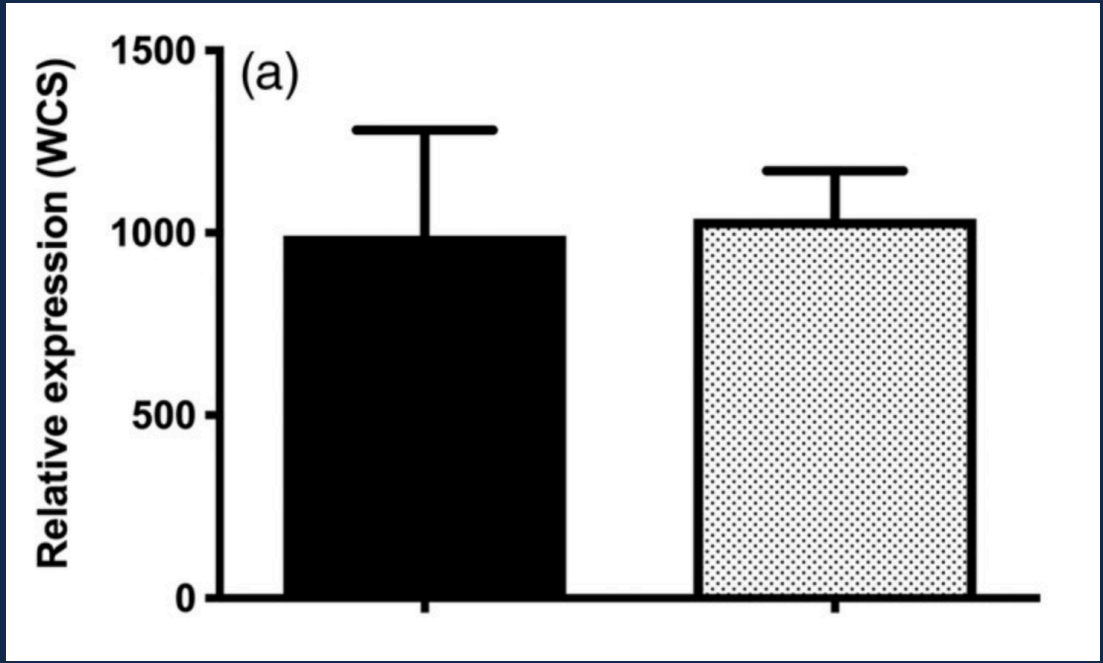
Atrazine resistance in waterhemp due to increased metabolism



Time course of atrazine metabolism

Ma et al. Plant Physiol. 163 (2013)

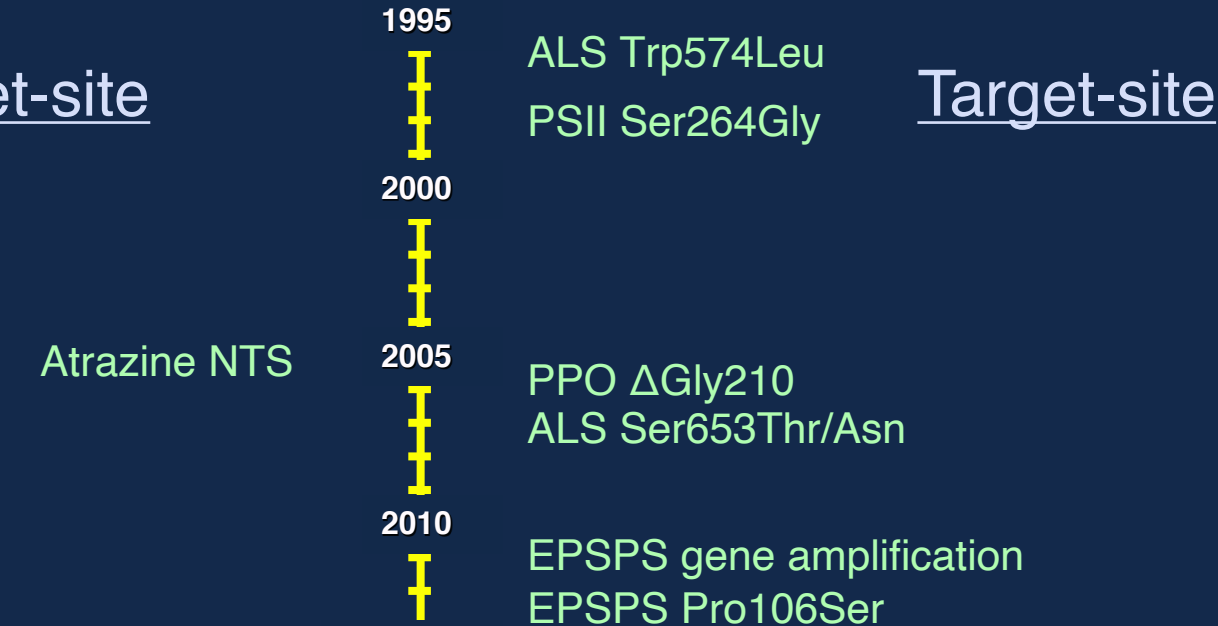
Increased metabolism due to increased expression of a GST



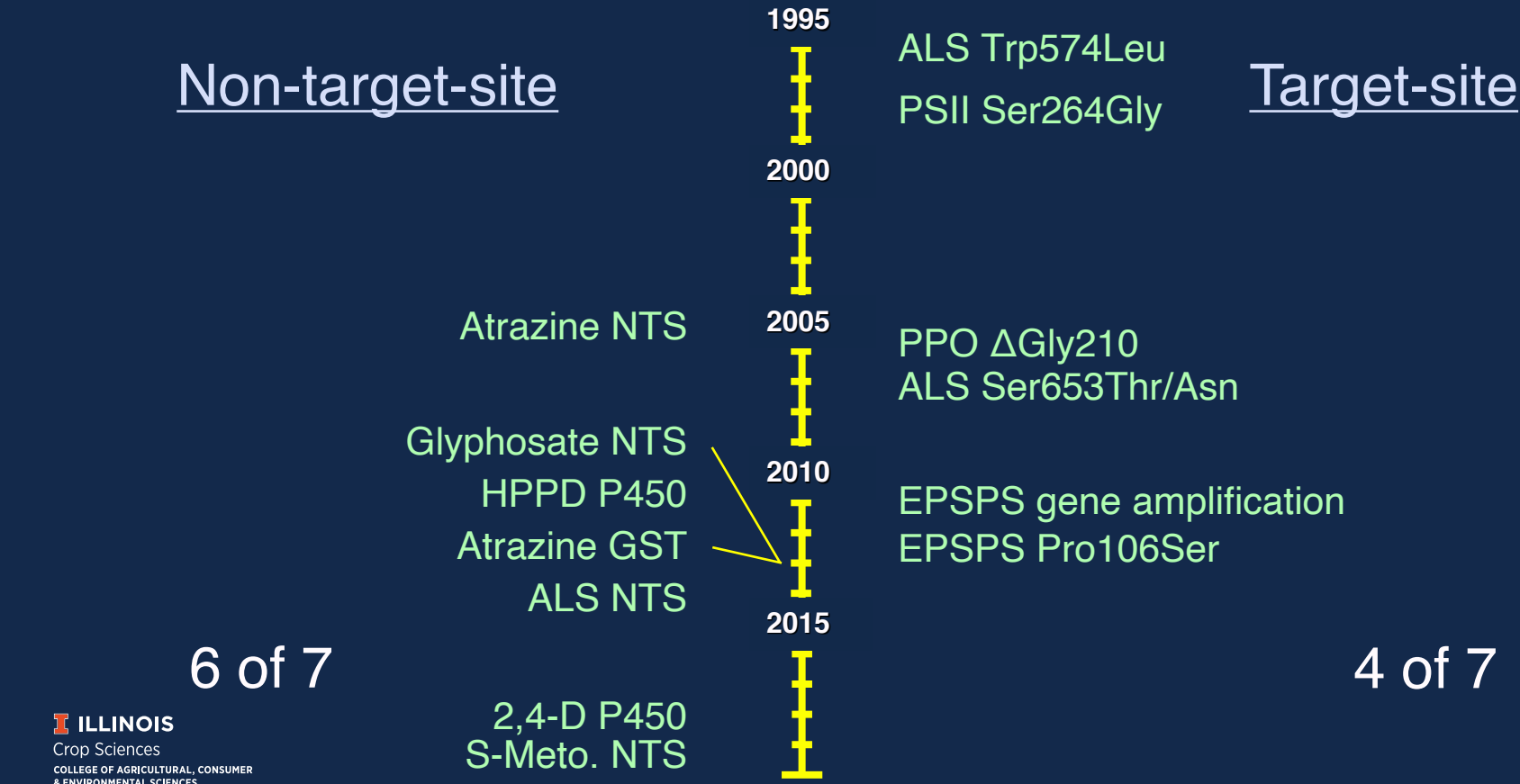
Relative GST expression in two resistant waterhemp populations

Evans et al. Plant Biotech. J. 15 (2017)

Metabolic resistance is becoming more common



Metabolic resistance is becoming more common



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TS and NTS resistance can co-exist in populations

Waterhemp plants from a single population with TS (uninjured) and NTS (chlorotic) resistance to ALS inhibitors

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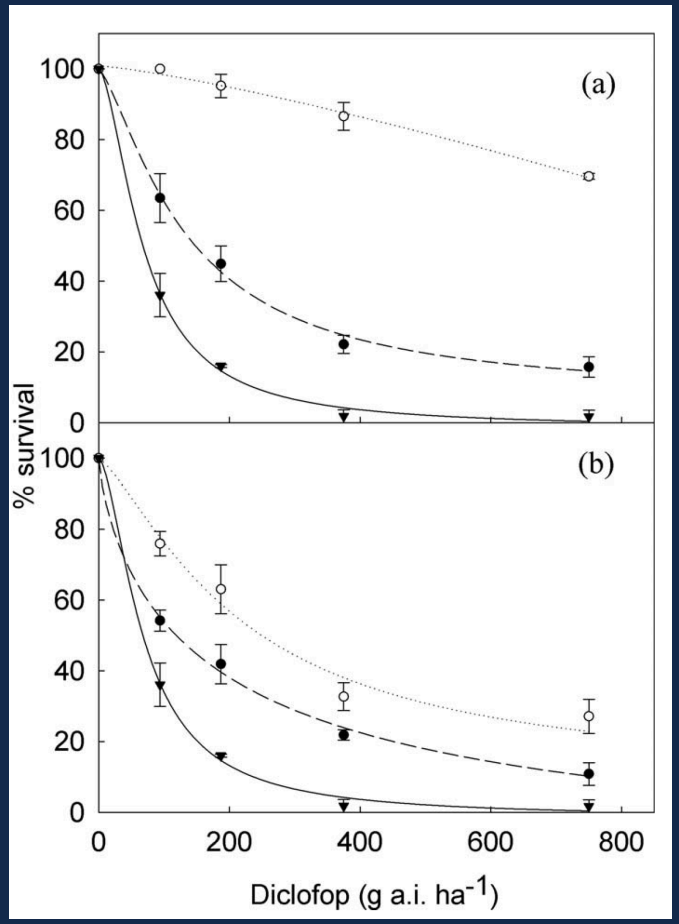
Practical implications of metabolic resistance

Cross resistance: When evolution of resistance to one herbicide results in resistance to another herbicide

- Metabolic resistance can confer cross resistance that is difficult to predict
- What other herbicides can the enzyme(s) metabolize?

Metabolic resistance can be a quantitate trait



Decrease in diclofop sensitivity after two generations of low-dose selection

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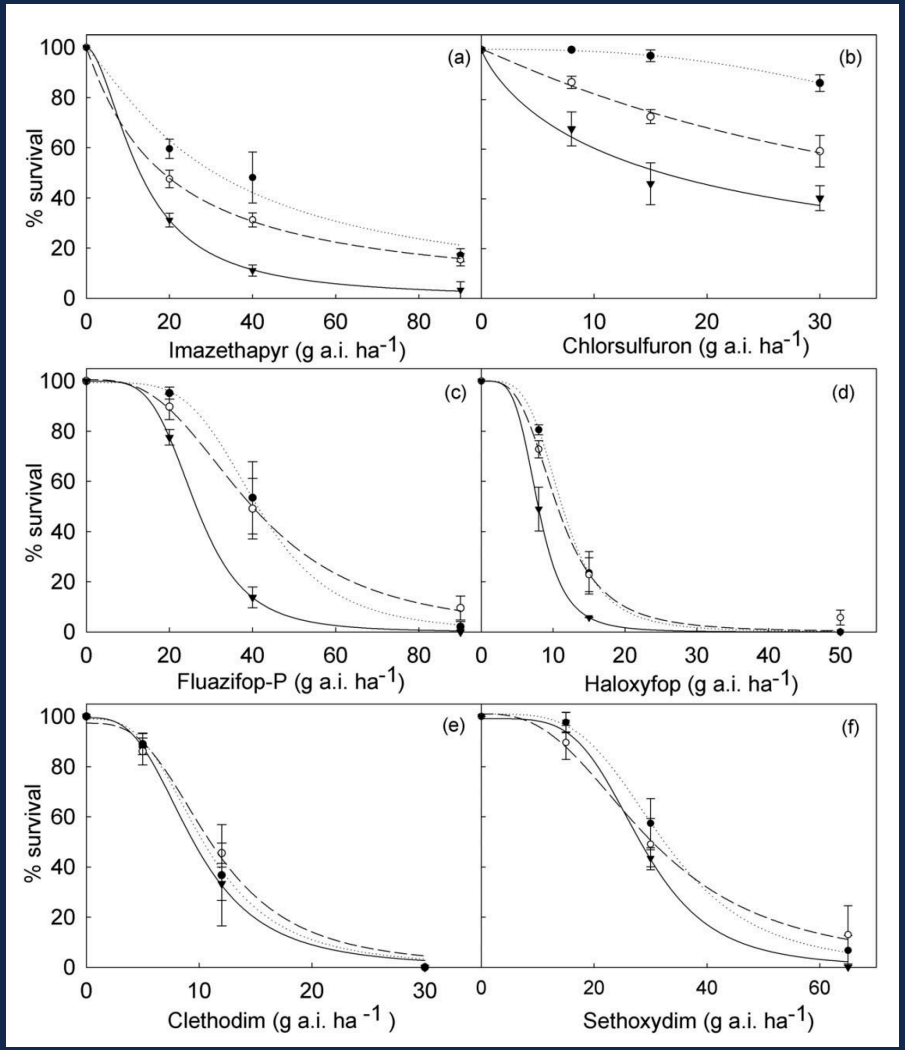
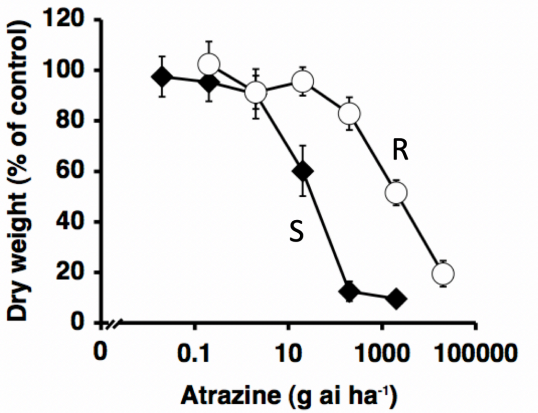
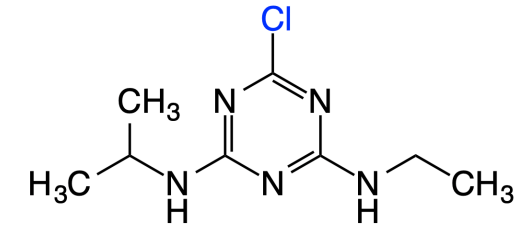


Also reduced sensitivity to other herbicides, including herbicides with different SOAs

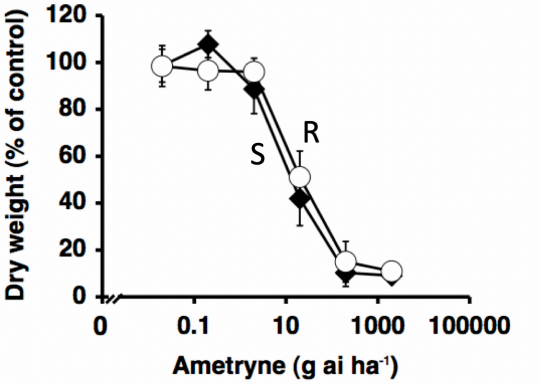
Manalil et al. Weed Sci. 59 (2011)

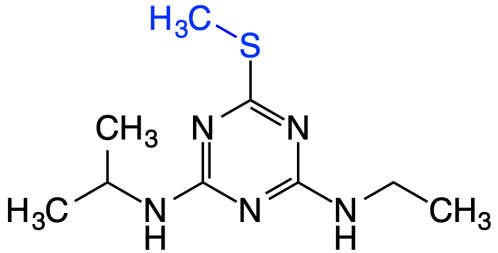
Sometimes there can be less cross resistance





Atrazine





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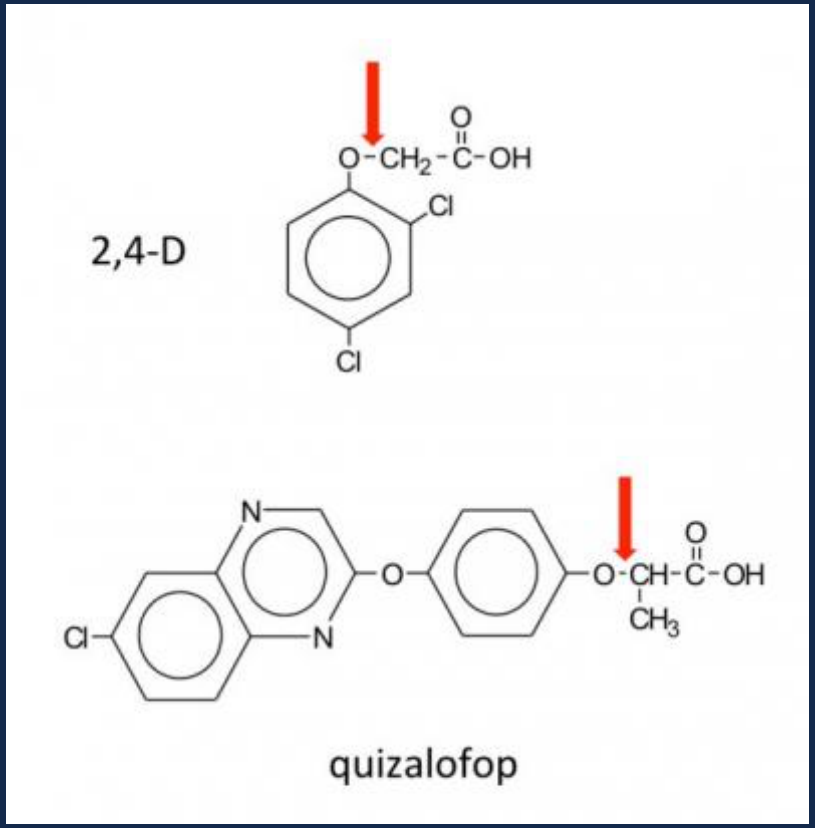
Narrow cross resistance conferred by waterhemp GST

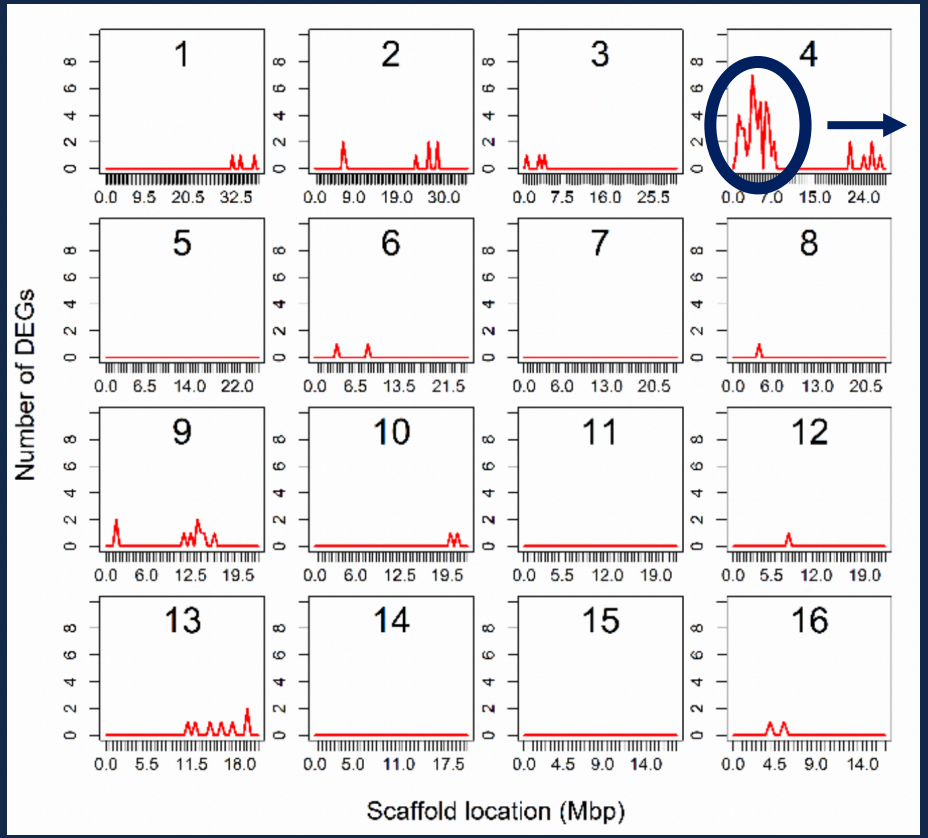
Commercial example of cross resistance



- Enlist
  - 2,4-D and “fop” resistance

But wait… there might be another level of complexity to cross resistance in weeds selected for metabolic resistance!

Mapping differentially expressed genes for 2,4-D resistance in waterhemp



"Hot-spot" of elevated gene expression

Are other herbicide-metabolism genes also overexpressed?

- e.g., 2,4-D selects a P450, adjacent to which is a GST that can metabolize another herbicide

What does this unpredictable cross resistance mean?

- Unlike with TS resistance, we cannot make informed recommendations regarding herbicide mixtures to delay resistance

Consider this…

- A waterhemp population with resistance to HPPD inhibitors also showed resistance to 2,4-D
- A 2,4-D resistant population also showed resistance to HPPD inhibitors
- Both populations showed resistance to chloroacetamides

What does this unpredictable cross resistance mean? (cont.)

- Mitigating resistance is more dependent on non-chemical weed management strategies

What does this unpredictable cross resistance mean? (cont.)

- With current herbicides, we are selecting for populations that have resistance to herbicides not yet commercialized
- Yet another hurdle for commercialization of new herbicides

Summary

- Metabolic resistance (and other forms of NTS resistance) is increasingly common in weed populations
- Our evolutionary understanding of metabolic resistance is in its infancy
  - Therefore, we do not know best strategies for mitigating such evolution
- We do know that it can and does confer unpredictable cross resistance
- Worst-case scenario: as weeds, such as waterhemp, continue to stack diverse herbicide-metabolism genes, this could be the beginning of the end of the chemical era of weed control
- We should start now to increase use of non-chemical weed-control strategies

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THANK YOU FOR YOUR ATTENTION!

Questions?