



Chlorothalonil Biological and Use Profile

Dennis Kelly, Syngenta

Chlorothalonil Use Profile

- A leading fungicide since 1966
 - Broad-spectrum efficacy
 - Multi-site activity (excellent resistance management partner)
- Effective against all four Fungi Classes:
 - Oomycetes
 - Ascomycetes
 - Basidiomycetes
 - Fungi Imperfecti
- Labeled for more than 65 crops
- Flexible application: by air, ground or chemigation

BRAVO Fungicide

Key Markets – Varies Globally

<u>North America</u>	<u>Latin America</u>	<u>Europe/ME/Africa</u>
Turf (Daconil)	Bananas	Wheat
Potatoes	Dry Beans	Pulses
Peanuts	Potatoes	Vegetables
Vegetables	Tomatoes	Coffee
Stonefruit		

Global registrations on many crops make MRLs a non-issue

Chlorothalonil Usage In CA

- Used on approximately 300,000 acres in CA. (Sprayed Acres)
- **Major use crops in CA:**

- Tomatoes (seeded)	12,400 A
- Tomatoes (TRSPLT)	106,600 A
- Tomatoes (fresh)	8,900 A
- Potatoes	84,400 A
- Almonds	41,000 A
- Onions	17,500 A
- Carrots	11,000 A
- Celery	11,000 A
- Broccoli	8,000 A

Chlorothalonil Crop Usage In CA

- Pistachio	5,000 A
- Lettuce	3,900 A
- Prunes	2,600 A
- Artichokes	1,900 A
- Cabbage	1,300 A
- Garlic	1,100 A

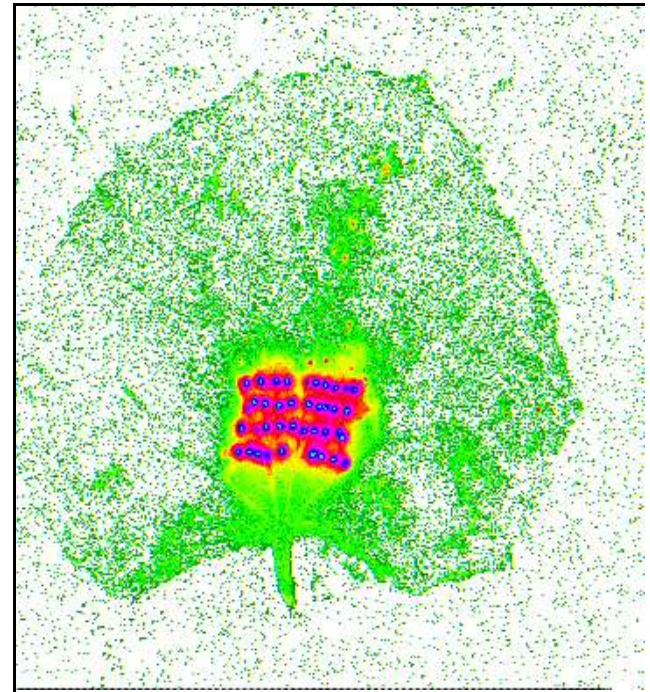
- **Other crops treated:**

Apricots, asparagus, green beans, cauliflower, corn, cucumbers, grasses, leeks, peaches, peppers (bell + chile), plums, pumpkins, ryegrass, strawberries, turf grass, watermelons,

Biological Attributes

- Excellent Protectant Fungicide
- Reliable disease control for many plant pathogens
- Effective formulations/rainfast
- Suitable for IPM programs
- Crop safety
- Worldwide Registrations

Radiolabeled chlorothalonil applied to leaf. Note – only slightly redistributed at area of contact. Not systemic.

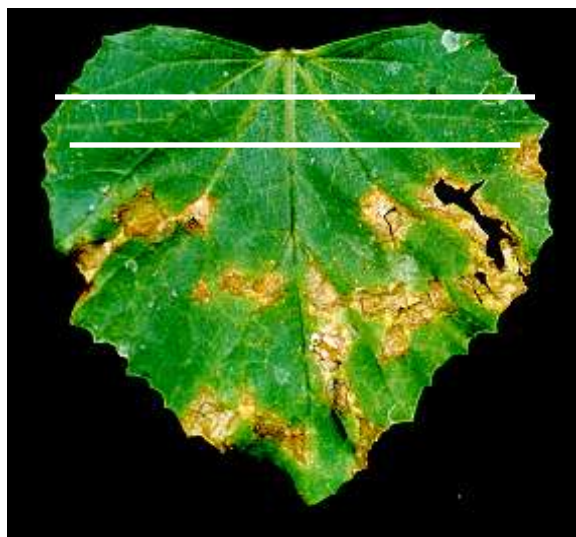


Coverage is Key !

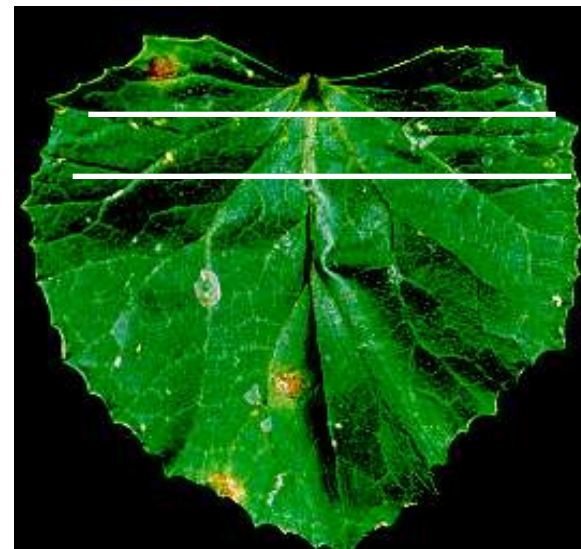
Fungicide applied between white lines, then entire leaf inoculated.
No disease where chlorothalonil applied. Azoxystrobin is systemic so disease control on most of leaf as product moves towards the tip.



Control

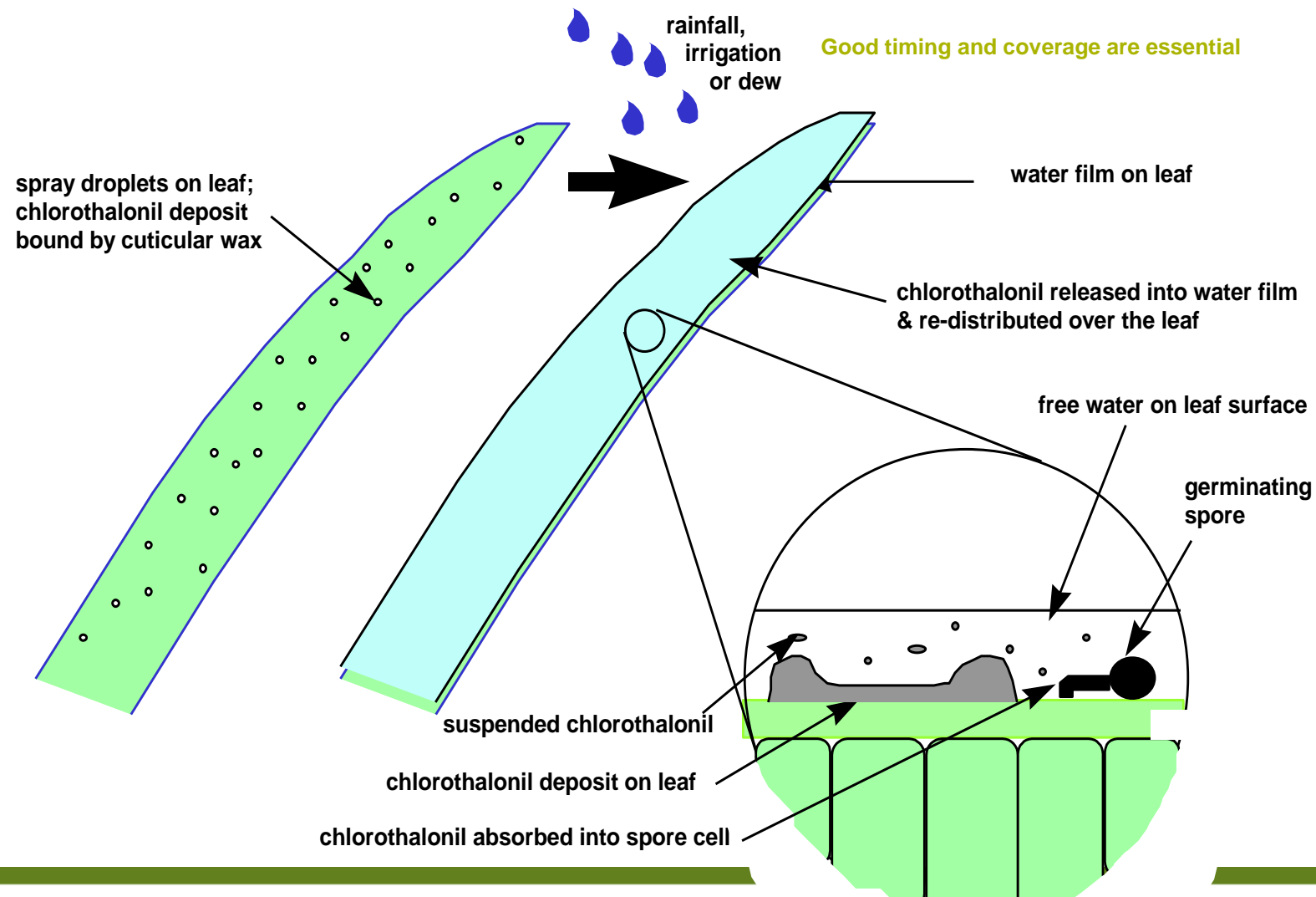


Chlorothalonil



Azoxystrobin

Behaviour of Bravo[®] on the Leaf .



Packaging

- Bravo 720 Weatherstik
 - 2 X 2.5 gal
 - Bulk – 4000 gallons
 - Grower brings own mini-bulk to fill – 60-100 gal
- Bravo Zn
 - 2 X 2.5 gal
 - Bulk – 4200 gallons
 - Grower brings own mini-bulk to fill
- Bravo Ultrex 82.5 WDG
 - 27.4 lb bag
- Other crop premixes (much smaller % of chlorothalonil products)
 - Ridomil Gold Bravo SC (0.33 lb ai mefenoxam + 3.34 lb ai chlorothalonil/ gal)
 - Tilt Bravo SE (0.3 lb ai propiconazole + 4 lb ai chlorothalonil/gal)
 - Quadris Opti SC (0.5 lb ai azoxystrobin + 5 lb ai chlorothalonil/gal)

Foliar Applied



Ground

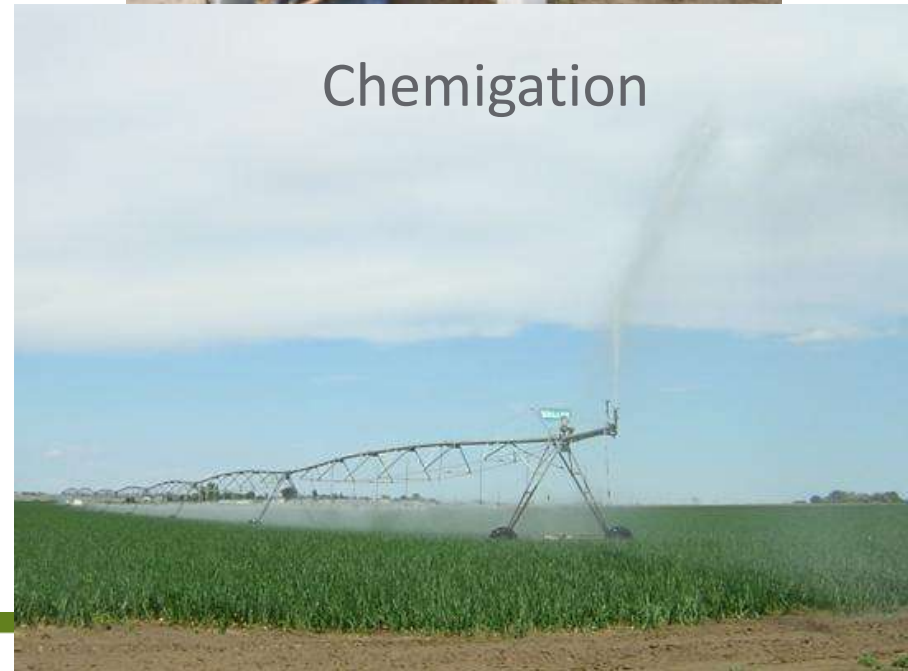
Aerial



Foliar Applied



Air-blast (type of ground)

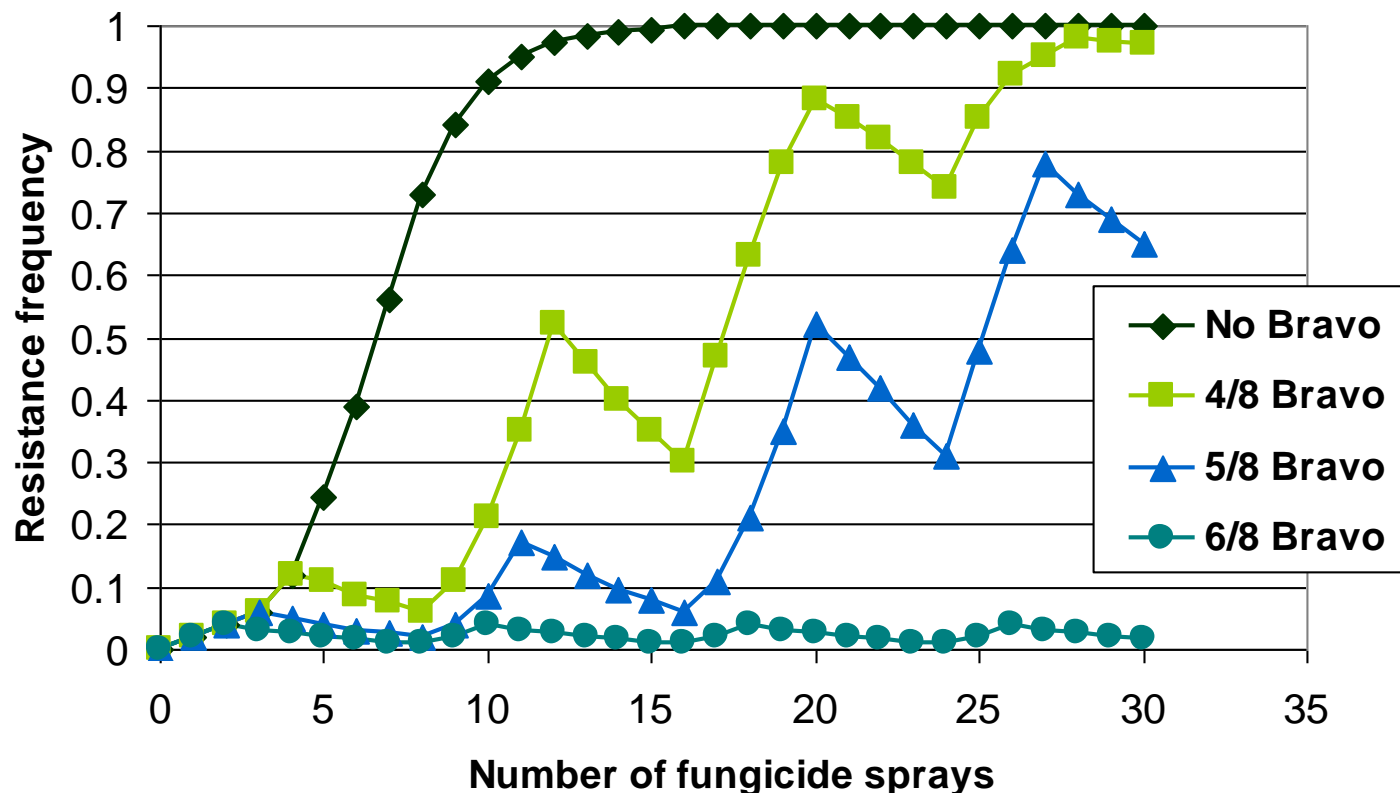


Broad Spectrum and a Resistance Management Tool

	Multi-site	All single site MOA				
	CTL	DMI	Strobilurins	Phenylamides	CAA	SDHIs
Ascomycetes	✓	✓	✓	✗	✗	✓
Basidio-mycetes	✓	✓	✓	✗	✗	✓
Fungi Imperfecti	✓	✓	✓	✗	✗	✓
Oomycetes	✓	✗	✓	✓	✓	✗

- No resistance
- Novel mode of action
- Growers depend on chlorothalonil as part of their rotational chemistry as a fungal resistance management strategy

Example of Use for Resistance Management



Alternation (or mixtures) slows development of resistance to single site mode of action fungicides.



Bravo WS – Full Season

Pristine alt/ w Bravo WS

Inspire Super – Full Season*

Pristine – Full Season

Typical Application Rates

- Vegetables
 - 0.75 – 3.0 lb ai/A per application
 - 9 - 18 lb ai/A (total load/season)
- Berries
 - 2.0 – 4.9 lb ai/A
 - 9 - 15 lb ai/A
- Tree Fruit/Tropical/Tree Nuts
 - 1.1 – 3.0 lb ai/A per application
 - 6 – 24 lb ai/A (total load/season)
- Peanut
 - 0.75 – 1.125 lb ai/A per application
 - 9 lb ai/A (total load/season)
- Potato
 - 0.75 – 1.125 lb ai/A per application
 - 11.25 lb ai/A (total load/season)
- Conifers
 - 2 – 4.1 lb ai/A per application
 - 16.5 lb ai/A (total load/season)

- 1.5 – 2 pints commonly used in annual crops (1.1 – 1.6 lb ai/A)
- 3 – 4 pints more common in perennial crops (2.25 – 3 lb ai/A)
- Higher rates used when
 - Disease present
 - Need longer interval
 - Conditions right for disease
 - Tougher disease to control

Turf Market - Dollar Spot, DMI Resistant

Daconil Ultrex



Check



Chlorothalonil RED-imposed fairway rates has led to increased use and resistance in other classes of fungicide chemistry such as DMIs.

Golf, Landscape and Ornamental Overview

- Use in pounds active ingredient
 - 86% in golf
 - 6% in ornamentals
 - 8% in sod/professional sports fields/commercial landscapes.
- Ranked the most important fungicide in market surveys.
- Important economical standard due to declines in
 - golf revenues,
 - ornamental purchases,
 - sod purchases (due to the housing market).
- Restricted from use on home lawns and turf sites associated with apartment buildings, daycare centers, playgrounds, playfields, recreational park athletic fields, athletic fields located on or next to schools (ie., elementary, middle and high schools), campgrounds, churches, and theme parks.

Turf Market – Rate Ranges

● Rate Range: Pre and Post Disease

- Pre disease rate range is 4.1 - 7.3 lbs ai/acre.
 - Rates and application intervals (7-14 days) are based on disease severity and location , either fairways or greens.
 - Most fairway applications are 4.1 lb ai/acre rate.
 - For copper spot, anthracnose, stem rust, and snow mold the label allows for up to 11.3 lbs ai/acre
- Post disease rate range is 8.25 - 11.3 lbs ai/acre.
 - Not common in golf. They are protecting an asset and not computing a yield gain vs input cost ROI like a farmer would.
 - There is no Economic Threshold of turf loss on a green.
 - If you don't have turf on the greens, you don't have a golf course, and you are out of business.

Turf Market – Golf Course Use

- Usage on the golf course:

- Average number of acres per course: 1999/2000 study
 - Greens - 2.9 acres/course
 - 72 lbs ai/acre limit in RED.
 - Tees - 2.7 acres/course
 - 52 lbs ai/acre limit in RED
 - Fairways - 31.9 acres / course
 - 26 lbs ai/acre limit in RED
 - Roughs - 66.8 acres/course
 - Roughs applications typically involve border passes around the fairways that protect the fairways from pathogens in the rough. The entire rough is not sprayed.
 - The border sprays in the roughs are typically reported as part of the fairway spray.

- **2003 Rate restrictions Due to RED**

- Prior to RED typical usage was 4.1 lbs ai/acre throughout the growing season
 - Typical April 1st to Oct. 30th season, usage would have been 57.4 lbs ai/acre on fairways.
 - Post RED, limit is 26.0 lbs ai/acre per year on fairways.
 - Over a 50% reduction.
 - Bent/poa fairways only have 3 months of use per season

Turf Market – Resistance Management

- **Chlorothalonil is the most important golf fungicide**
 - Controls major diseases such as dollar spot, anthracnose and brown patch
 - Broad spectrum, protectant fungicide.
 - No resistance has been detected following 40 years of use.
- **Chlorothalonil is often tank mixed with other fungicides for broader disease spectrum and resistance management :**
 - DMI and benzimidazole resistant dollar spot
 - QoI resistant anthracnose
 - Mixtures with QoI for dollar spot control.

Turf Market

- Application Methods:

- Typical spray technique consists of a ground vehicle with a mounted tank and a boom sprayer about 2 ft above the ground.
- Usually flat fan nozzles are used to provide a uniform coverage for the foliar application.
- Typical spray volumes are 40 gal – 90 gal/acre depending on application location
 - Golf fairway more likely to be lower end of range vs golf greens

- Example of a © The Toro Company golf Sprayer²

- Booms fold down to each side of the sprayer when applying.



Ornamental Market

- Main Uses:

- Chlorothalonil is utilized on a diverse number of indoor (greenhouse) and outdoor (nursery) crops.
 - Greenhouse use is focused on prevention of general leafspots, rusts and botrytis listed on the label.
 - Outdoor use (nursery) is focused on general leaf spot diseases, rusts and powdery mildew listed on the label.
- Christmas trees, conifers, and roses are the most often treated ornamental crops.

- Application Methods:

- Foliar applications are generally applied at or around 100 gal/acre while large plants may receive foliar applications at 200 gal/acre to achieve thorough coverage.

- High rate uses:

- Pachysandra had an outlier rate of 2.1 lbs of Chlorothalonil per 100 gal opposed to typical labeled rate of 1.0 lb per 100 gal for normal ornamental use.
 - Pachysandra will be removed from the label as a label amendment

- Christmas trees: (conifers)

- Label amendments in progress to clarify uses do not include forest application
 - Conifer uses include: conifer nursery beds, Christmas tree and bough production plantations, tree seed orchards. and landscape situations

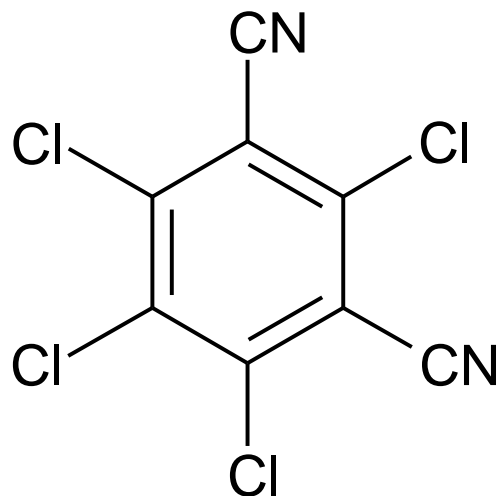


Chlorothalonil: Environmental Fate and Risk to Aquatic Organisms

Robert S I Joseph

Head of Environmental Safety North America, Syngenta

History of Chlorothalonil



- 1961 - 1st synthesized by Diamond Alkali
- 1963 field testing began
- 1966 first registered on turf
- 1970 first registered on crops and ornamentals
- 1998 acquired by Zeneca
- 2000 – merger with Novartis – now Syngenta
- Current – over 65 crops and 125 diseases

Fungicidal Mode of Action

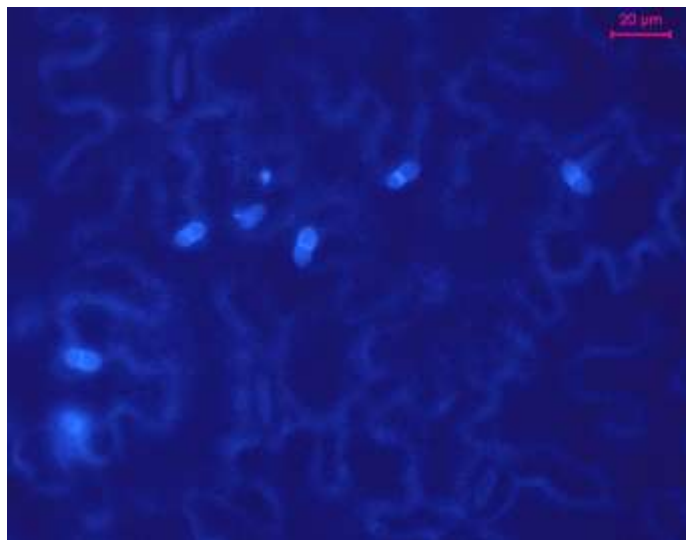
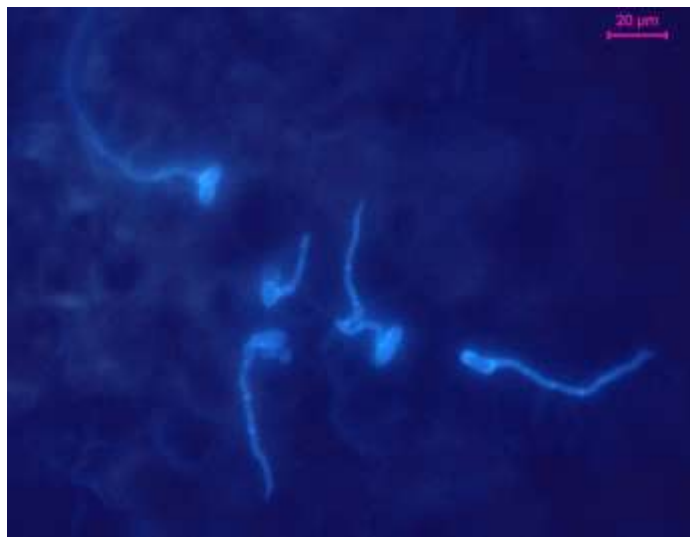
- Unique mode of action
- Primary target is sulfhydryl group of glutathione
- Causes interference with glutathione-dependent enzymes
- Key in several important physiological processes in fungi
 - disturbs cell metabolism
- As there are numerous enzyme targets, chlorothalonil is considered to have a multi-site mode of action and fungi are not likely to become resistant.
- Critical for resistance management

Site of Action

- Inhibits spore germination
- Conidia of *Mycosphaerella pinoides*

- Untreated

Treated



Environmental Safety Summary

- Chlorothalonil is of low toxicity to non-target terrestrial organisms
- Consequently does not present an unacceptable risk to these organisms
- Although chlorothalonil has high intrinsic toxicity to some aquatic organisms, does not result in adverse effects in actual field use
- Due to the very rapid rate of dissipation of chlorothalonil in aquatic environments resulting in low and transient exposure



Environmental Fate

Molecular Weight	265.91 g/mol
Vapor Pressure	5.72 x 10 ⁻⁷ torr
Henry's Law Constant	2.47 x 10 ⁻⁷ atm m ³ /mol
Log Kow	2.88
Aqueous solubility	0.8 mg/L
Soil partition coefficient	Mean 3840 L/kg (range 862-11300 L/kg)
Aqueous Photolysis Half-life	0.4 days
Surface water/sediment half-life	1.5 days (range 0.1 to 3.1 days)
Soil metabolism half-life	1-40 days
Hydrolysis half-life	stable

Understanding Environmental Fate

- Extensive database spanning 40 years
- Many fate studies done at unrealistic concentrations to facilitate analysis
- In late 1990s scientist at Syngenta identified that metabolism in soil was dose dependent
- At high (unrealistic) concentrations
 - half lives are several weeks
 - Primary metabolite is SDS-3701
- At concentrations that represent the EEC
 - Half lives in soil and water/sediment are hours to a few days
 - Metabolism is more complex and dominated by an initial reaction with glutathione or other sulphur nucleophiles

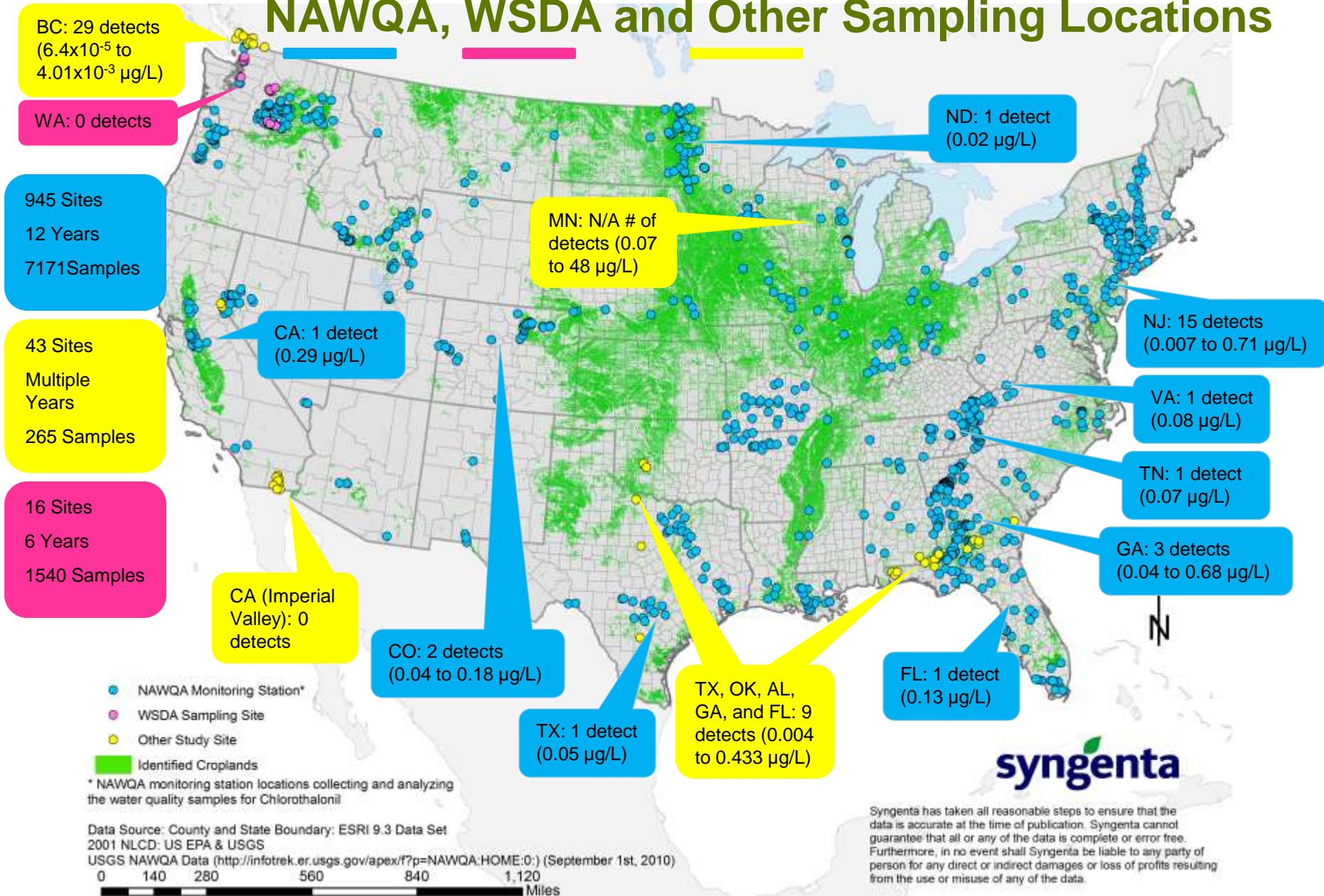
Fate in Water

- Chlorothalonil dissipates rapidly from water
- In absence of light rapid microbial degradation via glutathione pathway
 - Half-lives ranged from 0.1 to 3.1 days
 - Hurt and Oliver (2002), Kirkpatrick (1996) & Hatzenberler (1991)
 - Latest EPA assessments 1.5 days (90th centile)
- In the presence of sunlight degradation is rapid
 - Half-life <1 day [Kirkpatrick (1996)]
- Rapid dissipation supported by additional outdoor fate studies
 - Half-lives of 4, 7 and 8 hours
 - Gentle (1999) and Gentle and Tattersfield (2000)
- Adsorption to sediment is a potential dissipation pathway but less important due to rapid degradation

Water Monitoring

- Supports results from lab and field studies
- Extensive surface water monitoring show low levels of chlorothalonil in surface waters
- Collectively >9000 samples over 16 years nationwide
 - Only 64 detects (<1%)
 - Max detect in Ag = 0.71 µg/L
 - Max detect Turf = 48 ug/L
- NAWQA monitoring in California
 - Only one detect at 0.29 ug/L from 255 samples

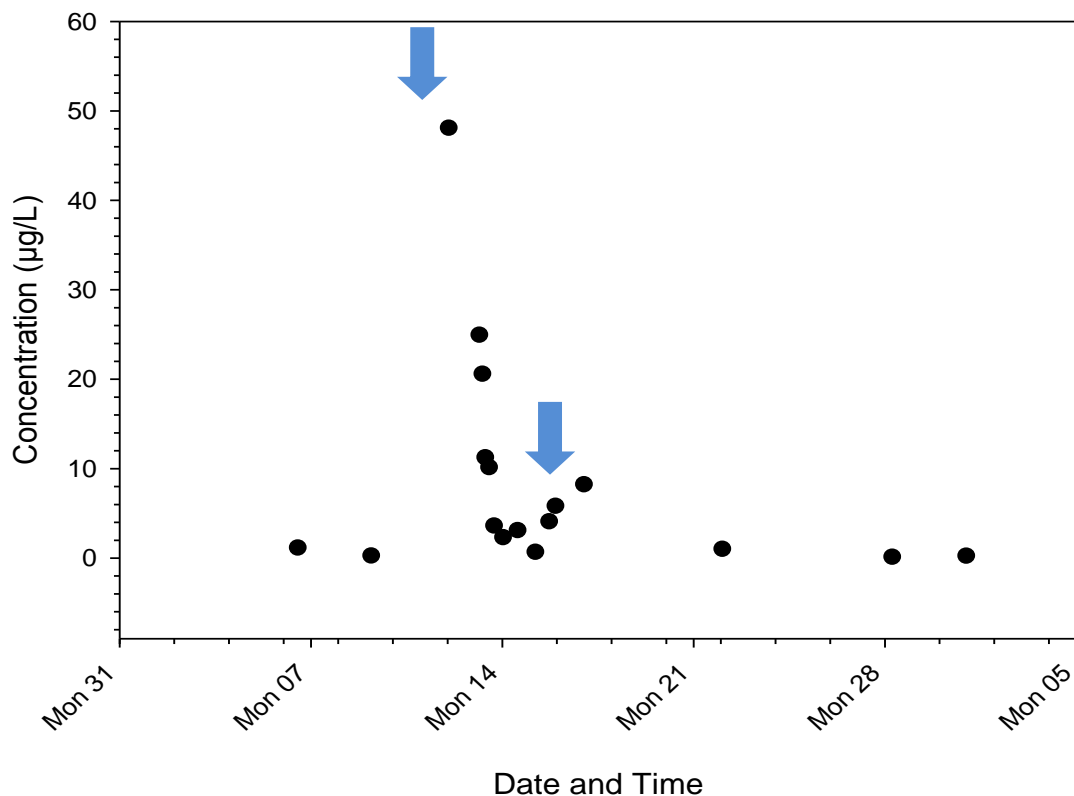
NAWQA, WSDA and Other Sampling Locations



Temporality of Highest CTL Concentrations (King and Balogh)

Temporally preceding and following values coinciding with the peak value of 48 µg/L provided via personal communication from Dr King.

Time Sample Taken	Measured Value (µg/L)
11/6/2005 12:29	1.17
11/9/2005 4:57	0.28
12/11/2005 1:06	48.11
13/11/2005 3:57	24.96
13/11/2005 6:37	20.60
13/11/2005 9:10	11.25
13/11/2005 12:26	10.16
13/11/2005 16:56	3.63
14/11/2005 0:41	2.32
14/11/2005 13:27	3.11
15/11/2005 5:12	0.68
15/11/2005 17:18	4.10
15/11/2005 22:43	5.84
11/16/2005 23:48	8.24
11/22/2005 1:14	1.03
11/28/2005 6:29	0.14
11/30/2005 23:31	0.25



Temporal distribution of data surrounding the maximal peak value of 48 ppb reported by Dr. King via personal communication for dates corresponding to those identified in Table 4. Blue arrows indicate precipitation on 11/12 (approximately 1 inch) and 11/15/2005 (approximately ½ inch).

Safety to Wildlife/Non-target Organisms

- Potential for direct effects through toxicity assessed through an ecological risk assessment
- Indirect effects through reduction in food supply or habitat



Ecological Risk Assessment

- Hazard – toxicity determined in laboratory studies
- Exposure – tier 1, worst-case model

$$\frac{\text{Exposure}}{\text{Toxicity}} = \text{Risk Quotient (RQ)}$$

- If $RQ < \text{trigger value}$ – low risk
- If $RQ > \text{trigger}$ – refine assessment, tiers 2 and above



Ecotoxicological Profile - Terrestrial

- Birds – Non-toxic
 - Oral $LD_{50} > 4640$ mg/kg, Dietary $LC_{50} > 10,000$ ppm
- Non-target arthropods – Harmless
- Bees - Non-toxic
 - $LD_{50} > 133$ μ g ai/bee
- Earthworms - Non-toxic
 - $LC_{50} > 404$ mg/kg soil



Terrestrial Risk

- Chlorothalonil is of low toxicity and consequently low risk to non-target terrestrial organisms,
 - including birds and mammals, bees and other non-target arthropods, earthworms, soil microorganisms and plants.
- In the terrestrial environment, chlorothalonil is rapidly degraded by microorganisms.
- The principle soil degradate is SDS-3701, has also been shown to be of low risk to soil organisms and birds and mammals.
- Chlorothalonil is not mobile in soil and does not leach to groundwater.
- The degradate SDS-3701 is more mobile than the parent, but the potential for leaching to groundwater is low.

Ecotoxicological Profile - Aquatic

- Fish – very highly to highly toxic
 - Acute $LC_{50} = 18 - 200 \mu\text{g/L}$
- Aquatic invertebrates – highly to moderately toxic
 - Acute $LC_{50} = 24 - >1600 \mu\text{g/L}$
- Aquatic Plants/Algae- very highly to highly toxic
 - $EC_{50} = 14 - 210 \mu\text{g/L}$

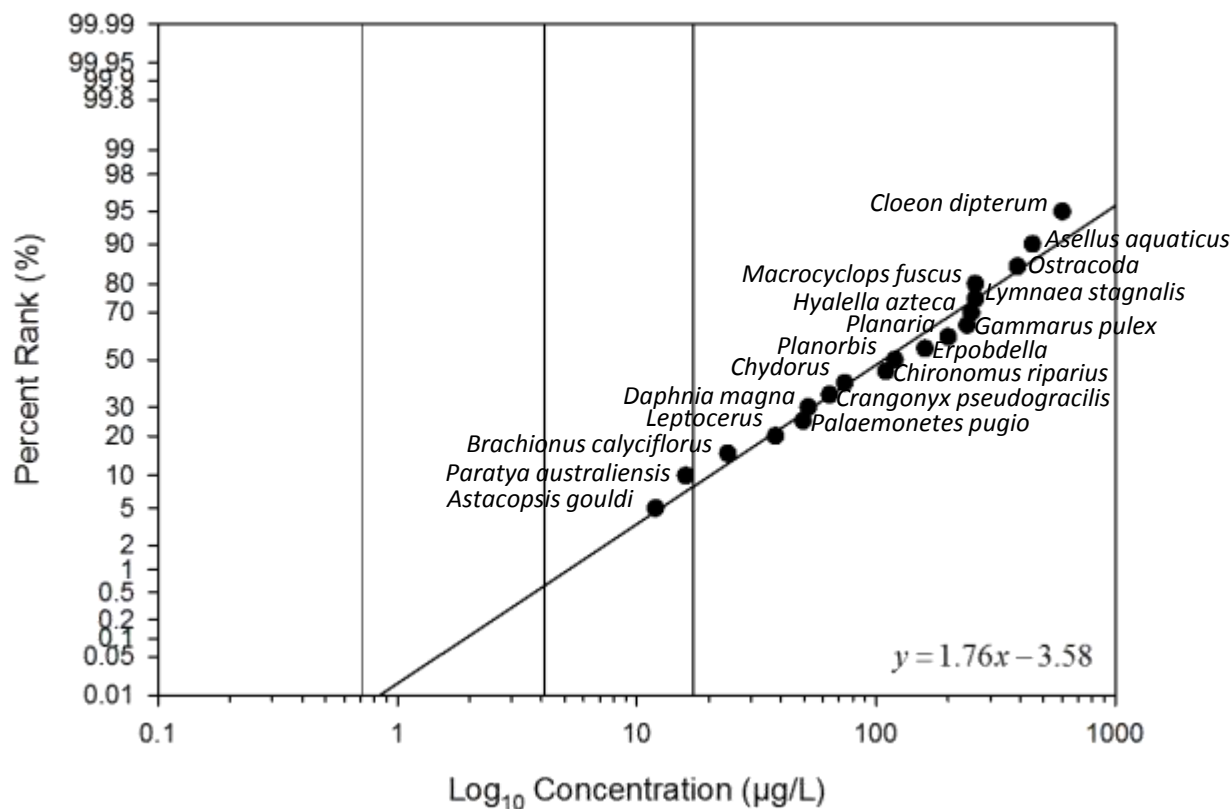
Aquatic Risk

- Laboratory studies show that chlorothalonil is highly toxic to some aquatic organisms
 - Chlorothalonil degradates are significantly less toxic.
- In water chlorothalonil is very rapidly degraded
 - Microbial and photolytic
- Minimizes exposure magnitude and duration
 - Reduces the risk
- Many uses pass non-endangered risk assessments at Tier II
- Higher tier risk assessments and studies have shown
 - the risk of any effects in aquatic environments is low and
 - there is very low potential for any long-term effects

Higher Tier Assessments

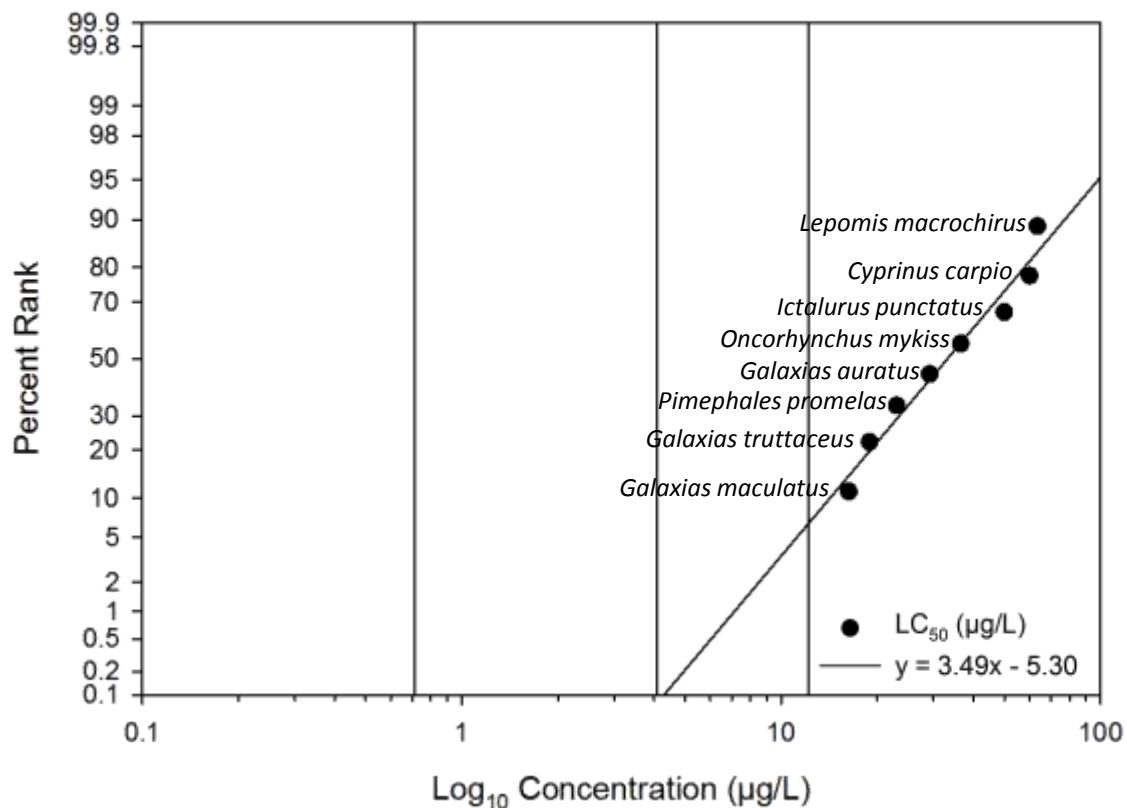
- Higher tier risk assessments confirm a low risk to aquatic organisms (Tier 3)
 - Species Sensitivity Distributions Assessments
 - Time to Effects Analysis Relative to Measured/Modeled Exposure Profiles
- Mesocosm studies also support a low risk to aquatic organisms (Tier 4)

Species Sensitivity Distribution: Invertebrates



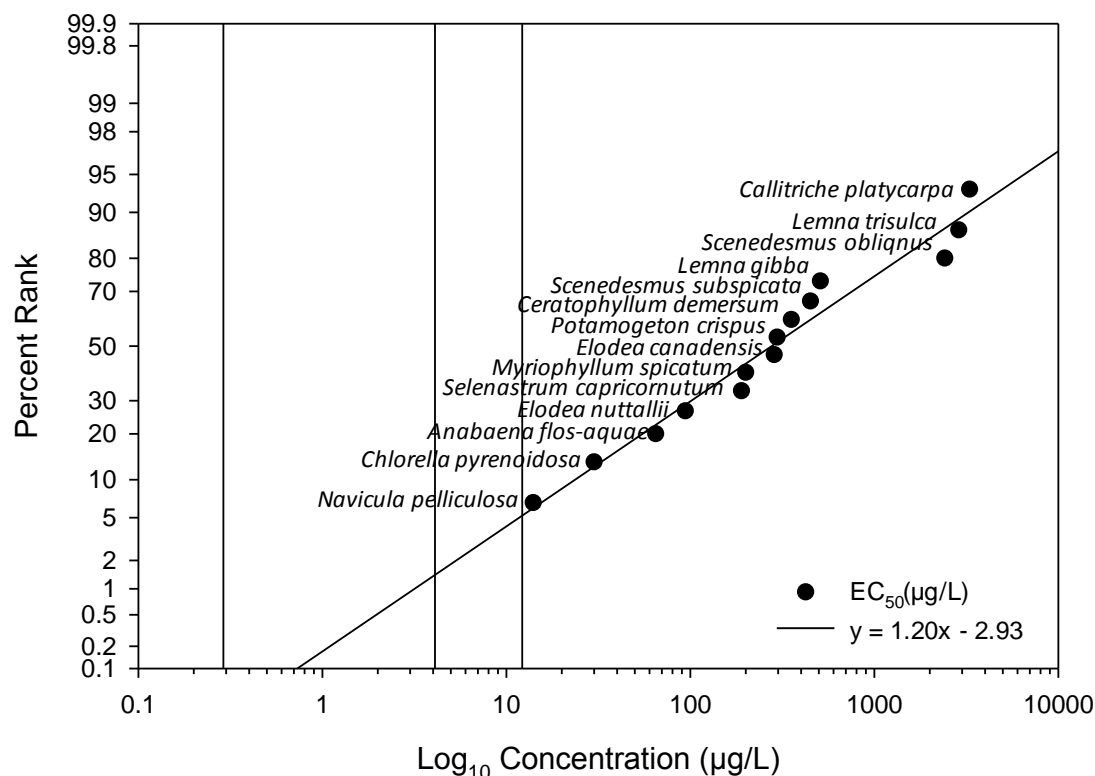
Vertical reference lines indicate exposure thresholds of 0.71, 4.1 and 17.2 µg/L, corresponding to the maximum chlorothalonil residue measured in agricultural systems in the U.S. (USGS, 2010), the upper 95th centile of monitoring data over 6 years at a golf course (King and Balogh, 2010), and the max 48 h time weighted average (TWA) concentration calculated from this same study.

Species Sensitivity Distribution: Fish



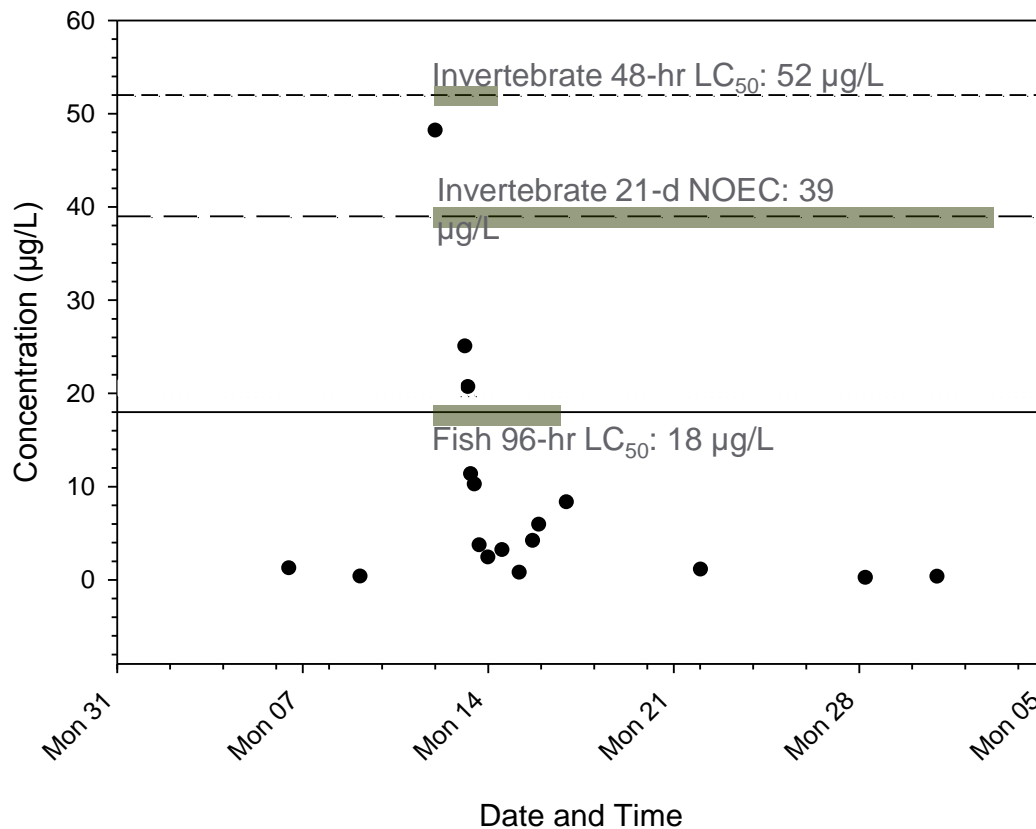
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Species Sensitivity Distribution: Plants



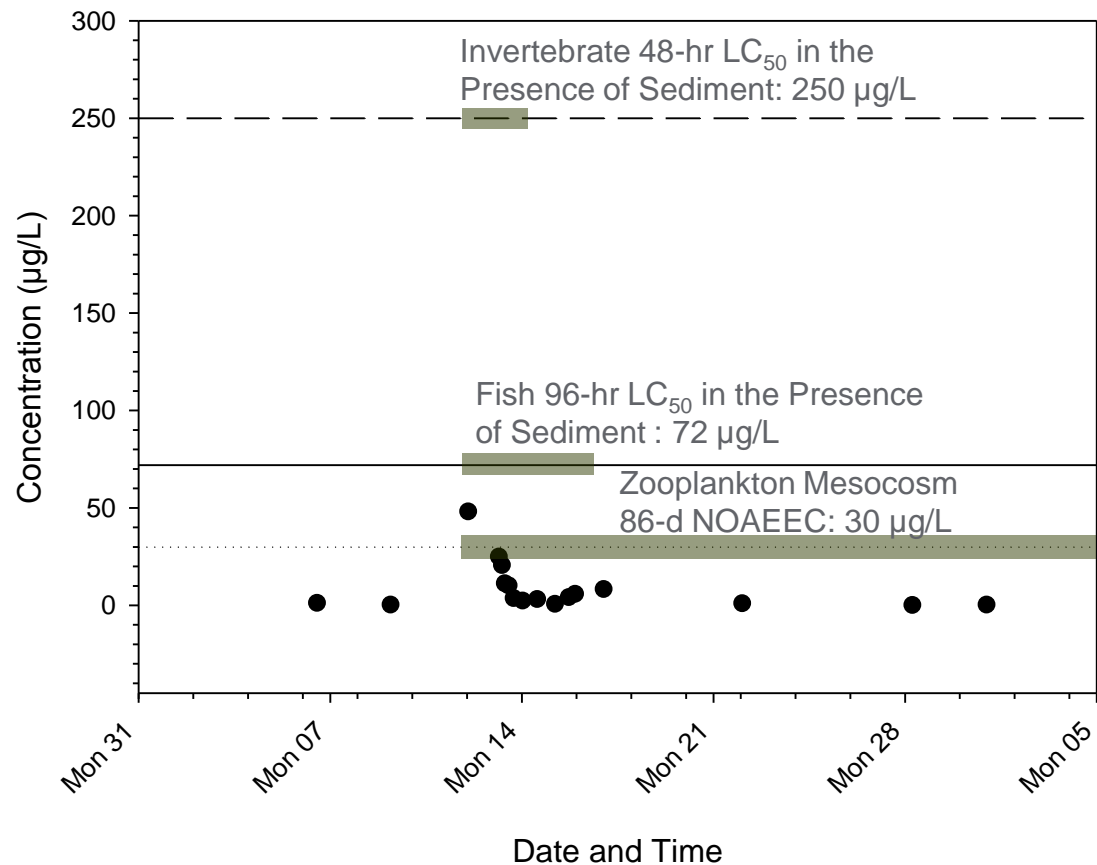
Vertical reference lines indicate exposure thresholds of 0.29, 4.1 and 12.2 µg/L, corresponding to the maximum chlorothalonil residue measured in agricultural systems in the Pacific Northwest (USGS, 2010), the upper 95th centile of monitoring data over 6 years at a golf course (King and Balogh, 2010), and the max 96 h time weighted average (TWA) concentration calculated from this same study.

Max Exposure Relative to Effects Thresholds and Duration



Comparison of fish and invertebrate toxicity thresholds versus peak chlorothalonil concentrations from data provided via personal communication from Dr. Kevin King. Thresholds for fish acute [LC_{50} : 18 $\mu\text{g/L}$; MRID: 45710219 (solid line)], invertebrate acute [LC_{50} : 52 $\mu\text{g/L}$; Ernst *et al.*, 1992 (short dashed line)], and invertebrate chronic [NOEC : 39 $\mu\text{g/L}$; MRID: 00115107 (long dashed line)].

Impact of Sediment on Toxicity



Conclusion: Chlorothalonil Aquatic Risk

- Chlorothalonil has high intrinsic toxicity to some aquatic organisms
- Chlorothalonil dissipates very rapidly in surface water
- Resulting in low and transient exposure to aquatic organisms
- Supported by monitoring data
- Results in a low risk to the aquatic environment

Chlorothalonil Summary

- Very important fungicide for disease control and resistance management
- Used on a broad range of crops
- Dissipates rapidly in both soil and water
- Low toxicity and low risk to terrestrial organisms
- Despite high intrinsic toxicity to some aquatic organisms, low risk due to low and transient exposure

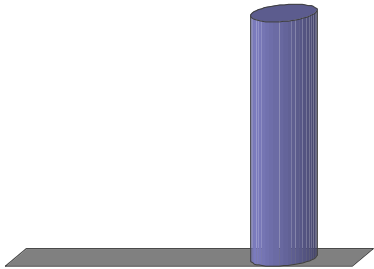


Azoxystrobin: Biological and Use Profile

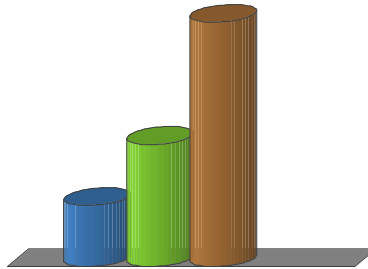
Azoxystrobin: Broad-Spectrum Persistent Disease Control

There are four classes of fungi. Strobilurins are the only fungicide that controls fungi in all four classes.

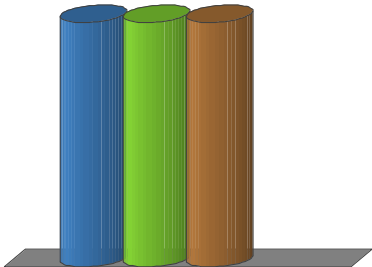
Phenylamides
(like Ridomil Gold®)



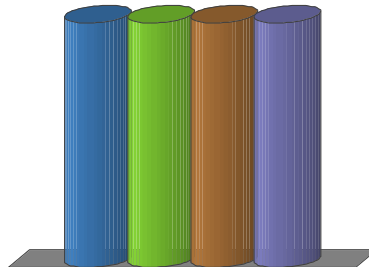
Dicarboximides
(like Rovral®)







Triazoles
(like Tilt)



Strobilurins
(Like Quadris)

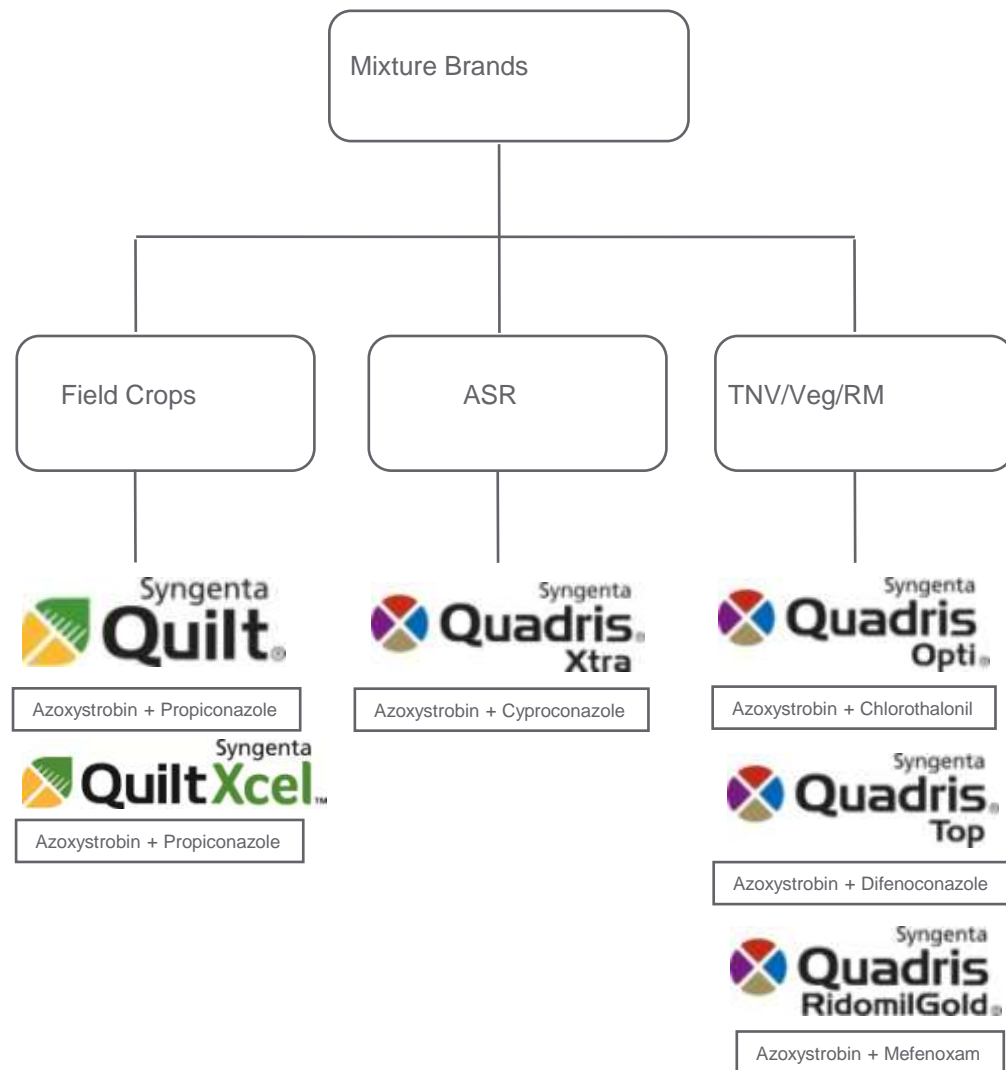
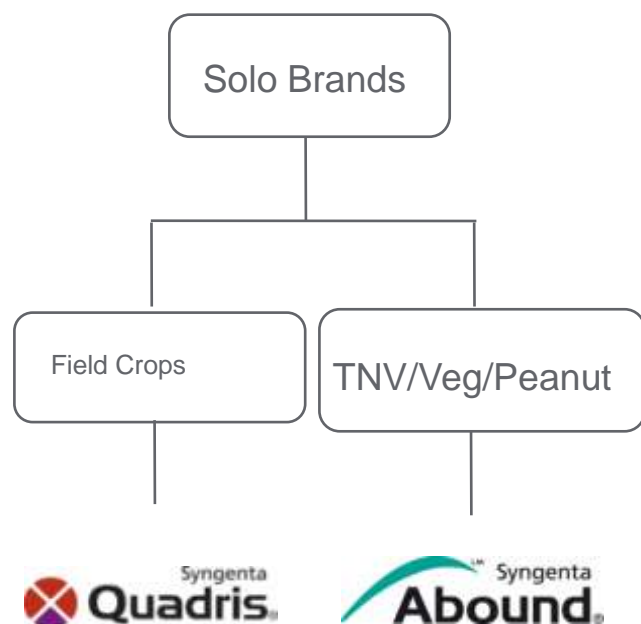


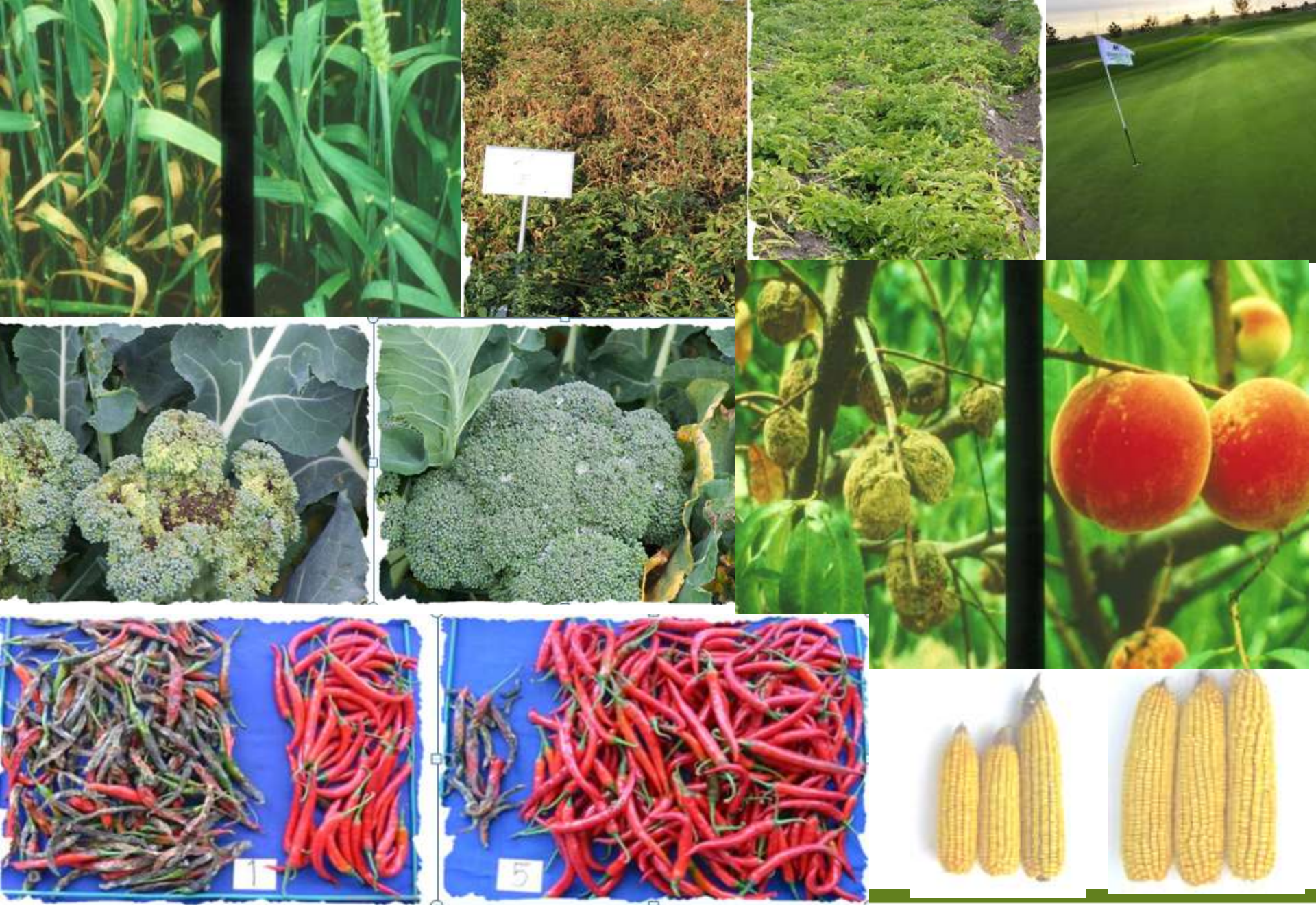
Class

- 1  Ascomycetes, e.g. Soybean pod and stem blight
- 2  Basidiomycetes, e.g. Soybean rusts & Aerial blight
- 3  Deuteromycetes, e.g. Alternaria leaf spot
- 4  Oomycetes, e.g. downy mildews

Unlike most other fungicides, azoxystrobin controls fungi in all four classes of fungi. This means broad-spectrum disease control.

Quadris family of brands





Azoxystrobin Usage in CA

- Used on approximately 325,000 acres in CA. (treated Acres)
- **Major crop use in CA:**
 - Cotton 85,500 A (seed treatment)
 - Almonds 41,500 A
 - Rice 41,000 A
 - Potatoes 34,400 A
 - Broccoli 19,200 A
 - Grapes 5,150 A (fresh)
 - Grapes 3,100 A (wine)
 - Lettuce 3,900 A (head)
 - Lettuce 3,400 A (romaine)
 - Lettuce 1,700 A (leaf)

Azoxystrobin Usage in CA

- **Major Crop Use in CA:**

- Strawberries 8,600 A
- Wheat 5,900 A (Fall)
- Wheat 3,900 A (Spring)
- Wheat 2,900 A (Winter)
- Garlic 7,000 A
- Onions 4,700 A
- Cantaloupe 2,450 A
- Honeydew 500 A
- Watermelons 2,000 A

Azoxystrobin Usage In CA

- **Major use crops in CA:**

- Artichokes	1,900 A
- Carrots	1,600 A
- Corn	1,600 A
- Celery	1,100 A
- Soybean	1,000 A

Other crops treated:

Apricots, barley, beans (dry + green), beets, blueberries, bok choy, cabbage, canola, cauliflower, cherries (sweet), chickpeas, cilantro, corn (sweet), cucumbers, fennel, grapefruit, grapes (raisin), grasses, kale, kohlrabi, leeks, melons, parsley, peaches, peas (green), peppers (bell+chile), pistachio, plums, prunes, radishes, raspberries, triticale, turfgrass, watermelons,

Quadris fungicide

Crop	Pounds a.i./A	Max pounds a.i./A
Artichoke, globe	0.18 – 0.25	1.5
Asparagus	0.1 – 0.25	1.5
Barley	0.1 – 0.2	0.4
Brassica Head and Stem	0.1 – 0.2	1.5
Brassica leafy greens	0.1 – 0.25	0.75
Bulb veg	0.1 – 0.25	1.5
Canola	0.1 – 0.25	0.45
Carrots	0.15 – 0.25	2.0
Celery	0.15 – 0.25	2.0
Clover	0.1 – 0.25	0.75
Corn	0.1 – 0.25	2.0
Cotton	0.1 – 0.15	0.44
Cucurbits	0.18 – 0.25	1.5
Herbs & Spices	0.1 – 0.25	1.5

Quadris fungicide

Crop	Pounds a.i./A	Max pounds a.i./A
Leafy Veg	0.1 – 0.25	1.5
Legume Veg	0.1 – 0.25	1.5
Mint	0.1 – 0.25	0.75
Non-grass animal feed	0.1 – 0.25	0.75
Oilseed crops	0.1 – 0.25	0.45
Pepper	0.1 – 0.25	1.0
Potato	0.1 – 0.25	2.0
Rice	0.15 – 0.25	0.7
Sorghum	0.1 – 0.25	0.75
Soy	0.1 – 0.25	1.5
Tobacco	0.1 – 0.2	0.52
Tomato	0.08 – 0.1	0.6
Veg, leaves of root & tuber	0.1 – 0.25	2.0
Veg, tuberous and corms	0.1 – 0.25	2.0

Quadris fungicide

Crop	Pounds a.i./A	Max pounds a.i./A
Watercrest	0.1 – 0.25	1.5
Wheat	0.07 – 0.2	0.4
Wild Rice	0.2 – 0.25	0.7



Untreated

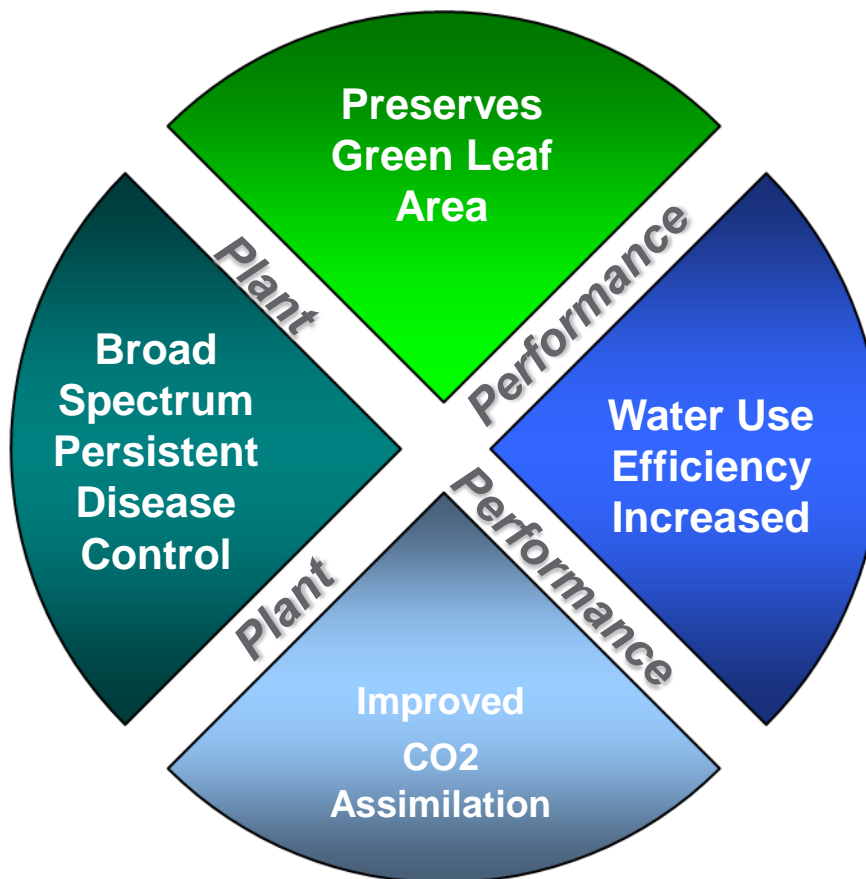
Azoxystrobin Plant Performance



By extending the
time for grain filling



By protecting
crops from a wide
range of yield
robbing diseases



By improving
tolerance to
drought



By enhancing
photosynthesis



Heritage Fungicide

Crop	Pounds a.i./A/application	Max pounds a.i./A/Season
Turf - Brown Patch, Pythium, Summer Patch, etc. Typical Use	0.27 – 0.54	5.0
Gray Snow Mold – 1 app.	0.95	

Heritage

Summer Patch Control



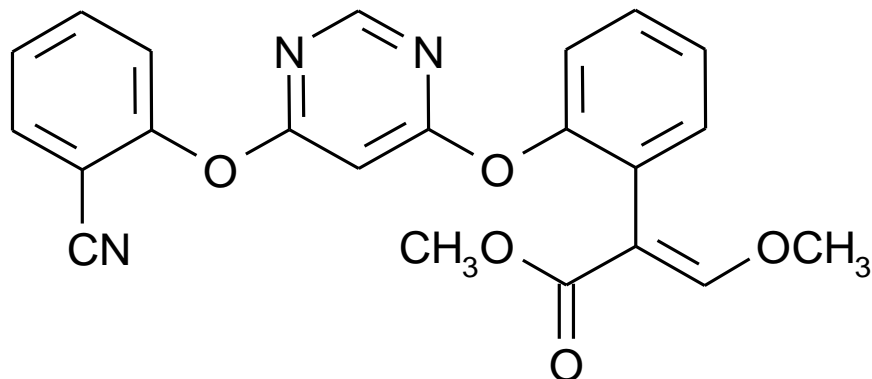
Heritage Pythium Control



Heritage

Brown Patch Control





syngenta

Azoxystrobin: Chemistry, Environmental Fate and Risk to Aquatic Organisms

Robert S I Joseph

Head of Environmental Safety North America, Syngenta

From the forest to the field



The strobilurin fungicides – *Oudemansiella mucida* and *Strobilurus tenacellus*



S. tenacellus

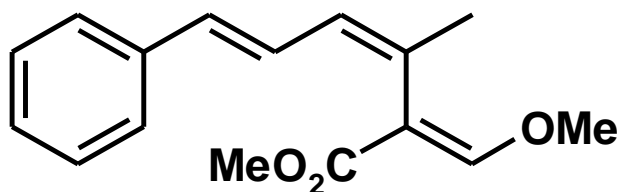
O. mucida

The Discovery Story

- **1969** Musilek et. Al. published on antifungal extracts from the fungus *Oudemansiella mucida*.

- They named this compound “Mucidin” – without proposing a structure.

- **1977** Timm Anke (Univ. Kaiserslautern) and Wolfgang Steglich (Univ. München) described Strobilurin A from *S. tenacellus* and reported broad spectrum activity along with chemical and physical chemistry data.



Strobilurin A

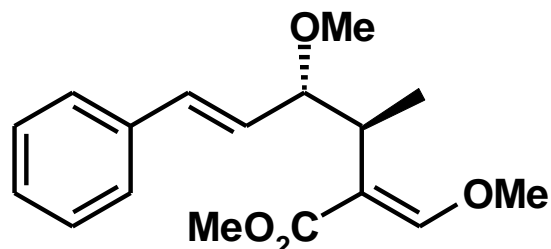


T. Anke



W. Steglich

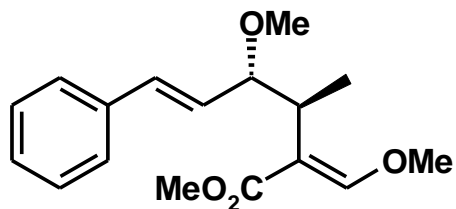
- **1979** Anke & Steglich reported on a closely related Oudemansin A



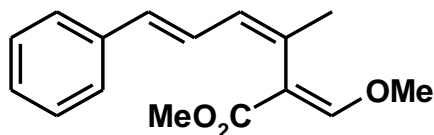
Oudemansin A

The Discovery Story

- 1982 ICI (Syngenta) obtained Oudemansin A from Timm Anke



Oudemansin A



Strobilurin A

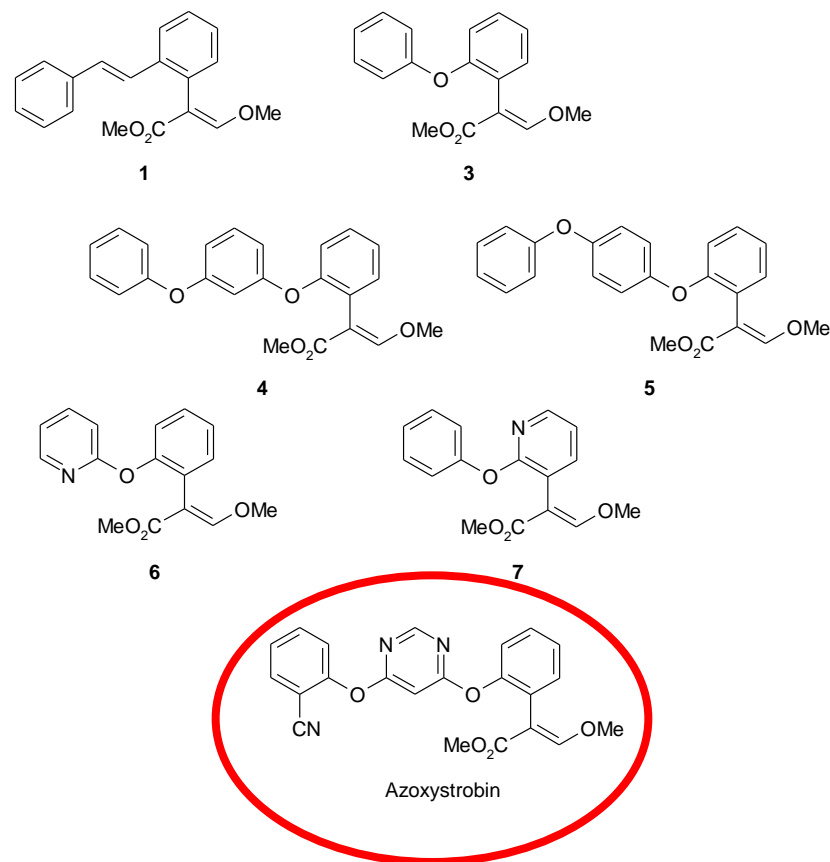
- ICI found broad spectrum activity in GH tests and started a synthesis program.
- Strobilurin A was a simpler structure and a more attractive lead for synthesis.
- Not available from academics, so obtained sample by total synthesis.
- There was great excitement !
However, when tested in the glasshouse there was **no activity**.

What was different between the forest and the field ?



The Discovery Story

- ICI scientists added UV stabilizers and got some activity.
- This began a synthesis program that would modify the structure to reduce UV degradation.
- 1400 analogues were synthesized before Azoxystrobin was discovered.
- Representing 50 man years of synthetic chemistry effort alone.

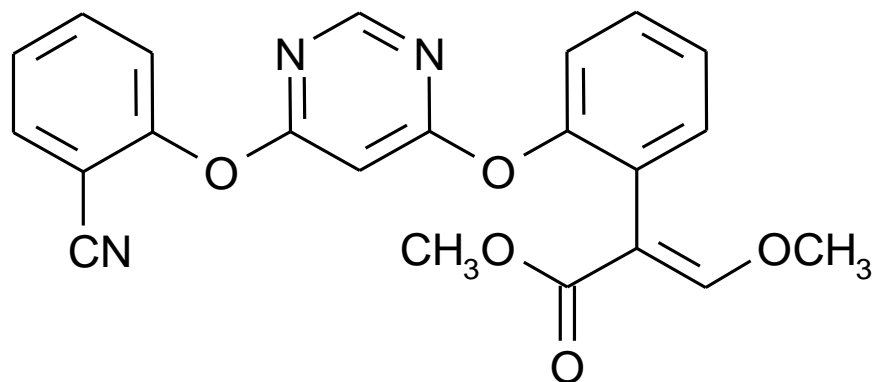


John Clough and Christopher Godfrey. "The Strobilurin Fungicides"

Figure 8. Milestones in the Discovery of Azoxystrobin

The Discovery Story

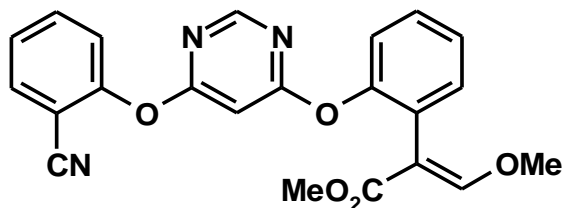
- ICI's Azoxystrobin was announced at the Brighton Conference Nov. 1992



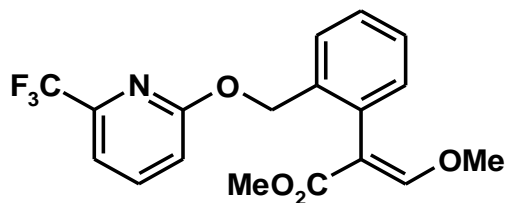
Azoxystrobin (ICIA5504)

A family of synthetic commercial strobilurins

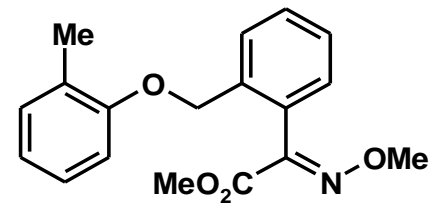
Examples, showing year of first sales



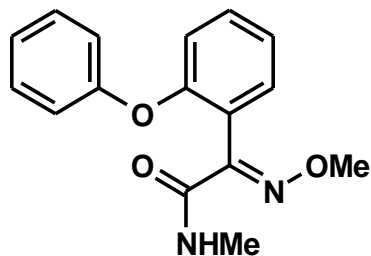
Azoxystrobin, Syngenta, 1996



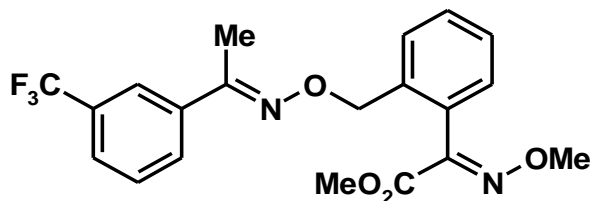
Picoxystrobin, Syngenta, 2002



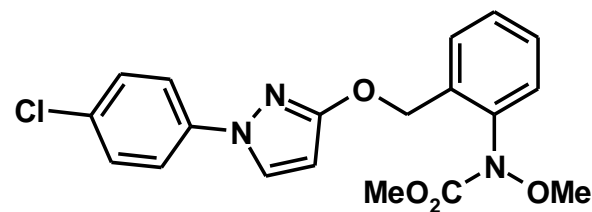
Kresoxim-methyl, BASF, 1996



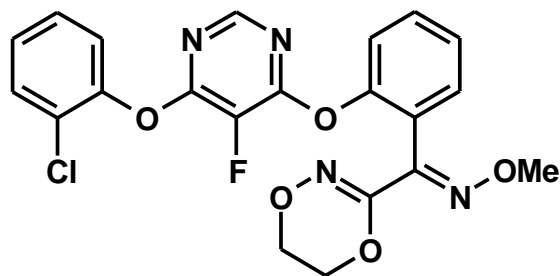
Metominostrobin, Shionogi, 1999



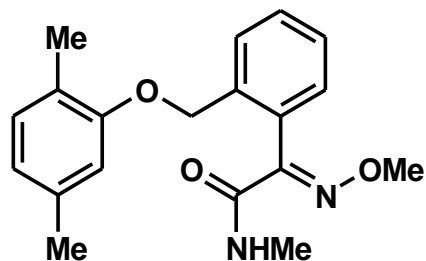
Trifloxystrobin, Bayer, 1999



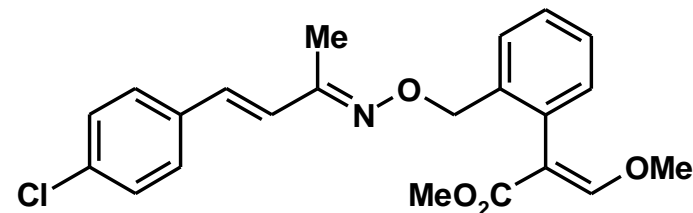
Pyraclostrobin, BASF, 2002



Fluoxastrobin, Bayer, ~2002



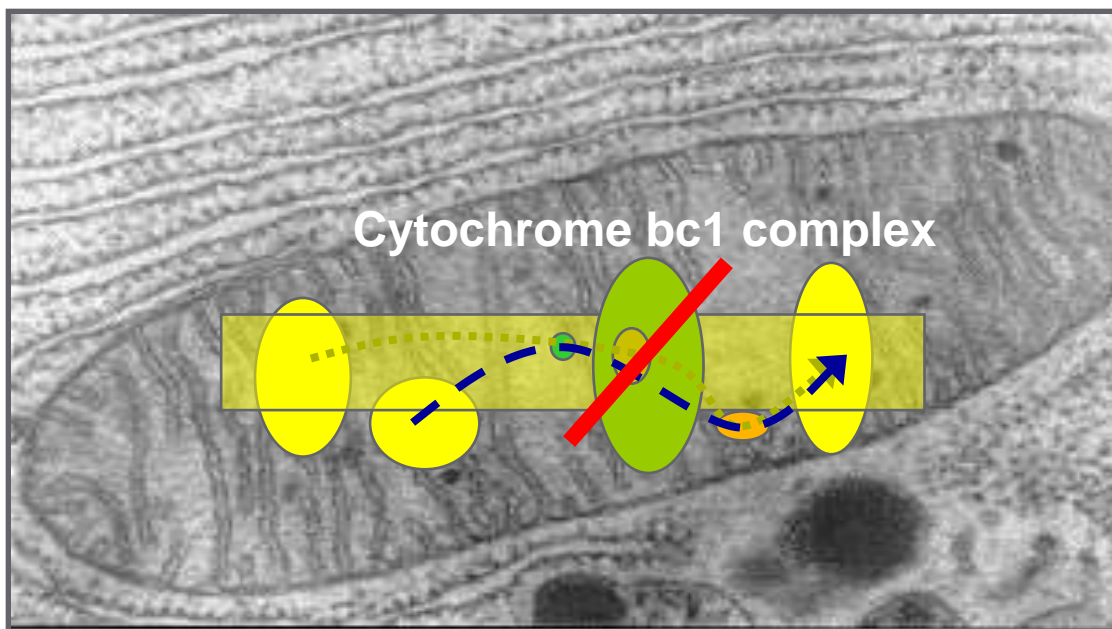
Dimoxystrobin, BASF, ~2002



Enestroburin, Shenyang, 2003

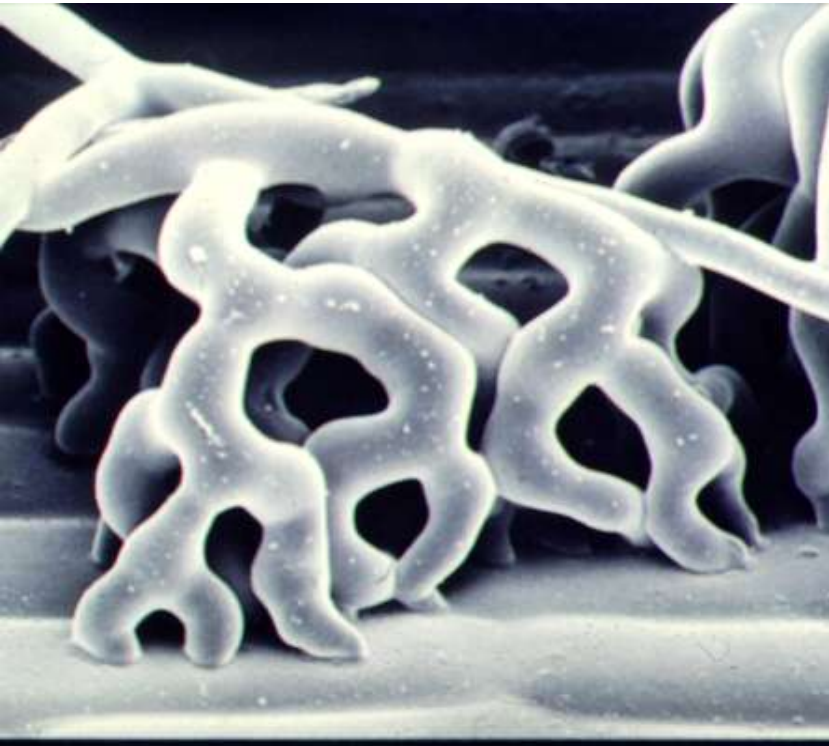
Mode of Action of Qol fungicides

- Qol fungicides inhibit energy production in the fungal pathogen, by disrupting essential energy generation processes in the mitochondria.

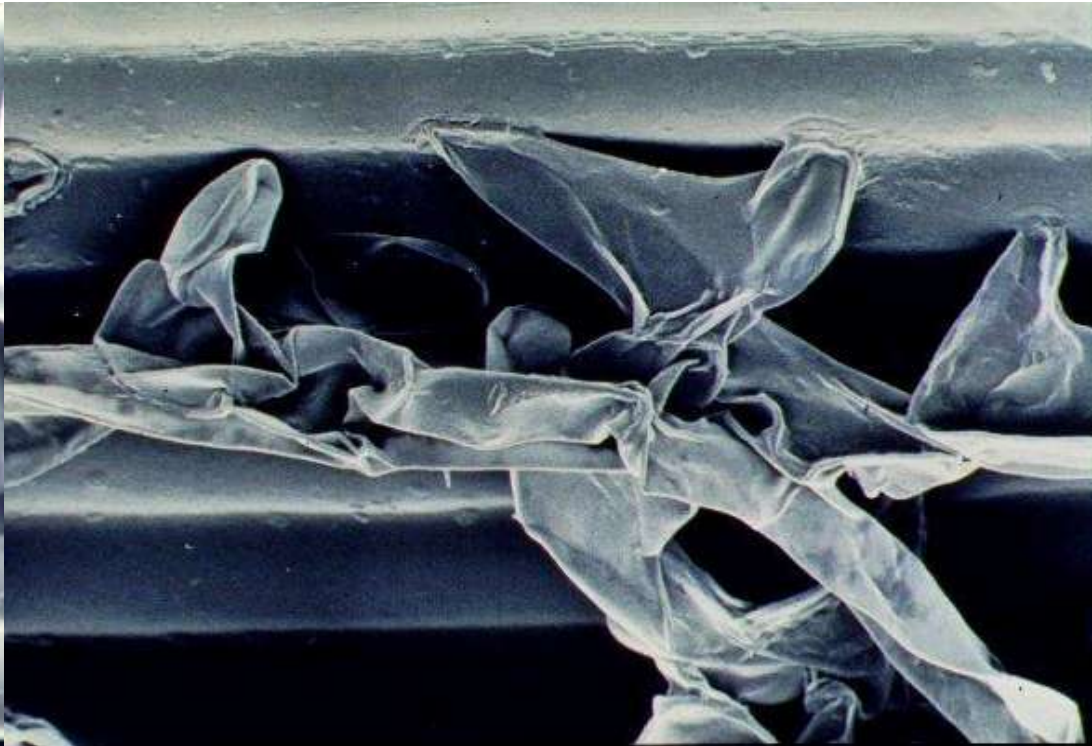


**Electron micrograph of
a mitochondrion**

Rhizoctonia solani



Untreated



Azoxystrobin

Azoxystrobin: Environmental Safety Summary

- Azoxystrobin is of low toxicity and consequently low risk to:
 - birds, mammals, bees and other non-target terrestrial organisms.
- Although highly toxic to aquatic organisms, actual field use of azoxystrobin results in a low risk of effects due to:
 - Azoxystrobin's low application rates and
 - Dissipation in the environment
- Registered as a reduced risk pesticide

Azoxystrobin: Physicochemical properties

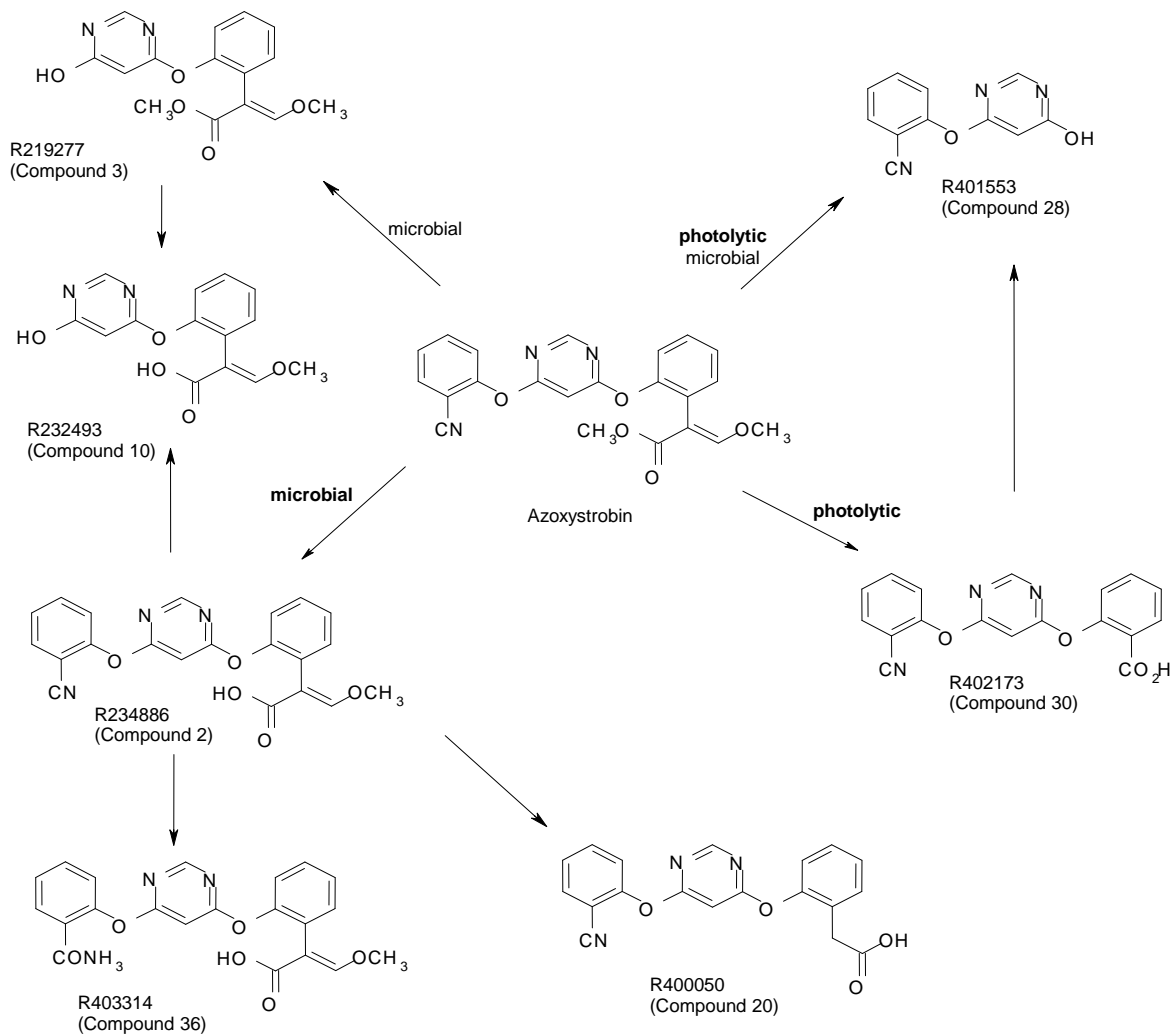
Molecular weight	403.4 g/mol
Water solubility	6 mg/L
Melting Point	116°C
Octanol/water partition coefficient	2.5 (log P _{ow})
Vapour pressure	8.2 x 10 ⁻¹³ torr (mm Hg)
Volatilisation rate (Henry's Law Constant at 20°C)	7.3 x 10 ⁻¹⁴ atm m ³ mol ⁻¹ (Non volatile)
Adsorption constant (K _{oc})	K _{oc} range from 300 to 1690 mL/g
Biodegradation in aquatic systems	Rapidly adsorbed on to the sediment (half-life < 7 days) Degraded in the total water/sediment system with a half-life of 205 days.
Photolytic stability	Half-life of 11 to 17days
Hydrolytic stability	Stable

Degradation of Azoxystrobin Under Field Conditions

- Lab soil metabolism half lives of 8-20 weeks
 - Primary metabolite is the acid R234886
 - Degradation is microbial
- Rapid photolytic degradation on the soil surface
 - Half life <2 weeks
 - Complex degradation pathway, 13 photoproducts identified
- Radiolabelled field study
 - Determine importance of microbial and photolytic pathways in field
 - Showed rapid dissipation with photolysis as the primary pathway
- Results confirmed in multiple field dissipation studies

Azoxystrobin: Fate in Soil

- Degrades via both photolytic and microbial pathways
- Metabolites are themselves readily degraded to CO₂
- Major degradates are Compounds 2, 28 and 30



Azoxystrobin Metabolites/Degradates

- Compound 2 (R234886)
 - Primary microbial degradate
 - Not fungicidally active
 - Considerably less toxic than azoxystrobin to fish and invertebrates.
- Compounds 28 & 30 (R401553 & R402173)
 - Primary photolytic degradates
 - Not fungicidally active
 - Considerably less toxic than azoxystrobin to fish and invertebrates.
- Conclusion : Only azoxystrobin needs to be considered in the risk assessment

Azoxystrobin: Ecotoxicological Profile Terrestrial

- Birds - practically nontoxic
 - oral $LD_{50} > 2000$ mg /kg, dietary $LC_{50} > 5200$ ppm
- Bees – nontoxic
 - $LD_{50} > 200$ µg/bee
- Non-target arthropods – harmless (IOBC)
 - No toxicity at >> field rates
- Earthworms
 - LC_{50} 284 mg/kg soil



Terrestrial Exposure

- Azoxystrobin is rapidly dissipated in soil
 - Soil photolysis and microbial degradation both important mechanisms.
- Breakdown products readily degraded
 - Only present at low levels and do not accumulate in soil.
 - Ultimately mineralized to carbon dioxide.
- Azoxystrobin and its breakdown products unlikely to leach
 - combination of degradation rates and
 - relatively low mobility in soil
- Azoxystrobin degradates are not biologically active
- Risk assessment only needs to focus on azoxystrobin

Terrestrial Risk

- Azoxystrobin is of low toxicity to terrestrial organisms
 - birds, mammals, bees and other insects, and earthworms.
- Azoxystrobin will not present an unacceptable risk to the terrestrial environment.
 - Based on a combination of low exposure and low toxicity



Azoxystrobin: Ecotoxicological Profile Aquatic

- Fish - highly to moderately toxic
 - acute $LC_{50} = 470 - 2160 \mu\text{g/L}$
- Aquatic invertebrates - very highly to moderately toxic
 - acute $EC_{50} = 55 - >4000 \mu\text{g/L}$
- Aquatic Plants/Algae – very highly to slightly toxic
 - $EC_{50} = 57 - 10000 \mu\text{g/L}$
- Low acute/chronic ratio
 - Lower potential for chronic risk



Aquatic Risk Assessment

- Assessed risk to fish, invertebrates and algae
- Exposure – tier 1, worst-case model GENEEC

$$\frac{\text{Exposure}}{\text{Toxicity}} = \text{Risk Quotient (RQ)}$$

- If RQ < trigger value = **low risk**
- If RQ > trigger – refine assessment, tiers 2 and above
- Some uses have RQs that marginally exceeded trigger values
- Tier II assessment conducted with refined exposure assessments
 - PRZM/EXAMS



Tier II Aquatic Risk Example

Aerial Use on Clover and Cotton

- Aerial application to clover and cotton (July 2008)
- Up to 3 applications at 0.25 and 0.15 lbs ai/acre respectively
- PRZM/EXAMS run with conservative fate parameters
 - DT_{50} soil = 161 days
 - No consideration of soil surface photolysis
 - DT_{50} water = 322 days
 - Aqueous photolysis = 23 days
 - K_d soil = 6.2
 - Spray Drift = 5%

PRZM/EXAMS Tier II Risk Assessment

Aerial application on clover

- Three applications of 0.25 lb/acre at 7 day intervals
- Acute risk assessment
- LOC = 0.5
- Risk quotients significantly below LOC

Organism	Exposure (µg/L)	LC50 µg/L	RQ
Fish	9.0	470	0.02
Aquatic Invertebrates	9.0	260	0.03

- **Acute and Chronic RQs for clover and cotton all less than LOC**
- Conclusions supported by results of mesocosm studies

Azoxystrobin: Environmental Safety Summary

- Azoxystrobin is of low toxicity and consequently low risk to:
 - birds, mammals, bees and other non-target terrestrial organisms.
- Although highly toxic to aquatic organisms, actual field use of azoxystrobin results in a low risk of effects due to:
 - Azoxystrobin's low application rates and
 - Dissipation in the environment.

Azoxystrobin Summary

- Broad spectrum fungicide – controls all four classes of fungi
- Used on a broad range of crops
- Low toxicity and low risk to terrestrial organisms
- High toxicity to aquatic organisms but low risk due to low exposure