

CHAPTER 19

Modes of Action for Fungicides

Fungicidal action is usually expressed in one of two physically visible ways: the inhibition of spore germination or the inhibition of fungus growth. Most fungicides prevent spore germination or kill the spore immediately following germination. Some of these chemical inhibitors or toxicants also retard or halt fungus growth when applied after the infectious stage has developed. The newer systemic fungicides have eradicant properties and stop the progress of existing infections.

What happens at the cellular level to cause these readily visible results? As currently viewed, all fungicides are metabolic inhibitors; that is, they block some vital metabolic process. A useful source that characterizes which processes are affected by which fungicides and one used in updating this chapter, is the Fungicide Resistance Action Committee (FRAC) website (<http://www.frac.info/>). In the coming pages we categorize the major modes of action of fungicides into seven broad groups and touch on miscellaneous others. The primary seven include inhibitors of:

- the electron transport chain
- nucleic acid synthesis
- mitosis and cell division
- protein synthesis
- lipid and membrane synthesis
- sterol biosynthesis
- multi-site processes

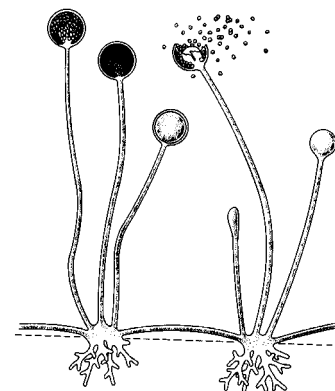
MITOCHONDRIAL ELECTRON TRANSPORT INHIBITORS

Organotin: Several organotin are in use, more abroad than in the United States. Fentin hydroxide is the oldest member of those used in this country. They inhibit oxidative phosphorylation by blocking ATP synthase and thus the formation of ATP (Figure 17-9). This is the primary mode, though they have other sites of interference.

Oxathiins: Also referred to as carboxamides. Only carboxin and oxycarboxin are currently in use. Carboxin inhibits glucose and acetate oxidation by

I have seen some medicate their seed before they sow it. They steep it in nitre and amurca to obtain a fuller produce in the deceitful pods.

Virgil, *Georgics*
(70 - 19 B.C.)



intact fungi and noncompetitively inhibits succinate, but not NADH_2 , oxidation by mitochondria. This effect occurs in the electron transport chain of respiration. Succinate accumulates in carboxin-treated cells of fungi, suggesting that inhibition of succinate oxidation at succinate dehydrogenase is the primary site of action. Oxycarboxin, though less toxic, has the same mode of action (Figure 17-9). A new member of this group that has a pending registration is boscalid (nicobifen).

Dinitrophenols: Dinocap, the only dinitrophenol fungicide, is sometimes lumped with binapacryl as dinitrophenylcrotonates. These products uncouple oxidative phosphorylation in the production of energy (Figure 17-9). The chemically related dinitroaniline product, fluazinam, has this same mode of action.

Strobilurins: Some members of this group are azoxystrobin, picoxystrobin, kresoxim-methyl, famoxadone, pyraclostrobin and trifloxystrobin. Derived from natural fungicides occurring in edible mushrooms and wood-decaying mushrooms, they show great promise as systemics and curatives for troublesome downy and powdery mildews, leaf spots and rusts. These compounds inhibit the establishment of competing fungi on plant surfaces. Their mode is to inhibit mitochondrial respiration by blocking electron transfer in cytochromes b and c1 (ubiquinol oxidase at the Q_o site).

Cyanoimidazoles and Thiophenecarboxamids: The single representatives of these new groups are cyazofamid and silthiofam, respectively. Cyazofamid appears to inhibit ubiquinone reductase (cytochrome bc1) but at the Q_i site rather than Q_o site attacked by the strobilurins. Silthiofam is a newly introduced product and is proposed to inhibit ATP production at an as yet undefined step.

NUCLEIC ACID SYNTHESIS INHIBITORS

Phenylamides: Included are metalaxyl, furalaxyl and benalaxyl. These materials depress nucleic acid synthesis, with RNA synthesis being usually the most sensitive process probably through interaction with RNA polymerase. Oxadixyl is closely related and acts by the same mechanism.

Pyrimidinols: These include dimethirimol, ethirimol, bupirimate and fenarimol. Only the latter is registered for use in the U.S. These materials appear to act by targeting adenosindeaminase.

Carboxylic Acids: The bactericide oxolinic acid, the only member of this class, is thought to exert its action by targeting DNA topoisomerase.

MITOSIS AND CELL DIVISION INHIBITORS

Benzimidazoles: The benzimidazoles include benomyl, thiabendazole, carbendazim and thiophanate. They are not toxic to fungi in their original state, but must be converted to their ester metabolites, which are known to be toxic entities. Carbendazim is the active moiety of benomyl. Benomyl is transformed to methyl-2-benzimidazole carbamate (MBC), which was later named carbendazim. These metabolites cause morphological distortion of germinating spores and are thought to upset cell division by inhibiting β -tubulin assembly during mitosis.

N-phenyl carbamates and Benzamids: The respective representatives of these groups are diethofencarb and zoxamide. These products, like the

benzimidazoles above, disrupt cell division by inhibiting β -tubulin assembly during mitosis.

PROTEIN SYNTHESIS INHIBITORS

Antibiotics: Cycloheximide is a protein synthesis inhibitor-it inhibits the incorporation of amino acids into protein. As a consequence of its interference with protein synthesis, it may also inhibit DNA synthesis. Cycloheximide is toxic not only to fungi but also to plants and it has an oral LD₅₀ of 2.5 mg/kg, by far the most toxic of the fungicides.

Streptomycin inhibits protein synthesis by binding to the ribosome (30 S subunit), one molecule of streptomycin per ribosome. It also causes misreading of the genetic code, though this is not likely the primary effect. Other fungicidal antibiotics (blasticidin-S and kasugamycin) also appear to exert their effects by inhibiting protein synthesis. The one exception, however, is validamycin, a glucopyranosyl antibiotic that appears to inhibit cell wall synthesis, not through any protein interaction, but rather by affecting polysaccharide synthesis. In particular, validamycin inhibits biosynthesis of trehalase and inositol.

Anilinopyrimidines: Cyprodinil, mepanipyrim and pyrimethanil, the three members of this group are proposed to effect their action by disrupting protein synthesis; specifically through inhibition of methionine biosynthesis.

LIPID AND MEMBRANE SYNTHESIS INHIBITORS

Thiadiazoles: Etridiazole is the only fungicide belonging to the thiazoles. The unstable five-member ring of the thiazoles is broken rapidly under soil conditions to form either the fungicidal $-N=C=S$ or a dithiocarbamate, depending on the structure of the parent chemical. The isothiocyanate inactivates $-SH$ or $-SR$ groups in amino acids, proteins and enzymes contained within the individual pathogen. Although etridiazole has multisite activity (inhibits respiration and melanin biosynthesis), it is proposed that the main target may be lipid peroxidation which can affect membrane synthesis.

Dicarboximides: Included are iprodione, procymidone and vinclozolin. Although members of this group induce effects similar to the phenylamides recent evidence supports a different target site of action, namely interference with NADH cytochrome c reductase in lipid peroxidation.

Carbamates: It is proposed that iodocarb and prothiocarb target the cell membrane and affect fatty acids in ways that alter membrane permeability.

Organophosphates and Others: Edifenphos, iprobenfos and pyrazophos appear to inhibit phospholipid biosynthesis specifically by interacting with methyltransferase. However, tolclofos methyl, also an organophosphate, is proposed to induce its effect through lipid peroxidation similar to etridiazole. Interestingly other fungicides from different chemical classes also appear to effect lipid peroxidation (chloroneb, dicloran and PCNB).

STEROL BIOSYNTHESIS INHIBITORS

Ergosterol is the major sterol in most fungi and it plays a vital role in membrane structure and function, analogous to that of the structurally