31. SYSTEMIC FUNGICIDES – Benomyl, carboxin, oxycarboxin, Metalaxyl, Carbendazim,- characteristics and use

The idea is earlier but 1960 only commercial systemic fungicides have come to market. A systemic fungicide is a compound that is taken up by a plant and is then translocated within the plant, thus protecting the plant from attack by pathogenic fungi or limiting an established fungal infection.

If a candidate chemical is to be an effective systemic fungicide the following criteria must be satisfied. It must be fungicidal or to be converted into an active fungitoxicant within the host plant. It must possess very low phytotoxicity. It must be capable of being absorbed by the roots, seeds or leaves of the plant and then translocated, at least locally, within the plant. The earlier protectant fungicides applied as foliar sprays formed dried deposits on the leaves of the host plant, protecting it from fungal attack. However the deposits are of course gradually removed by the effects of weathering and cannot protect new plant growth formed after spraying or any part of the plant not covered by spraying. These disadvantages can be overcome by the use of systemic fungicides which since penetrates the plant cuticle. They also offer the possibility of controlling an established fungal infection. Therefore systemic fungicides should exhibit both protectant and eradicant activity.

**Benzimidazoles**

These represent a new era in fungicide use when they were introduced in late 1960s.
The most important members of this group are **benomyl** [methyl –1-(butyl carbamoyl) benzimidazole-2- carbamates] TN: Benlate and **thiobendazole**. Both are wide spectrum systemic fungicides effective against many pathogenic fungi including powdery mildews and soil borne pathogens. These fungicides may persist in plants for several months. Benomyl was introduced in 1967. It was synthesized from cyanide and methylchloroformate. Benomyl and thiabendazole are both wide spectrum systemic fungicides active against many pathogenic fungi including powdery mildews and soil-borne pathogens, *Verticillium alboatrum* on cotton and black spot on roses.

- Du-pont; Benlate LD$_{50}$: > 9590
- Foliar fungicide in wine grape fruits, vegetables, citrus, cereal seed dressing.

Benomyl is the more active compound and is widely applied as a foliar spray, seed dressing or to the soil for control of grey mould (*Botrytis cinerea*), apple scab (*Venturia inequalis*) canker and powdery mildew (*Podosphaera leucotricha*), leaf spot (*Cercospora beticola*), major fungal diseases of soft fruits and some pathogens of tomato and cucumber. In aqueous solution benomyl is rapidly hydrolysed to methyl benzimidazole – 2 – carbamate and this is probably the active fungitoxicant **carbendazim** which is used as a wide spectrum systemic fungicide formulated as 50 per cent WP.

**Metalaxyl**

- Metalaxyl is included in the phenylamides group of systemic fungicides.
- The compounds of this group show protective and systemic activity against Oomyceles causing foliar, root and crown diseases in wide range of crops eg. downy mildews and late blight. The first members of this group Metalaxyl and Furalaxyl were introduction by Ciba-Geigy in 1977 (Metalaxyl = Ridomil). With a high activity at low rates of foliar or soil application metalaxyl controls diseases caused by air or soil borne comycetes in crops like potatoes, grapes, tobacco, cereals, hops and vegetables.
- A wettable powder formulation with mancozeb, (a complex of Zn and Mn salts fungicides) is widely used as a foliar spray against blight on potatoes. Metalaxyl has the broadest spectrum of fungicidal activity of this group of fungicides; it is good against downy mildew on vines, lettuce, maize and Pythium diseases and can be formulated as a seed dressing.

**E) Carbendazim (Bavistin, Derosol)**
Foliar fungicide in grapes, fruits, vegetables, cereals, cereal seed dressing

LD$_{50}$: 15,000  Carbenda in methylbenzimidazole-2-carbamate is used as a wide spectrum systemic fungicide and may be formulated as a 50% w.p. for control of *Botrytis, Gloeosporium* rots, powdery mildews and apple scab. Carbendazim is absorbed by the roots and foliage of plants and is quicker acting than Benomyl.

The activity of the benzimidazole fungicides (Benomyl, thiabendazole and carbendazim) is due to the inhibition of nuclear division due to their action on the microtubule assembly and the resistance developed in fungi is the result of mutant strains possessing an altered microtubule assembly.

**Carboxin and related compounds (Oxathiins)**

Oxathiins are another group of heterocyclic compounds with interesting systemic fungicidal properties. *Carboxin* and the sulphone analogue known as *oxycarboxin* are primarily effective against basidomycetes class of fungi which includes such economically important group of fungal pathogens rusts, smuts and bunts of cereals and the soil fungus *Rhizactonia solani*.

![Chemical structure of Carboxin](image)

The fungitoxicity is due to inhibition of glucose and acetate oxidative metabolism and RNA and DNA synthesis.

**Carboxin and Oxycarboxin**

Oxathins are another group of heterocyclic compounds with systemic fungicidal properties. Examples are Carboxin (5, 6 dihydro-2-methyl-1, 4 oxathin-3-carboxanilisde) (Vitavax) and the sulphone analogue known as Oxycarboxin (Plantvax).

LD$_{50}$: 3820  LD$_{50}$: 2000

Seed dressing: cereals, cotton  Sol and foliar fungicide
smuts & Rests  Rusts
Carboxin is prepared by reaction of $\alpha$-chloroacetoacetanilide and 2-thiothanol followed by cyclization. Oxycarboxin is obtained by subsequent oxidation of carboxin with hydrogen peroxide. Both are fairly water soluble and are not phytotoxic. They are active against Basidiomycetes class of fungi causing rusts, smuts and bunts of cereals and soil fungi *Rhizoctonia solani*. Carboxin can be formulated with other fungicides like thiram, copper oxine.

**C) Oxycarboxin**

Oxycarboxin has systemic action against rusts of cereals, and vegetables and seed treatment or soil application can be done. Carboxin is absorbed and translocated by plant roots. In water, soil and plants; the compound is oxidised to sulphoxide but further oxidation to sulphone was not observed. The sulphone is much less fungicidal and so oxidation causes loss of activity. The primary mode of action of carboxin and related compounds probably involves the blocking of succinate oxidation in the mitochondria of sensitive fungi.

**Antibiotics**

Antibiotics are chemicals produced by living organisms that are selectively toxic to other organisms. The first successful antibiotic against human diseases was penicillin discovered by Fleming (1929) but it has never achieved commercial significance as a systemic fungicide.

*Glitoxin*, an antifungal antibiotic produced by the soil fungus *Tricoderma viride* inhibited the growth of *Botrytis* and *Fusarium* spores at 2-4 ppm concentration but the compound was too unstable for use as a soil fungicide.

*Streptomycin* and *cycloheximide* are antibiotics obtained from the culture filtrates of *Streptomyces griseus* is used for the control of bacterial pathogens of plants.

*Griseofulvin* isolated in 1939 from *Penicillium griseofulvum* is an important antifungal antibiotic showing a wide spectrum of activity especially against *Botrytis* in lettuce and *Alternaria solani* on tomato.

*Blasticidin*, a pyrimidine derivative isolated from *Streptomyces griseochromogenes* give excellent control of rice blast and also inhibits certain bacteria. The antibiotic *polyoxin D* is another pyrimidine derivative which is toxic towards several fungi including rice blast. The fungi toxicity is due to interference with chitin synthesis.
Melanin Biosynthesis Inhibitors (MBIs) act on the pathogen to prevent it penetrating the plant epidermis; these compounds block melanin synthesis in a variety of Ascomycetes and fungi imperfecti. They provide practical control of rice blast and experimental control of some Colletotrichum species. Tricyclozole prevents the rigidity of penetration by Pyricularia oryzae. Validamycin is an aminoglucoside antibiotic active mainly against Rhizoctonia diseases and has been widely used to control rice sheath blight. Probenazole related to saccharin is effective by root application against rice blast and bacterial leaf disease Xanthomonas oryzae. It is not fungi toxic Invitro and probably acts indirectly by enhancing the resistance response of the host plant.

Aminopyrimidines
Some 30 years ago there is a series of 2-amino-4-hydroxypyrimidines had specific systemic activity against powdery mildews. These structure activity studies led to development of dimethrinol and ethrinol. Dimethrinol discovered in 1965, showed outstanding systemic activity by root application against certain powdery mildews in vegetables and some ornamentals.

Piperazine, pyridine, pyrimidine, imidazole and triazole fungicides
These fungicides are considered together because they all show a common biochemical target, namely synthesis of ergosterol; they are methylation inhibitors.

Triforine is the only piperazine derivative showing systemic activity against powdery mildews on cereals and vegetables.

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\begin{array}{c}
\text{C}_3\text{H}_3\text{CHNHCHC} \\
\text{N} \\
\text{N} \\
\text{C}_3\text{H}_3\text{CHNHCHC}
\end{array}
\]

Buthiobate and pyrifenox are pyridine fungicides. Buthiobate is used mainly in Japan against powdery mildews while pyrifenox controls a wide range of leaf spot pathogens of fruits and vegetables.
Triarimol, fenarimol and nunarimol are pyrimidine derivatives introduced by Eli Lilly in the late 1960s. Triarimol has been withdrawn due to its undesirable toxicological properties. Fenarimol, a systemic and protective fungicide is used as a foliar spray to control a broad spectrum of powdery mildews, scabs, rusts and leaf spots. Nuarimol is used against powdery mildews in cereals.

Fenarimol

Nunarimol

Imazalil, the first imidazole agricultural fungicide (1960) is now used as seed dressing in cereals.

Prochloraz

Imazalil

Prochloraz (Boots, 1973) is a broad spectrum fungicide with good activity against ascomycetes and fungi imperfecti but rather less activity against basidamycetes.

Triflumizole controls a wide range of pathogens Viz., powdery mildews and scabs.

Triadimefon [(1-(4-chlorophenoxy) 3,3-dimethyl –1-(1,2-triazol –1yl) butan-1-one)] TN: Bayleton has systemic activity against a broad range of plant pathogens effective at rates of 0.1 – 2.0 ppm. This discovery led to the introduction of several 1,2,4- triazole fungicides.
Triadimefon
These fungicides owe their fungitoxicity due to their ability to inhibit ergosterol biosynthesis. Ergosterol is a major sterol in many fungi where it plays a major role in membrane structure and function.

**Morpholine fungicides**
*Dodemorph* (roses) and *tridemorph* (cereals) are systemic foliar fungicides effective against powdery mildews at 0.75 litres ha$^{-1}$.

![Dedemorph](attachment:image1)

![Tridemorph](attachment:image2)

$_{CH_3}^N \_O \_CH_3$

$_{CH_3-(C_{n}H_{2n})-N-O-CH_3}$

$n = 10, 11, 12 (60-70\%) \text{ or } 13$

**Organo phosphorus fungicides**
Today more than 100 OP compounds show fungicidal action. However relatively few compounds are of practical use as fungicides, Many are phytotoxic and very specific against fungal species.

One of the first Op fungicides was *triamiphos* claimed to be the first systemic commercial fungicide. Since then many compounds were derived. *Pyrazophos* TN: Afugan is a foliar systemic fungicide effective against apple powdery mildew.

*Triclophos – methyl* is effective against Rhizactonia and other soil borne diseases as a drench in vegetables and against black scarf and canker in seed potatoes.

*Iprofenfos* TN: Kitazin P introduced in 1968, is a systemic rice fungicide applied as granules in paddy water to control rice blast and it inhibits mycelial growth in tissues.

*Edifenphos* is also very effective against rice blast.
OP fungicides have shown to block the synthesis of phospholipids. The reduction in phospholipids alters the membrane structure, increasing the permeability and consequent loss of vital cellular components and eventually killing the fungus.

**Phenyamides and related compounds**
- *Metaloxyl* – broad spectrum
- *Furalaxyl* – soil drenching
- *Benalaxyl* – potato blight
- *Oxadixyl* – with mancozeb to control potato blight

**Carbamates**
- *Prothiocarb* – ornamentals
- *Propamocarb* – Fruits and vegetables
- *Cymaxanil* – Potatoes and vines

**Miscellaneous compounds**
*Isoprothiolane* – systemic fungicide against rice blast

**Dithiolane**
*Formaldehyde* (Formalin 40 %) is used as seed dressing and soil sterilant
Substituted
*azepenes* – systemic fungicidal activity against leaf spot, powdery mildew and rust diseases.

**Recent potent fungicides for future use**

**Chlorooximes**
Very effective broad spectrum fungicide. Substituents in the oxime moiety plays a key role in the biological activity.

**Cyano-oximes** : The most active compound in this group is Cymoxanil which controls grape vine downy mildew disease. The analogous compound a propargyll derivative, is
equally effective. After isosteric replacement of the acetylenic triple bond by the cyanide triple bond the resulting compound showed enhanced activity against downy mildew

**Aryl sulfonylallyl trichloromethyl sulfoxides**: A series of 2-aryl sulfonylallyl trichloromethyl sulfoxides, have been found effective as broad spectrum fungicides with residual activity against grape downy mildew

\[
\text{CH}_2 - 0 \\
\text{II}
\]

\[
\text{ArSO}_2\text{C} - \text{CH}_2 - \text{S} - \text{CCl}_3
\]

**β methoxyacrylates with oxime ether side chain:**

Azoxystrobin, is a well known broad spectrum fungicide which facilitates the control of a wide range of major plant pathogens. If the central pyrimidine ring is replaced with an oxime ether moiety, it yields a highly effective fungicide. Analogous compounds containing a heterocyclic moiety instead of phenyl ring were also prepared to ascertain the fungicidal activity.

**Pyrimidine derivatives**: A series of novel 2-anilinopyrimidine compounds, based on lead compound were synthesized and introduced to the market in 1994. The synthetic compound mepanipyrim, exhibited excellent activity against grey mould of vine and vegetables, scab of apple and pear and brown rot of peach.

**Biofungicides**

These comprise of antibiotics and a few microbes such as *Pseudomonas cepacia*, *Peniophora gigantea* and *Trichoderma viride* which control a number of fungi associated with major crops

**Mode of action of fungicides**

**Non systemic**

The toxic action of sulphur in the cell is still not clear, however, several theories have been proposed from time to time. The theory accepted at present is that sulphur acts as hydrogen acceptor in metabolic systems to form H\(_2\)S, and in doing so disrupts the normal hydrogenation and dehydrogenation reactions in the cell. But in case of Cu fungicides, the Cu ions precipitate or inactivate the proteins (enzymes of sulphhydryl group) and thus kill the spores.

The mercury fungicides also act either as vapour or in ionic form and destroy
sulphydryl group of (SH) enzymes. Organomercurials are more toxic than the inorganic mercuric ones due to enhanced lipid solubility facilitating diffusion through the spore membrane to the site of action.

The mode of action of quinone derivatives may be due to binding of the quinone nucleus to SH and -NH2 groups in the cell leading to disturbance in the electronic transport systems. The activity of captan and related analogues may thus involve the role of Cl and S atoms of the molecule leading to inactivation of sulphydryl group of enzymes.

**b) Systemic**

The general mode of action of systemic fungicides is associated with a) interference with the electron transport chain influencing the energy budget of the cell, b) reduction in the biosynthesis of new cell material required for growth and development of the organism, and c) disruption of cell structure and permeability of cell membrane.

Benomyl and its related compounds interfere with mitosis in cell division in angiosperms and fungi. Benzimidazoles, thiophanates, oxathins, phenylamides (metalaxyl derivatives) influence DNA synthesis and are also mitosis inhibitors. The triazole group of fungicides interfere with the biosynthesis of fungal steroids and ergosterol which are important constituents of the cell wall. Pyrimidine derivatives inhibit purine biosynthesis and several pyridoxal dependent enzymes. The mode of action of morpho lines is still not well understood but appears to be inhibition of sterol biosynthesis. The mode of action of organ phosphorus fungicides is different from insecticides due to the absence of cholinesterase enzyme in fungi. The widely accepted theory is that it inhibits permeation through cytoplasmic membrane of the substrates for chitin synthesis.

The thiono compounds appear to be inactive against fungi and this may be due to fungus being unable to activate the thiono group to the ox on form by oxidation. The effect of penetration into the fungal hyphae depends on the polarity of the P=O group and needs to be balanced by a larger lipophilic group such as, the second thiophenyl group in case of edifenphos, cyclohexyl group in case of cerezin, benzyl mercaptan in case of kitazin or kitazin-P and the phenyl radical in the case of inezin.

**Metabolism**

The stability of fungicides in soil depends on chemical structure, nature of soil and climatic conditions. In general, the fungicides are not as stable as organochlorine
insecticides. The most versatile dithiocarbamate group of compounds, decompose in acidic soils to give non-toxic amines and carbon disulfide. Metabolism of alkyltin compounds in liver microsomal monooxygenase system and in mammals leads to the following sequence of detannylation (carbon-tin cleavage) reaction

The first step reaction product possessed increased toxicity and potency as inhibitors to mitochondrial respiration whereas in the subsequent steps the reaction product possesses less potency and has altered nature of biocidal activity.

The carboximides such as captan, folpet, captafol are hydrolysed under neutral and alkaline conditions. Chloroneb degrades to the phenolic derivative but reconversion to parent molecule is a microbial process and this might be the probable reason for long term effectiveness of chloroneb in soil.

Benzimidazole systemic fungicides like benomyl, thiabendazole and thiophanate methyl are first converted to carbendazim, an active ingredient at the site of action. These are finally degraded to non toxic compounds such as aniline, phenyl diamine and cyanoaniline. The breakdown of benomyl into MBC occurs by intramolecular process in slightly acidic or neutral media. A hydrogen bond is formed between the free electron pair of the N atom of the benzimidazole ring and hydrogen on the nitrogen of the butylcarbamoyl side chain, forming an unstable four membered ring which opens up to yield MBC and butylisocyanate. The cyanate rapidly forms butylcarbamic acid with water which in turn decomposes into CO2 and butylamine. The major metabolites of dimethirimol are ethirimol and 2-amino derivative.

Benomyl and thiophanate-methyl, in plants decomposes first to MBC which then gives photoproducts) like carbomethoxyguanidine (i), carbomethoxyurea (ii) and guanidine (iii) other minor compounds depending on the nature of the solvents used Piperazine, a metabolite of the fungicide triforine in barley degraded to non toxic products such as iminodiacetic acid, glycine, and oxalic acid on the surface of the plants by photodecomposition Chlorthalonil, 2,4,5,6-tetrachloroisophthalonitrile, in benzene solvent was photodegraded to amonophenyl adduct 3,5,6-trichlorobiphenyl-2, 4-dicarbonitrile, (i) as major photoproduct and disulfides. chlorophenyl methyl carbonate and an unknown product.