

DITHANE: keeping An Old Friend Going!



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Dithane ® : Keeping an Old Friend Going: What's Involved?

- History and Noteworthy features
- The Market
- Challenges: The hurdles of re-registering a 45 year old broad spectrum fungicide in Europe
- Dithane Annex III: Journey to GAP harmonisation
- Why do we still need mancozeb? What are the benefits still in potato?
- The Future

1961: what were you doing?

- USA breaks off diplomatic relations with Cuba (03 Jan) followed by Cuban missile crisis and “Bay of Pigs” later that year (17 April)
- First man in space (Yuri Gagarin) (12 April)
- Amnesty International was formed in London (July)
- East Germany erected the Berlin wall (13 Aug)
- OPEC was formally constituted
- Mancozeb first registration in 1961 by Rohm & Haas Co. and by E.I. Du Pont De Nemours and Co.
- Mancozeb was born in troubled times and still very important today!

1940's - The first broad-spectrum foliar fungicide

The dithiocarbamates



(exists as a coordination complex of Zn & Mn)

Mancozeb

- **Low toxicity to plants, animals, and the environment.**

FRAC group: M3

- Ethylenebisdithiocarbamates (EBDC) were one the most important breakthroughs in disease control. *Phytophthora*, *Venturia*, *Alternaria*, *Septoria*
- EBDC chemistry first commercialized in 1943/4 as nabam and thiram. Later came Ferbam, zineb, maneb.
- Mancozeb first registration in 1962 by Rohm & Haas Co. and by E.I. Du Pont De Nemours and Co.
- Although strictly protectants, EBDC fungicides continue to be critical components of many resistance management and integrated disease management programs.

Noteworthy Features

Mancozeb

- Very broad spectrum protectant fungicide.
- Low risk of resistance due to multi-site mode of action
- High margins of crop safety
- Low persistence in the environment (rapidly degraded in soil and water, not present in air).
- Cost benefit over non-EBDC's
- Commonly formulated as wettable powder, water dispersible granular and flowable formulations when used alone or in tank mixtures. Commonly used in combinations with other fungicides.

Dithane® Brand Mancozeb -

- Tradition and confidence for 45 years
- Packaging and formulation quality
- Preferred partner of systemic and penetrant fungicides
- Formulation technology, consistent particle size, packaging, rain shield technology in Dithane NT DF/WG®
- Technical regulatory support
- Manufacturing leadership

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The Market: Mancozeb Still A Leading Fungicide (Agrobases 2007)

- **2007**
 - Tebuconazole leading the market
 - Mancozeb #2 with > 500 MM\$
 - Innovation (Septoria resistance & Soybean rust positions) led growth

- **1997**
 - Mancozeb was the leading active with 401 MM \$ (Distr. Level)
 - No Strobilurin was among the Top 10

Leading Actives in LYLC (*) 2007	
TEBUCONAZOLE	525.14
MANCOZEB	501.05
AZOXYSTROBIN	372.88
PYRACLOSTROBIN	329.57
EPOXICONAZOLE	302.83
CHLOROTHALONIL	228.31
PROPICONAZOLE	219.07
PROTHIOCONAZOLE	202.63
CYPROCONAZOLE	178.64
TRIFLOXYSTROBIN	156.73

Leading Active in LYLC (*) 1997	
MANCOZEB	406.46
CHLOROTHALONIL	230.58
EPOXICONAZOLE	207.91
PROPICONAZOLE	181.69
METALAXYL	157.23
TEBUCONAZOLE	144.03
COPPER-OXYCHLORIDE	129.53
CYPROCONAZOLE	114.24
SULPHUR	113.65
CYMOXANIL	111.75

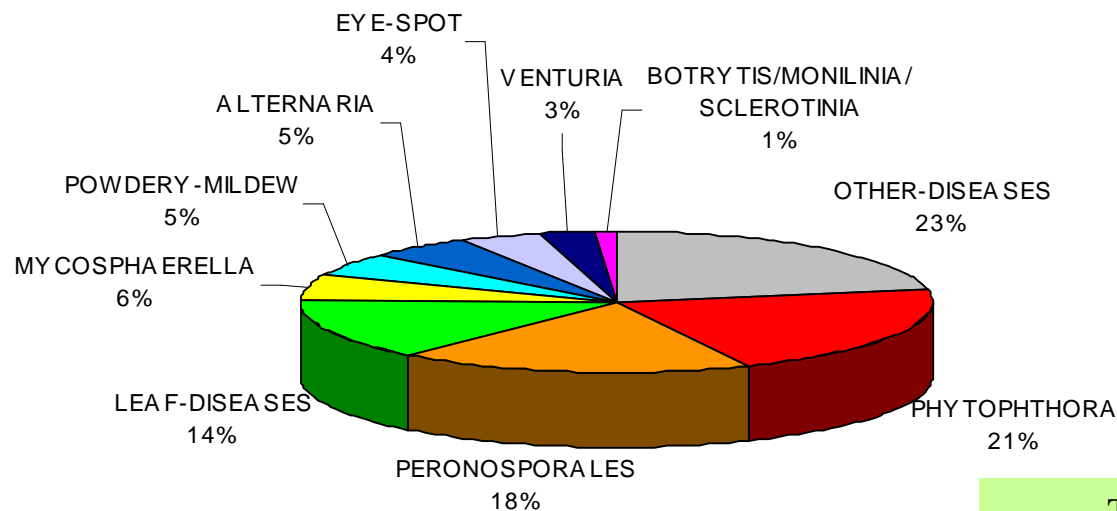
(*) LYLC= Last years last crop in 2007

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Mancozeb: Targeted Disease (Agrobase, Globally 2007)

- Dithane ® controls the broadest number of diseases in the greatest number of crops of any fungicide.
- Registered on > 70 crops for >400 diseases (Phycomycetes, Ascomycetes, Deuteromycetes, Basidiomycetes).
- Mancozeb based products are primarily focused on Oomycete diseases (*Phytophthora* and *Peronospora*), but Leaf diseases are important targets as well



Top 10 Disease Groups
(96% of Mancozeb Products Value)

The Challenges

- High use rate product.
- Regulatory landscape post 91/414 is uncertain.
 - Hazard based criteria - endocrine disruption ??? (high level of uncertainty, no agreed definitions). May affect mancozeb and many other fungicides especially DMI's in cereals.
 - Possible candidate for substitution but derogation may be possible under commission. Potential disease resistance issues, loss of all mancozeb mixture products and impact on yield.
- Continual and sustained pressure from NGOs
- Many generic competitors, price pressure, supply pressure
- Regulatory challenges: Annex III : The Journey to Harmonisation

Dithane ® Annex III: Journey to GAP harmonisation

Current situation:

- Old and outdated labels,
 - Rate differences for same crop and disease
 - No. applications and interval differ
 - Crops registered in some countries and not others
 - Water volumes differ greatly
 - Some registrations based on very little data
-
- Mancozeb is Annex I listed (Q2 2005)
 - Sales dominated by grapes, potatoes, apples, vegetables
 - Multinational Partners had similar priorities (grapes, potatoes, tomatoes, cucurbits, onions)
 - Registrations on further 30-40 crops – each crop less than 1% of total sales of mancozeb!
 - Over 15 Annex III dossiers from DAS and Multinational Partners for June 2008
 - **Essential to find an cost effective way to manage Annex III!**

Dithane ® Annex III: Journey to GAP harmonisation

The Strategy

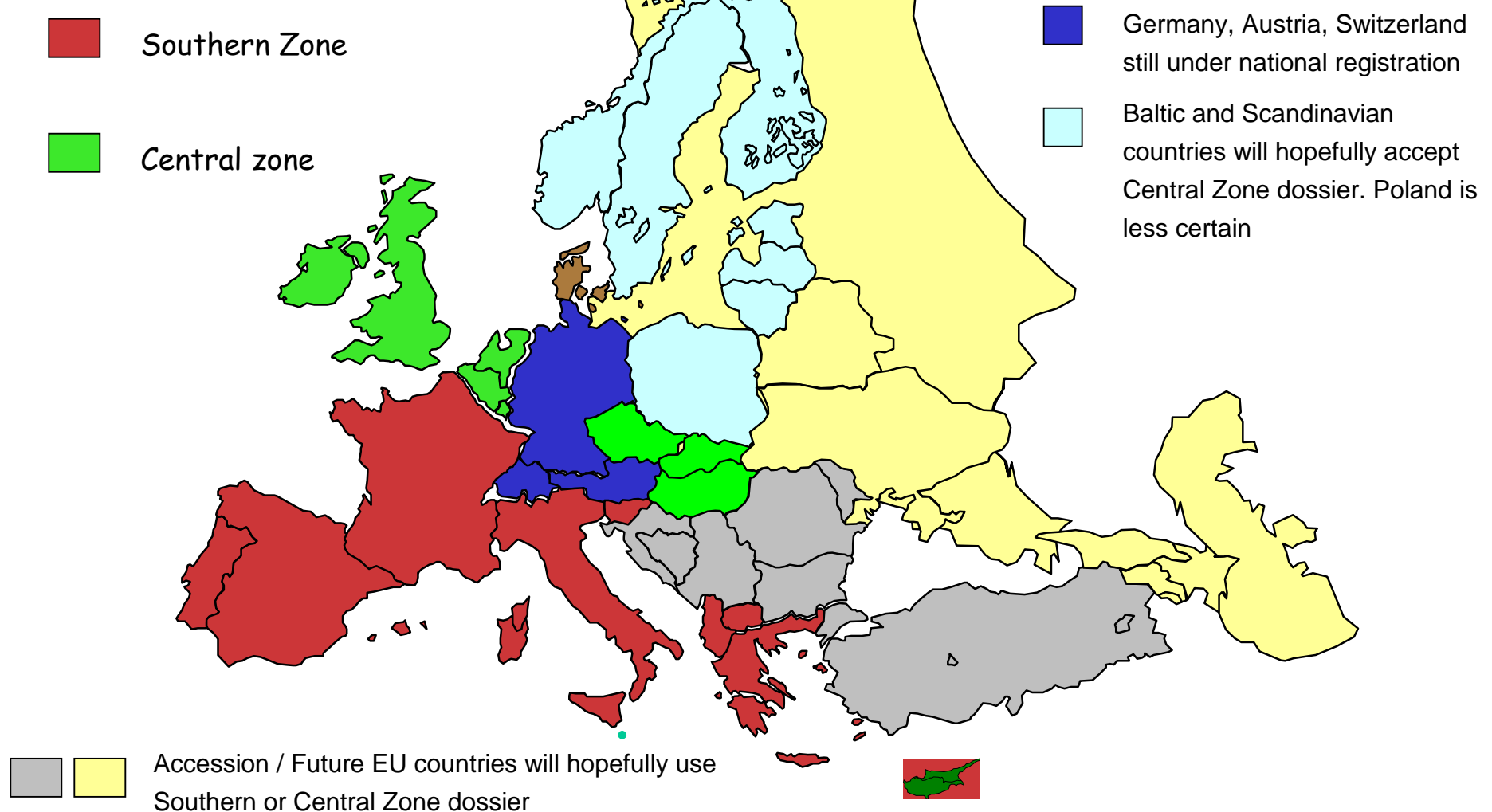
- Zonal approach to re-registration (UK and Greece as lead MS for Central and Southern Zones)
- Opportunity to maintain important uses (e.g. potato) and minor uses.
- Harmonize GAP and label for each crop across countries
- Stewardship of mancozeb across all DAS Multinational customer registrations to achieve “risk envelope” based on DAS mancozeb
- Success will need pragmatic approach from the MS authorities especially in regard to detailed discussions on efficacy and key risk assessments
- This exercise is very time consuming!

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Dithane® Annex III EU Work Sharing



Current work sharing Proposal



The Proposal at Annex III

- Doses: Max 1.6 kg a.s. (2 kg prod) in most crops (Potato) with up to 2 kg a.s. (2.5 kg pr/ha). Considerable dose reduction in some crops (tree fruit)
- Applications (straight): Max 8 potato, 5 tomato, 1-4 in other crops
- Interval between application (7 day potato), up to 28 days in some crops.
- Mancozeb has an extensive list of EU MRLs
 - Dithane ® Annex III core dossier and national supplements supports 29 crops in the North and Central Zone and 40 crops in the Southern Zone
- A combination of “off label” approvals, label extension submissions and mutual recognition applications will be used to try to achieve similar label recommendations with in the zones

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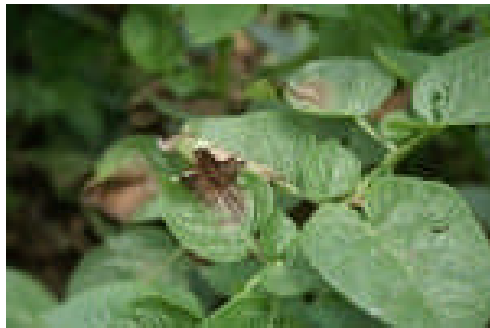


The timetable: so far!

- **April 2008** - Final Version of Annex III “core dossier” sent to UK/Greece
- **June 2008** – Draft Registration Report sent to UK/Greece
- **June 2008** – “Core dossier” and where required national supplements to all MS
- **June 2009** - UK/Greece Zonal Evaluation on CIRCA
- **June 2010** – Re-registration across in all EU MS!

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Why do we still need mancozeb in potatoes?



Mancozeb: Why still needed in Potatoes

- Vital component for many potato blight sprays either as a straight or as formulated mixture
- Cost effective protectant
- Resistance management tool - Multi-site, low resistance risk with no confirmed resistance in 40+ years of use
- Excellent blend partner for other fungicides as resistance management tool and protectant element. If you lose mancozeb, you lose all the co-formulations
- Still an excellent Protectant, contact fungicide, especially oomycete's
- Alternaria control (which many newer late blight actives do not offer)
- Micro-nutrient benefits
- Dithane ® offers regulatory, quality and formulation benefits over other mancozebs

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Potatoes – Oomycetes multi-site market segment of multi-site actives applied alone or in formulated mixture (Agrobase)

- Super developed area treated France 2,664,000 Ha
- Super developed area treated Germany 1,755,000 Ha
- Super developed area treated UK 893,000 Ha

Active Substance	List	Annex 1 Status	% of SDA Ha treated France	% of SDA Ha treated Germany	% of SDA Ha treated UK	MOA/ Code (FRAC)	Chemical Class
Mancozeb	1	In	62%	44%	37%	M3	Dithiocarbamate
Metiram	1	In	0.6%	1.7%	0%	M3	Dithiocarbamate
Maneb	1	In	7%	8.7%	0%	M3	Dithiocarbamate
Chlorothalonil	1	In	3%	0%	1.7%	M5	Chloronitrile
Copper	3A	Pending	1.3%	0.3%	0%	M1	Inorganic
Folpet	2	In	0.6%	0%	0%	M4	Phthalimide
Propineb	1	In	1%	0%	0%	M3	Dithiocarbamate

Agrobase 2006

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Site of Action of Common Potato Blight Active Ingredients

Mitosis & cell division

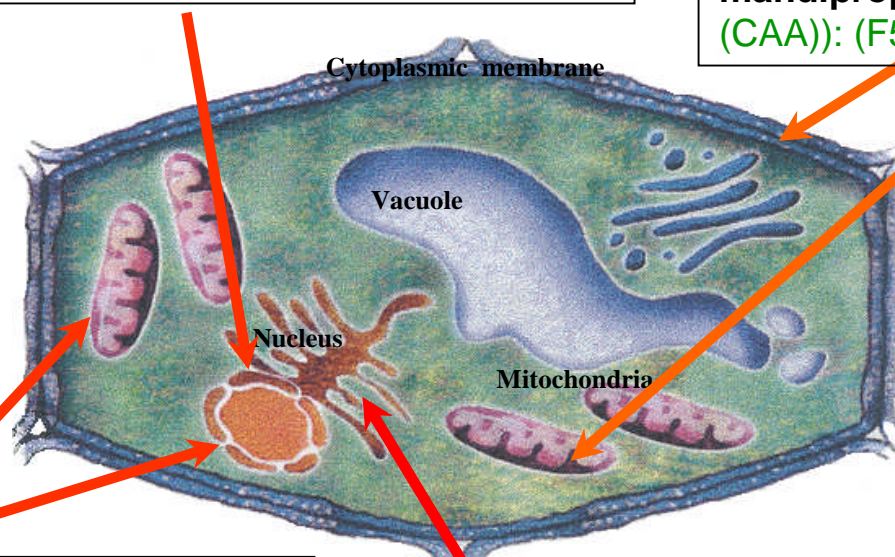
fluopicolide (43): Spectrin like proteins (B5)
zoxamide (22): Beta tubulin assembly in mitosis (B3)

Lipid and membrane synthesis

Propamocarb (28) F4 (cell membrane)
dimethomorph (40), bentiavalicarb (40),
mandipropamid (40) (Carboxylic acid amides
(CAA)): (F5)

Unknown MOA

cymoxanil (27)
Fosetyl-al (33)
Phos acid (33)



Respiration

famoxadone (11); fenamidone
(11) Complex III, cytochrome bc1
QoI (C3)
cyazofamid (21), ambisulbrom
(21): Qil (C4)
fluazinam (29): Uncouplers of
oxidative phosphorylation (C5)

Multi site contact activity

Mancozeb & other MBC's (Thiol
inhibitor, 6 different pathways) (M3)
copper (M1), chlorothalonil (M5)

Nucleic acid synthesis

benalaxyl (4); metalaxyl M (4)
PhenylAmides RNA Polymerase (A1)

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Combined Resistance Risk Diagram based on inherent fungicide risk, inherent pathogen risk and agronomic risk (KUCK 2005)

↓ Fungicide Classes *	↓ Fungicide Risk	Combined Risk			↓ Agronomic Risk
benzimidazoles dicarboximides phenylamides QoI fungicides	high = 6	6 3 1,5	12 6 3	18 9 4,5	high = 1 medium = 0.5 low = 0.25
carboxamides SBI fungicides anilinopyrimidines phenylpyrroles	medium = 4	4 2 1	8 4 2	12 6 3	high = 1 medium = 0.5 low = 0.25
multi site fungicides (e.g.dithiocarbamates) MBI-R inhibitors SAR inducers	low = 1	1 0,5 0,25	2 1 0,5	3 1,5 0,75	high = 1 medium = 0.5 low = 0.25
Pathogen risk →		low = 1	medium = 2	high = 3	
Pathogen groups * →		seed borne pathogens (e.g. <i>Pyrenophora</i> sp. <i>Ustilago</i> sp.) soil-borne pathogens (e.g. <i>Phytophthora</i> sp.) rust fungi <i>Rhizoctonia</i> sp. <i>Fusarium</i> sp.	<i>Uncinula necator</i> <i>Gibberella fujikuroi</i> <i>Tapesia</i> sp. <i>Rhynchosporium secalis</i> <i>Pyrenophora teres</i> <i>Septoria tritici</i> <i>Sclerotinia</i> sp. <i>Monilinia</i> sp. <i>Cercospora</i> sp. <i>Phytophthora infestans</i> /other modes of action	<i>Erysiphe graminis</i> <i>Botrytis cinerea</i> <i>Plasmopara viticola</i> <i>Magnaporthe grisea</i> <i>Venturia inaequalis</i> <i>Mycosphaerella fijiensis</i> <i>Phytophthora infestans</i> /RNA polymerase	

FRAC:Pathogen Risk Dec 2005

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If you lose mancozeb, you lose all these Fungicidal a.i.s in co-formulation with mancozeb and any future mixture products for use in potato and grape vine

Benalaxyl	Fenamidone
Benalaxyl M (Kiralaxyl)	Folpet
Benthiavalicarb	Fenbuconazole
Copper	Fosetyl-al
Copper+Folpet	Fosetyl+cymox
Copper+Sulphur	Fosetyl-al+Benalaxyl
Cymoxanil	Fosetyl-al+Iprovalicarb
Cymoxanil+copper	Iprovalicarb
Cymoxanil+Copper+Folpet	Mefenoxam
Cymoxanil+Folpet	Metalaxyl
Cymoxanil+Fosetyl-al	Myclobutanil
Cymoxanil+Metalaxyl	Sulphur
Dimethomorph	Zoxamide
Famoxadone	

Actives used in potato highlighted in yellow

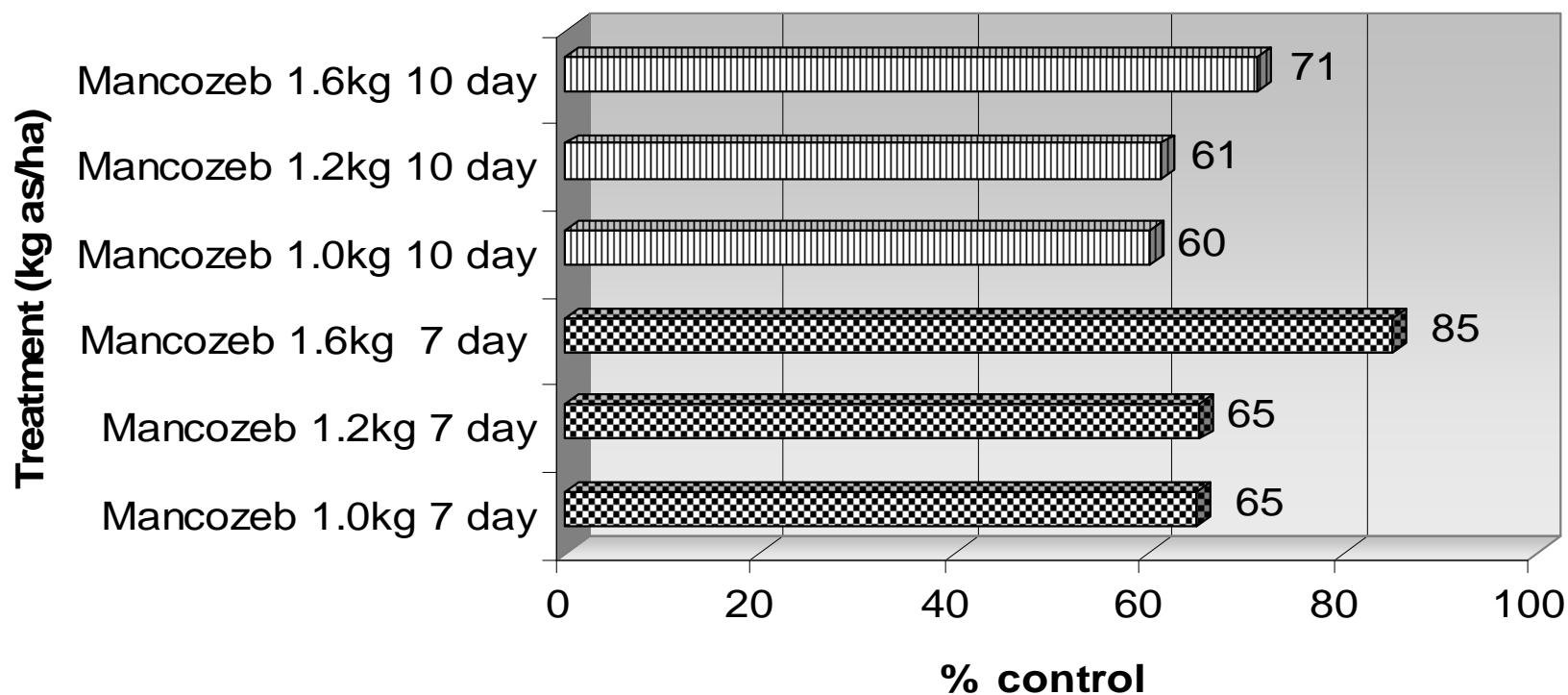
- In 2007 approx \$165MM of mancozeb (33% of total) was sold for use in mixtures with a combined value of \$400MM.

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Central Zone

Mancozeb dose response (7 trials) against late blight of potato (PHYTIN)

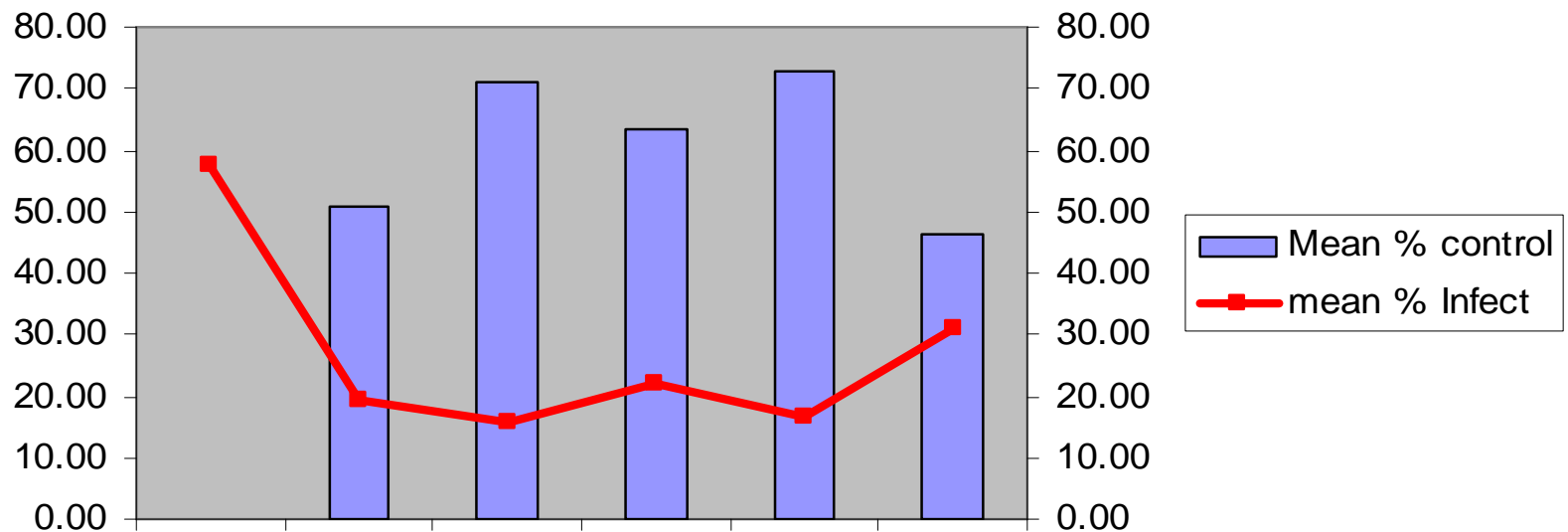


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Southern Zone

Alternaria solanum In Potato (S.Europe mean 6 trials)



Treatment	% infect min max
UNTREATED	39 to 73
Mancozeb 1.2 kg as	19
Mancozeb 1.6 kg as	14 to 20
CURZATE MDF 3kg pr/ha	14 to 33
ACROBAT MZ 2.5 kg pr/ha	15 to 21
SHIRLAN 0.4l pr/ha	21 to 45

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Dithane ® Micronutrient Effect



Micronutrient Effect & Importance of Water Solubility

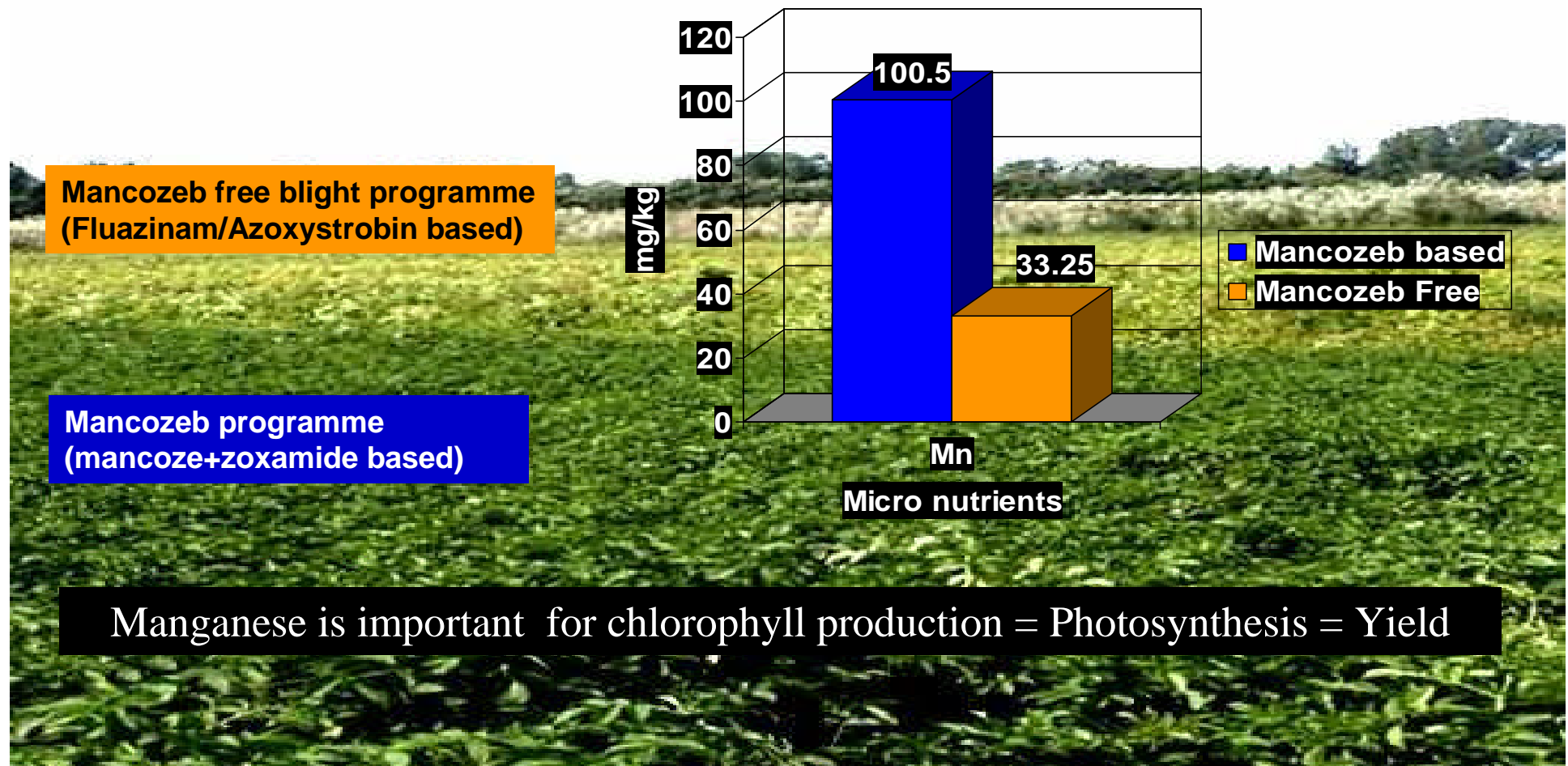
		Zn	Mn		
	Mol. Weight	Amount per lb. of Product	Amount per lb. of Product	H ₂ O Solubility	Biologically Activity
Maneb 75DF	265	0 g	71 g	696 mg/gal	Fast acting, poor residual activity (too water soluble)
Dithane DF (mancozeb)	271	7g	54 g	23 mg/gal	Controlled release of AI due to proper water solubility and balance of Mn + Zn-outer shell
Polyram® 80 DF (metiram)	1089	65g	0 g	0.4 mg/gal	Slow acting due to very low water solubility of Zn salt

- Dithane ® is very **Selective and Safe** for Approved Uses

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2005 Demo - Potato Forsøg DK -Sweden - Mancozeb vs. Mancozeb free



Mancozeb free blight programme
(Fluazinam/Azoxystrobin based)

Mancozeb programme
(mancoze+zoxamide based)

Manganese is important for chlorophyll production = Photosynthesis = Yield

Dithane ® – The Best Gets Better

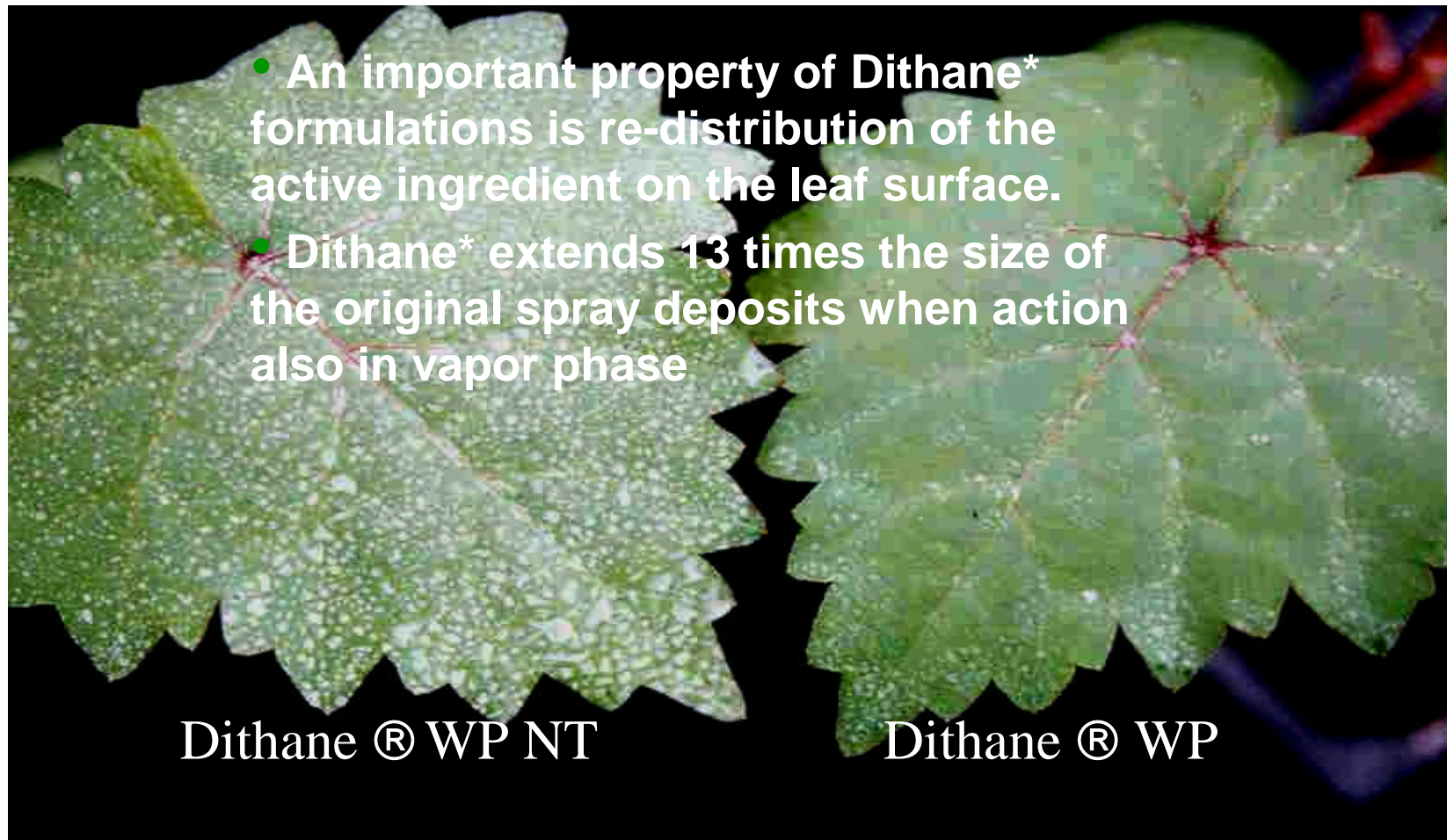
Forty plus years of experience has resulted in a leadership position in manufacturing and fundamental research to improve Dithane ® efficacy and product delivery systems. This has created a Dithane* fungicide product which provides a competitive advantage over generic mancozeb through the following distinguishing attributes:

- Breadth of Reach
- Formulation Innovation / Quality
- Packaging
- Regulatory Leadership

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Dithane ® WP NT Rainfast Test on Grape Vine: Greenhouse - 1 inch (2.5cm) rain



- An important property of Dithane* formulations is re-distribution of the active ingredient on the leaf surface.
- Dithane* extends 13 times the size of the original spray deposits when action also in vapor phase

Dithane ® WP NT

Dithane ® WP

DAS Regulatory Leadership

- **Regulatory / Issue Management**
 - **Support All Re-registration activities for straight and mixture customers using DOW Dithane**
 - **Maximize all uses / sales of Dithane ®.**
 - **Leadership in EBDC / Mancozeb Task Forces & Consortiums**
 - **Work closely w/ EPA et al, Commodity Groups & Key Influencers, supermarkets and import tolerances**
 - **Communicate Globally to Internal & External Stakeholders**
 - **Provide Technical Support for Issue Management**

The Future of Dithane ®

- **Positive recommendation of mancozeb for Annex I received 2Q '05**
- **Mancozeb is fully supported by Dow AgroSciences now and in the future**
- **Annex III zonal dossiers submitted to EU MSs 2Q 08 and re-registration anticipated 2010**
- **Revisions to 91/414 and move to hazard based criteria may threaten long term future registration status of mancozeb under endocrine disruption theme and substitution. Outcome unknown at moment but short term is OK.**
- **Vital to retain mancozeb as a resistance management tool for potato growers and broad spectrum cost effective protectant for minor crop growers**

Remember 1961: Good things were born in troubled times

Thank You

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