Kirk-Othmer Encyclopedia of Chemical Technology.

FUNGICIDES, AGRICULTURAL

Pathogenic fungi cause a substantial reduction in expected crop yields; further losses can result during storage of harvested crops. Although there are over 100,000 classified fungal species, no more than 200 are known to cause serious plant disease. Most plants are resistant to the majority of potential pathogenic fungi in their environment. However, a limited number of fungal pathogens are able to delay or prevent the onset of defense responses of certain plant species, or have developed mechanisms to counteract specific plant defense reactions. For those fungi that can seriously affect economically important plants (Table 1), means have been sought to control these infections by crop rotation and husbandry, genetic manipulation of the plant species (see Genetic engineering, plants), and external treatment of plants using agricultural fungicides.

Agricultural fungicide application accounts for about 20% of all pesticide use. More than $\$5.6 \times 10^9$ was spent worldwide on these fungicides in 1991 (1). Agricultural fungicides can be applied to the soil to control fungi that are resident there, to the seed or foliage of the plant to be protected, or to harvested produce to prevent storage losses. Those applied to the soil are in many instances nonselective, volatile soil sterilants, such as formaldehyde (qv), which kill all soil organisms, including fungi. Soil and crop storage fungicides, which represent only a very small fraction of the fungicides used, are covered elsewhere (2, 3) (see Soil chemistry of pesticides). Seed and foliar-applied agricultural fungicides, listed in Table 2, are discussed herein.

The word fungicide might suggest a compound that nonselectively kills all fungi, but even compounds having an unspecified mode of action can exhibit a remarkable degree of selectivity against different fungi. In addition, some fungicides are more properly called fungistats because their action controls the spread of disease without actually killing the pathogen.

Because of the wide diversity of chemical structures encountered, fungicides are classified herein as being nonsystemic or systemic. The nonsystemic fungicides have a protectant mode of action and must be applied to the surface of a plant generally before infection takes place. These do not translocate from the site of application. The systemic fungicides can penetrate the seed or plant and are then redistributed within to unsprayed parts or subsequent new growth, rendering protection from fungal attack or eradicating a fungus already present.

1. Nonsystemic Fungicides

From 20 to 25 nonsystemic fungicides are utilized in agriculture, although use is declining. These are some of the oldest known fungicides and cover a wide range of chemistry from simple inorganic salts to highly complex organic structures. Selective accumulation by spores plays a dominant role in the toxicity of many of these compounds. The majority are regarded as general cell poisons and can be used only when they are not able to penetrate host plant tissue in appreciable amounts. The fungal pathogen is controlled before it infects the plant so that the resulting efficacy is primarily achieved through protecting the plant rather than curing the disease. The mode of action, ie, biochemical basis for activity, of most known nonsystemic fungicides is generally nonspecific, and inhibition at multiple sites results ultimately in interference with energy producing or transferring processes which disrupts fungal respiration and membranes (4).

Table 1. Important Diseases of Crop Plants

	Pathogen	
Fungal class	Scientific name	Common name
Phycomycetes subclass oomycetes	*Phytophthora infestans*	potato late blight
	Plasmopara viticola	downy mildew of grape
	Pseudoperonospora cubensis	cucumber downy mildew
	Pythium spp.	damping off diseases
Ascomycetes	*Erysiphe graminis*	powdery mildew of wheat/barley
	Gaeumannomyces graminis	take-all of oats and wheat
	Podosphaera leucotricha	apple powdery mildew
	Pyrenophora teres	net blotch of barley
	Pyricularia oryzae	rice blast
	Rhynchosporium secalis	leaf scald of barley
		brown rot of pome fruit
	Sclerotinia spp.	leaf spot of brassicas and legumes
	Sphaerotheca fuliginea	cucurbit powdery mildew
	Uncinula necator	grape powdery mildew
	Venturia inaequalis	scab of apple
	Mycosphaerella fijiensis	sigatoka disease of bananas
Basidiomycetes	*Puccinia* spp.	leaf rusts of wheat and oats
		black scurf of potato
	Rhizoctonia spp.	sheath blight of rice
		sharp eyespot of wheat
	Tilletia spp.	bunts of wheat
	Uromyces spp.	bean rusts
	Ustilago spp.	smuts of wheat, barley, oat, and maize
Deuteromycetes		early blight of potato
	Alternaria spp.	tobacco brown spot
		leaf spot of brassicas
	Botrytis spp.	grey mold of grape and other crops
	Cercospora spp.	leaf spot of sugarbeet
		brown eyespot of coffee
	Fusarium spp.	wilts, broad range of hosts
		ear blight of wheat
	Helminthosporium spp.	root and foot rot of wheat
		leaf spot of maize
	Pseudocercosporella herpotrichoides	eyespot of wheat
	Septoria nodorum	glume blotch of wheat
	Septoria tritici	wheat leaf blotch

1.1. Sulfur

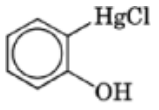
Sulfur became firmly established as an agricultural fungicide in the nineteenth century, when the preparation of lime sulfur was reported in 1802 to control mildew on fruit trees (5). Elemental sulfur, in the form of flowers of sulfur, was the first effective nonsystemic protectant fungicide. Although toxicologically one of the safer fungicides, sulfur must be applied frequently and in large quantities to be effective, causing handling difficulties and leading in some instances to phytotoxicity. Sulfur is an effective inhibitor of fungal spore germination and may affect several target sites in fungal cells. It probably exerts fungicidal efficacy *in vivo* by reduction to H_2S, which both reacts with proteins (qv) and chelates to heavy metals to disrupt cellular processes, including respiration.

1.2. Copper

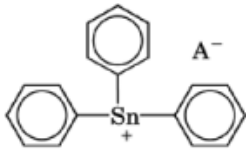
Although copper sulfate was used for treating the seed-borne disease wheat bunt (*Tilletia* spp.) as early as 1761, widespread use was limited by its inherent phytotoxicity. In 1882, it was observed (6) that grapevines that had been coated with a mixture of copper sulfate and lime to deter grape pilferage, were not infected with grape downy mildew (*Plasmopara viticola*). This observation resulted in the development of a fungicide called Bordeaux mixture, the exact composition of which is unclear. Many copper fungicides are available for a wide variety of applications, eg, the sulfates (Bordeaux mixture), oxides and oxychlorides, and a variety of organic salts such as copper naphthenates and copper quinolinates. Crops protected using copper compounds include vines, fruit, coffee (qv), cocoa, and vegetables. Most copper fungicides work by inhibiting fungal spore germination. Sensitive fungi are affected by the uptake of copper salts and its subsequent accumulation, which then complexes with amino, sulfhydryl, hydroxyl, or carboxyl groups of enzymes resulting in inactivation of the fungus (7).

1.3. Mercury

The first successful use of mercury as a fungicide occurred in 1913 (8). The first seed treatment compound developed was chloro(2-hydroxyphenyl)mercury [90-03-9] (**1**). Subsequently, a number of organic mercury derivatives having general formula RHgX have been used. These compounds are extremely restricted because of high toxicity and persistence in the environment, and are totally banned in many countries.



(**1**)



(**2**) A^- = acetate
(**3**) A^- = hydroxide

1.4. Tin

The fungicidally active tin compounds are organotins. Many of the most fungicidal compounds, eg, the tripropyl and tributyl tins, are too phytotoxic for direct application to plants and the success of tin compounds as fungicides require balancing efficacy against phytotoxicity. The triphenyl tin compounds fentin acetate [900-95-8] (**2**) and fentin hydroxide [76-87-9] (**3**), used primarily in controlling diseases of potato and sugar beet, are less phytotoxic. These compounds control disease by inhibition of the mitochondrial adenosine triphosphatase (ATP-ase) involved in oxidative phosphorylation (9). The high cost of tin, the concerns about heavy metals in the environment, and the phytotoxic potential of these compounds continue to be critical factors influencing use.

1.5. Thiocarbamate and Thiurame Derivatives

The thiocarbamate family of fungicides was discovered in the 1930s as a result of research in the rubber industry for accelerators in the curing of rubber, and the subsequent broad screening of those compounds (10). These are broad-spectrum fungicides (with the exception of the powdery mildews) that have a multisite action on the fungus and interfere with its metabolism in many ways. The key products to emerge from this group (Fig. 1) are the thiocarbamates: ferbam [14484-64-1] (**4**); ziram [137-30-4] (**5**; and thiram [137-26-8] (**6**), and the ethylene bis-dithiocarbamates: nabam [142-59-6] (**7**; zineb [12212-67-7] (**8**; maneb [12427-38-2] (**9**); and mancozeb [8018-01-7] 1. These compounds are still widely used on many crops, especially top fruit (orchard fruits), vines, and field vegetables. In the case of the dimethyl-thiocarbamates, the anion (**11**, generated *in vivo*, acts as an inhibitor of essential copper-containing enzymes, whereas the ethylene bis-dithiocarbamates are converted to the ethylene diisothiocyanate (**12**, the primary toxic agent, which binds preferentially to SH groups of fungal enzymes (11). Because these compounds do not have a specific mode of action on the fungus but interfere with it in a number of ways, there is only a low risk of fungal resistance developing. The principal pressure against continued use has come from regulatory concerns about the effects of residues such as ethylene thiourea on human health.

Table 2. Alphabetical List of Fungicides

Common name	Trademark	Company	Year of intro-duction	Molecular formula	Structure number
anilazine	Dyrene	Bayer AG	1955	$C_9H_5Cl_3N_4$	(**34**)
benalaxyl	Galben	Agrimont SpA	1981	$C_{20}H_{23}NO_3$	(**77**)
benomyl	Benelate	E. I. du Pont de Nemours	1968	$C_{14}H_{18}N_4O_3$	(**45**)
blasticidin S	Bla-S	Karen, Kumiai, Nihon	1959	$C_{17}H_{26}N_8O_5$	(**91**), (**92**)
bupirimate	Nimrod	ICI Plant Protection	1972	$C_{13}H_{24}N_4O_3$	(**82**)
buthiobate	Denmert	Sumitomo Chemical Co.	1975	$C_{21}H_{28}N_2S_2$	(**55**)
captafol	Difolatan	Chevron Chemical Co.	1961	$C_{10}H_9Cl_4NO_2S$	(**15**)
captan	Orthocide	Chevron Chemical Co.	1949	$C_9H_8Cl_3NO_2S$	(**13**)
carbendazim	Bavistin	BASF AG	1972	$C_9H_9N_3O_2$	(**44**)
carboxin	Vitavox	Uniroyal Inc.	1966	$C_{12}H_{13}NO_2S$	(**35**)
chinomethionat	Morestan	Bayer AG	1960	$C_{10}H_6N_2OS_2$	(**29**)
chloroneb	Demosan	E. I. du Pont de Nemours	1967	$C_8H_8Cl_2O_2$	(**18**)
chlorothalonil	Bravo	Fermenta Plant Protection	1975	$C_8Cl_4N_2$	(**21**)
chlozolinate	Serinal	Agrimont SpA	1980	$C_{13}H_{11}Cl_2NO_5$	(**24**)
cymoxanil	Curzate	E. I. du Pont de Nemours	1977	$C_7H_{10}N_4O_3$	(**93**)
cyproconazole	Alto	Sandoz AG	1982	$C_{15}H_{18}ClN_3O$	(**65**)
dichlofluanid	Euparen	Bayer AG	1965	$C_9H_{11}Cl_2FN_2O_2S_2$	(**16**)
dichlone	Phygon	Uniroyal Inc.	1943	$C_{10}H_4Cl_2O_2$	(**20**)
dicloran	Allisan	Boots (now Schering AG)	1960	$C_6H_4Cl_2N_2O_2$	(**19**)
diclomezine	Monguard	Sankyo Co. Ltd.	1988	$C_{11}H_8Cl_2N_2O$	(**30**)
dimethirimol	Milcurb	ICI Plant Protection	1968	$C_{11}H_{19}N_3O$	(**81**)

Table 2. ***Continued***

Common name	Trademark	Company	Year of intro-duction	Molecular formula	Structure number
dinocap	Karathane	Rohm and Haas	1946	$C_{18}H_{24}N_2O_6$	(**17**)
dithianon	Delan	E. Merck	1963	$C_{14}H_4N_2O_2S_2$	**(28)**
dodemorph	Milan	BASF AG	1967	$C_{18}H_{35}NO$	(**71**)
dodine	Cyprex	American Cyanamid Co.	1957	$C_{15}H_{33}N_3O_2$	(**27**)
ediphenphos	Hinosan	Bayer AG	1968	$C_{14}H_{15}O_2PS_2$	(**83**)
ethirimol	Milcap	ICI Plant Protection	1969	$C_{11}H_{19}N_3O$	(**80**)
etridazole	Terrazole	Uniroyal Inc.	1969	$C_5H_5Cl_3N_2OS$	(**31**)
fenarimol	Rubigan	Eli Lilly (now DowElanco)	1975	$C_{17}H_{12}Cl_2N_2O$	(**57**)
fenfuram	Pano-ram	Shell Research Ltd.	1974	$C_{12}H_{11}NO_2$	(**38**)
fenpiclonil	Beret	CIBA-GEIGY AG	1988	$C_{11}H_6Cl_2N_2$	(**32**)
fenpropidin	Patrol	Dr. Maag (now CIBA-GEIGY)	1986	$C_{19}H_{31}N$	(**74**)
fenpropimorph	Corbel	Dr. Maag (now CIBA-GEIGY)	1979	$C_{20}H_{33}NO$	(**73**)
fentin acetate[a]	Brestan	Hoechst AG	1954	$C_{20}H_{18}O_2Sn$	(**2**)
fentin hydroxide[b]	Du-ter	N.V. Philips-Duphar	1954	$C_{18}H_{16}OSn$	(**3**)
ferbam	Fermate	E. I. du Pont de Nemours	1931	$C_9H_{18}FeN_3S_6$	(**4**)
flusilazole	Nustar	E. I. du Pont de Nemours	1982	$C_{16}H_{15}F_2N_3Si$	(**67**)
flutriafol	Impact	ICI Plant Protection	1982	$C_{16}H_{13}F_2N_3O$	(**69**)
flutolanl	Moncut	Nihon Nohyaku Co. Ltd.	1976	$C_{17}H_{16}F_3NO_2$	(**37**)
folpet	Phaltan	Chevron	1952	$C_9H_4Cl_3NO_2S$	(**14**)
fosetyl-Al	Aliette	Rhône-Poulenc Agrochimie	1977	$C_9H_{18}AlO_9P_3$	(**94**)
fuberidazole	Voronit	Bayer AG	1966	$C_{11}H_8N_2O$	(**43**)
furalaxyl	Fongarid	CIBA-GEIGY AG	1976	$C_{17}H_{19}NO_4$	(**76**)
imazalil	Fungaflor	Janssen Pharmaceuticals	1973	$C_{14}H_{14}Cl_2N_2O$	(**59**)
imibenconazole	Manage	Hokko Chem. Ind. Ltd.	1988	$C_{17}H_{13}Cl_3N_4S$	(**70**)
iprobenphos	Kitazin P	Kumiai Chemical Ind.	1966	$C_{13}H_{21}O_3PS$	(**84**)
iprodione	Rovral	Rhône-Poulenc Agrochimie	1970	$C_{13}H_{13}Cl_2N_3O_3$	(**25**)
isoprothiolane	Fuji-one	Nihon Nohyaku Co. Ltd.	1975	$C_{12}H_{18}O_4S_2$	(**85**)
kasugamycin	Kasumin	Hokki Chem Ind. Ltd.	1965	$C_{14}H_{25}N_3O_9$	(**92**)
mancozeb	Dithane M-45	E. I. du Pont de Nemours	1961		(**10**)
maneb	Dithane M-22	E. I. du Pont de Nemours	1950	$C_4H_6MnN_2S_4$	(**9**)
mepronil	Basitac	Kumiai Chem. Ind. Ltd.	1981	$C_{12}H_{19}NO_2$	(**39**)
metalaxyl	Ridomil	CIBA-GEIGY AG	1977	$C_{13}H_{21}NO_4$	(**75**)
methfuroxam	Trivax	Uniroyal Inc.	1976	$C_{14}H_{15}NO_2$	(**40**)
metsulfovax	Provax	Uniroyal Inc.	1986	$C_{12}H_{12}N_2OS$	(**41**)
myclobutanil	Systhane	Rohm and Haas Co.	1984	$C_{15}H_{17}ClN_4$	(**68**)
nabam	Parzate	E. I. du Pont de Nemours	1943	$C_4H_6N_2Na_2S_4$	(**7**)
nuarimol	Trimidal	DowElanco	1976	$C_{17}H_{12}ClFN_2O$	(**58**)
ofurace	Oturanic	Chevron Chem. Co.	1982	$C_{14}H_{16}ClNO_3$	(**78**)
oxadixyl	Sandofan	Sandoz AG	1979	$C_{14}H_{18}N_2O_4$	(**79**)
oxycarboxin	Plantvax	Uniroyal Inc.	1966	$C_{12}H_{13}NO_4S$	(**36**)
polyoxin B	Polyoxin AL	Hokko Chem. Ind. Co.	1968	$C_{17}H_{25}N_5O_{13}$	(**91**)
polyoxin D	Polyoxin Z	Hokko Chem. Ind. Co.	1968	$C_{17}H_{23}N_5O_{14}$	(**92**)
prochloraz	Sportak	Boots (now Shering AG)	1974	$C_{15}H_{16}Cl_3N_3O_2$	(**60**)
procymidone	Sumisclex	Sumitomo Chemical Co.	1969	$C_{13}H_{11}Cl_2NO_2$	(**26**)
propiconazole	Tilt	Janssen Pharmaceuticals	1979	$C_{15}H_{17}Cl_2N_3O_2$	(**63**)
pyroquilon	Funorene	Pfizer Inc.	1980	$C_{11}H_{11}NO$	(**87**)
quintozene	Botrilex	I.C. Farben (now Bayer AG)	1930	$C_6Cl_5NO_2$	(**17**)
tebuconazole	Folicur	Bayer AG	1983	$C_{16}H_{22}ClN_3O$	(**64**)
tetraconazole	Eminent	Agrimont SpA	1986	$C_{13}H_{11}Cl_2F_4N_3O$	(**66**)
thiabendazole	Mertect	Merck and Co.	1986	$C_{10}H_7N_3S$	(**42**)
thiophanate methyl	Topsin M	Nippon Soda Co. Ltd.	1969	$C_{12}H_{14}N_4O_4S_2$	(**46**)
thiram	Tersan	E. I. du Pont de Nemours	1931	$C_6H_{12}N_2S_4$	(**6**)
triadimefon	Bayleton	Bayer AG	1975	$C_{14}H_{16}ClN_3O_2$	(**62**)

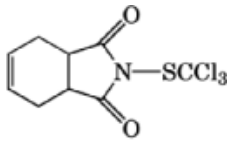
Table 2. ***Continued***

Common name	Trademark	Company	Year of intro-duction	Molecular formula	Structure number
triarimol	Trimidal	DowElanco	1969	$C_{17}H_{12}Cl_2N_2O$	(**56**)
tricyclazole	Beam	DowElanco	1972	$C_9H_7N_3S$	(**86**)
tridemorph	Calixin	BASF AG	1969	$C_{19}H_{39}NO$	(**72**)
triforine	Cela W524	Celamerck (now Shell)	1967	$C_{10}H_{14}Cl_6N_4O_2$	(**54**)
vinclozolin	Ronilan	BASF AG	1975	$C_{12}H_9Cl_2NO_3$	(**23**)
zineb	Dithane Z-78	Rohm and Haas	1943	$C_4H_6N_2S_4Zn$	(**8**)
ziram	Milbam, Zerlate	E. I. du Pont de Nemours	1930	$C_6H_{12}N_2S_4Zn$	(**5**)

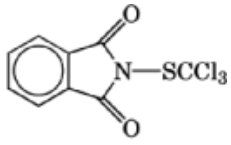
[a] CAS Registry Number [900-95-8].
[b] CAS Registry Number [76-87-9].

1.6. Phthalimides and Some Trichloromethylthiocarboximides

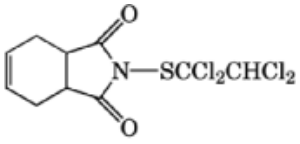
The fungicidal efficacy of this chemistry was recognized in the 1950s. The phthalimide derivatives are excellent, broad-spectrum fungicides which can be applied to the foliage roots, or seed of a crop. The most important products in this chemistry are captan [133-06-02] (**13**), folpet [133-07-3] (**14**), captafol [2425-06-1] (**15**), and, more recently, dichlofluanid [1085-98-9] (**16**), which is structurally different but has a similar mode of action. As in the case of the dithiocarbamates, these compounds react with thiol groups in fungi, releasing thiophosgene and H_2S (12). The thiophosgene may subsequently react with thiol and amino groups in the enzymes (13). Differences in uptake between fungal species are considered responsible for the differences in fungicidal spectrum between specific compounds. The U.S. Environmental Protection Agency (EPA) and other regulatory bodies have raised questions concerning the safety of the phthalimides, in particular captan and captafol, and some restrictions have been imposed on their usage (14).



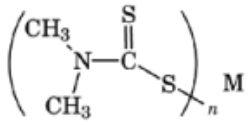
(**13**)



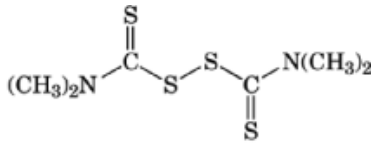
(**14**)



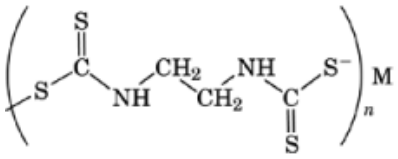
(**15**)



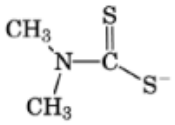
(**4**) M = Fe, n = 3
(**5**) M = Zn, n = 2



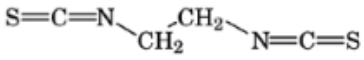
(**6**)



(**7**) M = Na, n = 2
(**8**) M = Zn, n = 1
(**9**) M = Mn, n = 1
(**10**) M = Mn, Zn, n = 2

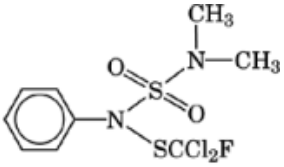


(**11**)



(**12**)

Fig. 1. Thiocarbamate nonsystemic fungicides.



(**16**)

1.7. Aromatic Hydrocarbons

The aromatic hydrocarbon fungicides were among the earliest compounds to replace sulfur in the treatment of powdery mildews of fruit. This diverse group of substituted aromatic hydrocarbons is shown in Figure 2. Two of the earliest were quintozene [82-68-8] (**17**) (also known as PCNB) and dinocap [131-72-6] (**18**). Some of the more important compounds in this class in the 1990s include chloroneb [2675-77-6] (**19**) and dichloran [99-30-9] (**20**). Most of these compounds were utilized for the control of soil and seed-borne diseases. Whereas quintozene and chloroneb are known to possess some whole plant systemicity, this is not generally the case for the group as a whole. The efficacy of some members of this class of fungicides is also facilitated by marked vapor action. They tend to be inhibitory to mycelial growth rather than the preinfection stages of the various pathogens and control a broad spectrum of Oomycetes (see Table 1) and other pathogenic fungi, including *Rhizoctonia*, *Botrytis*, *Ustilago*, *Alternaria*, and *Helminthosporium* (15). The mode of action is considered to be inhibition of the enzyme NADPH-cytochrome C reductase, which results in the generation of free radicals and/or peroxide derivatives of flavin which oxidize adjacent unsaturated fatty acids to disrupt membrane integrity (16) (see Enzyme inhibitors).

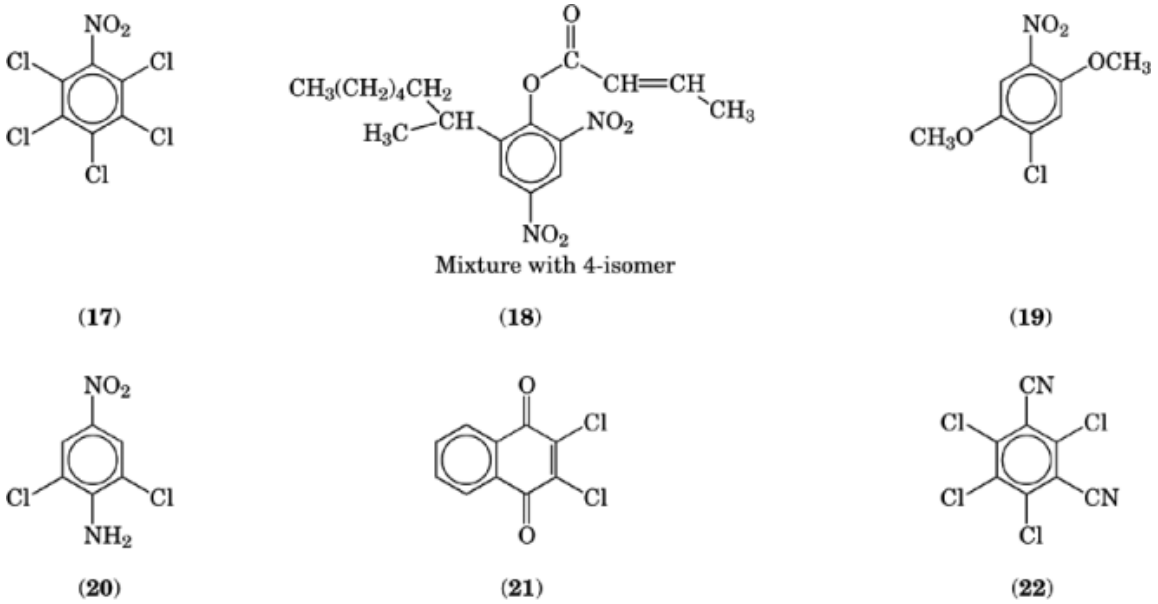
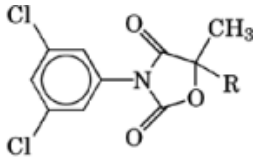


Fig. 2. Aromatic nonsystemic fungicides.

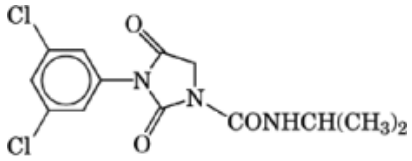
Although compounds such as dichlone [117-80-6] (**21**) and chlorothalonil [1897-45-6] (**22**) are also aromatic hydrocarbons and widely effective against a broad range of pathogens, these apparently have a different mode of action involving binding to SH groups of fungal enzymes. Use of the various aromatic hydrocarbons has declined because of replacement by more efficacious fungicides having broader antifungal spectrum.

1.8. Dicarboximides

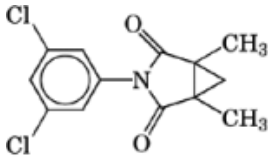
The dicarboximides, introduced in the early 1970s, are characterized by a cyclic imide group represented by an oxazolidinedione, eg, vinclozolin [50471-44-8] (**23**) and chlozolinate [84332-86-5] (**24**); a hydantoin, eg, iprodione [36734-19-7] (**25**); and a succinimide, eg, procymidone [32809-16-8] (**26**). Although the fungicidal spectrum is similar to that of the aromatic hydrocarbons (17), dicarboximides inhibit spore germination more effectively than mycelial growth and cause increased branching and swelling of the germ tubes and hyphal tips. The mode of action, as in the case of the aromatic hydrocarbons, is the inhibition of the enzyme NADPH-cytochrome C reductase (18).



(**23**) R = $CH{=}CH_2$
(**24**) R = $COOCH_2CH_3$



(25)



(26)

1.9. Miscellaneous Nonsystemics

A wide variety of other types of compounds which cannot be easily grouped chemically have been developed and used as protectant fungicides (Fig. 3). These are important fungicides for specialty markets. Some of the more significant examples are a guanidine salt, eg, dodine [2439-10-3] (**27**); a quinone, eg, dithianon [3347-22-6] (**28**); a quinoxaline, eg, chinomethionat [2439-01-2] (**29**); a pyridazine, eg, diclomezine [62865-36-5] (**30**), a thiadiazole, eg, etridiazole [2593-15-9] (**31**); a pyrrole, eg, fenpiclonil [74738-17-3] (**32**); a quinoline, eg, ethoxyquin [91-53-2] (**33**); and a triazine, eg, anilazine [101-05-3] (**34**). These compounds are mostly enzyme poisons, binding with -SH or amino groups of fungal enzymes or interfering with fungal membrane structure and function.

2. Site-Specific Systemic Fungicides

In general, the systemic fungicidal treatment of crop plants is only possible using inhibitors of fungal-specific targets, and there has been considerable progress in developing agricultural fungicides having high levels of fungal specificity. Elucidation of the biochemical mechanisms of action of compounds has led to the discovery of some novel compounds. Many of the fungicides introduced since the 1970s have been systemic fungicides which inhibit fungal growth at various stages of fungal development. These fungicides are often active at very low levels compared with nonsystemics and tend to exhibit a much narrower activity spectrum as a consequence of their action against a specific biochemical target. Precise biochemical targets have been defined for many of the different classes of fungicide chemistries. Some have a biochemical target site in common. The selectivity of systemic fungicides can be attributed to differences in a number of factors. These include uptake and accumulation in the fungal cell, inherent differences at the target site, differences in metabolism of the fungicide by the plant or fungi, and the degree of importance of the target system to the survival of the fungus.

2.1. Mitochondrial Respiration Inhibitors

The carboxanilides, discovered in 1964, were among the first systemic commercial fungicides capable of protecting the unsprayed new growth of plants from fungal attack (19). The principal fungicides in this class of mitochondrial respiration inhibitors are carboxin [5234-68-4] (**35**); oxycarboxin [5259-88-1] (**36**); flutolanil [66332-96-5] (**37**); fenfuram [24691-80-3] (**38**); mepronil [55814-41-0] (**39**); methfuroxam [28730-17-8] (**40**); and metsulfovax [21452-18-6] (**41**). These compounds, shown in Figure 4, were mainly active against the

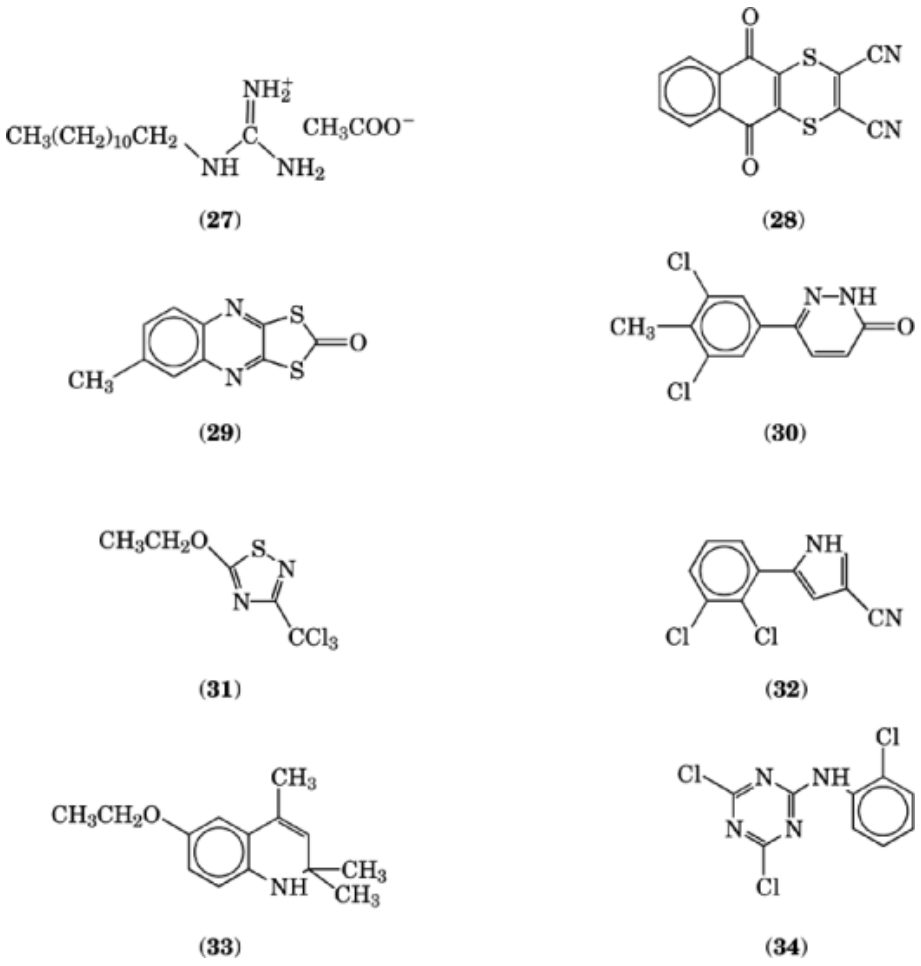


Fig. 3. Miscellaneous nonsystemics.

Basidiomycetes (see Table 1), a class of fungi which includes such important pathogens as the rusts (*Puccinia* spp.), smuts (*Ustilago* spp.), and bunts of cereals. They are used as both seed and foliar fungicides against rusts of coffee beans (*Uromyces* spp.) and ornamentals (plants grown for decorative reasons). The mode of action of the carboxanilides involves interference with succinate metabolism. Studies using whole cells (20) and later isolated mitochondrial preparations (21, 22) led to the conclusion that the primary target is the succinate dehydrogenase complex of the mitochondrial respiratory chain, which is inhibited by these compounds. Genetic and molecular biology studies (23–26) have confirmed this conclusion.

Because of the initial selectivity of carboxanilides to Basidiomycete fungi, it was thought at one time that the molecular site of action of carboxin (**35**) might be unique to Basidiomycetes. Subsequently, however, analogues emerged which demonstrated activity against non-Basidiomycete fungi (27, 28). This suggested that selectivity was based not on differing carboxamide affinities for the succinate dehydrogenase complexes of various fungi, but rather on metabolic factors or permeability differences, such as mitochondrial penetration. Resistance to the carboxanilide fungicides has been noted across this class of compounds, and has contributed to a decline in usefulness.

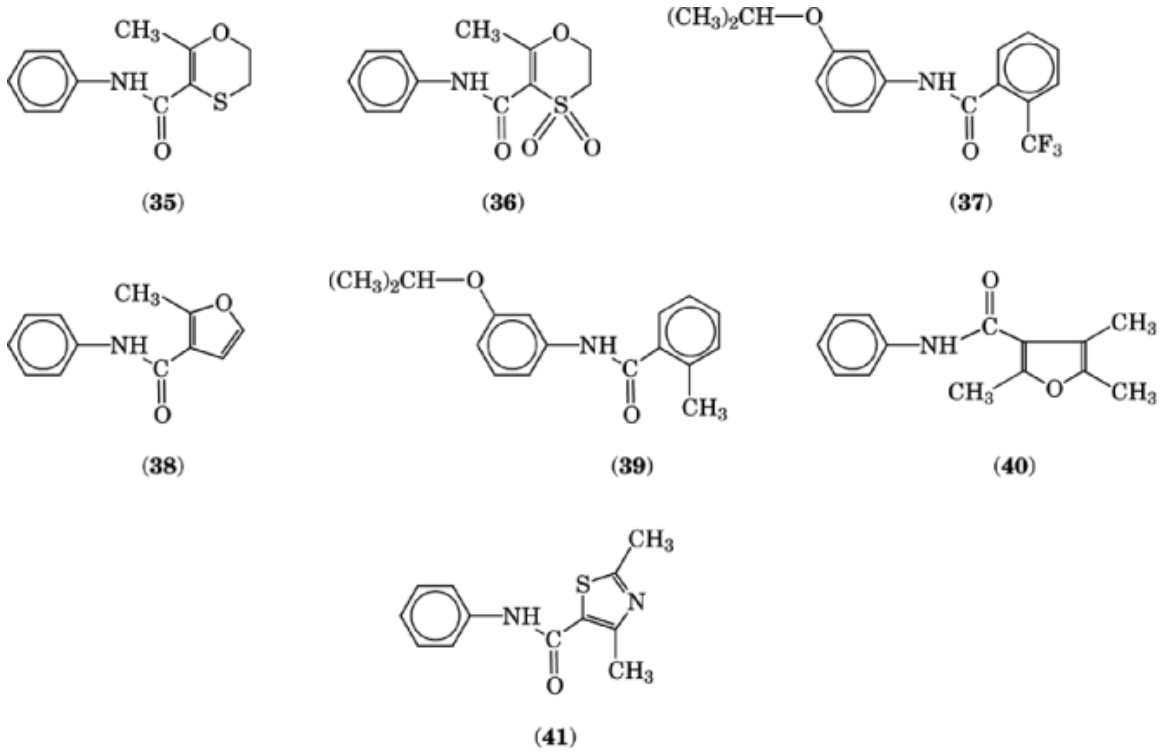
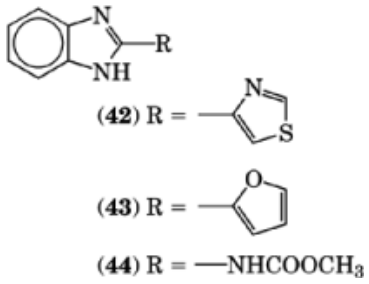
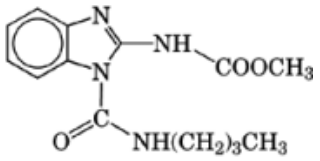


Fig. 4. Mitochondrial respiration inhibitors.

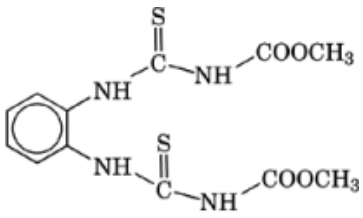
2.2. Microtubulin Polymerization Inhibitors

The benzimidazoles were first reported to have systemic fungicidal activity in 1964 (29). Prominent examples include thiabendazole [148-79-8] (**42**); fuberidazole [3878-19-1] (**43**); carbendazim [10605-21-7] (**44**); benomyl [17804-35-2] (**45**); and thiophanate methyl [23564-05-8] (**46**). Benomyl (**45**), the most widely used member of this group is almost certainly inactive as a fungicide until it is converted in plants and soil to carbendazim (**44**). Likewise, thiophanate and thiophanate methyl (**46**) are nonfungitoxic until converted to carbendazin (**44**).





(**45**)



(**46**)

Whereas most Ascomycetes, Deuteromycetes (see Table 1), and Basidiomycetes are sensitive to the fungicides, the Phycomycetes (Oomycetes and Zygomycetes) are inherently resistant. The primary mode of action has been identified as specific binding to the β-tubulin subunit of fungal tubulin. Because β-tubulin is a principal component of the fungal cytoskeleton, the resulting interference with assembly of the microtubules leads to a disruption of both mitosis and meiosis (30). All organisms except bacteria and blue-green algae possess microtubules. The benzimidazoles are characterized, however, by a remarkable selectivity for fungi that probably depends on differences in molecular structures of the binding sites of the microtubules. There is a high margin of safety of carbendazim and related compounds to plants. This may have a basis in low tubulin binding in plants, as has been demonstrated for mammalian tubulin. Resistance, observed shortly after the introduction of benomyl (**43**), has increased throughout the world (31). Studies have suggested that single-site mutations in the β-tubulin gene are responsible for the resistance (32, 33).

2.3. Inhibitors of Sterol Biosynthesis

The discovery of compounds that inhibit ergosterol biosynthesis in fungi was one of the most significant advances in the history of fungicide research (34). Sterols are known to be essential for all eukaryotes, either synthesized *de novo* from acetate or taken up from the environment. In fungi, the early steps in the pathway from acetate culminate with the cyclization of squalene epoxide to produce lanosterol [79-63-0] (**47**), $C_{30}H_{50}O$. Figure 5 presents the steps involved in the biosynthesis of the principal sterol in most fungi, ergosterol [57-87-4] (**33**), $C_{28}H_{44}O$, a component in membrane structure.

Fungicides that inhibit sterol biosynthesis have utility only against those fungi that synthesize their sterol complement. Consequently, these compounds are generally not efficacious against grape downy mildew and potato late blight (*Phytophthora infestans*), which satisfy their sterol requirements by mycelial uptake. Because of the importance of ergosterol in fungal membranes, any reduction in its availability to fungi increases the permeability to electrolytes and leads to a severe leakiness of membrane-enclosed compartments. This structural role can only be filled by ergosterol and even closely related sterols are apparently inadequate. The primary result of sterol biosynthesis inhibition is the accumulation of sterol precursors and the depletion of the demethylated sterol pool. The precursors are incorporated into the plasma membrane, eventually replacing ergosterol and arresting fungal growth and reproduction. This effect is fungistatic in character so that removal of the inhibitor results in full recovery of cell viability. The accumulation of sterol precursors not only affects the permeability of membranes, but also the active transport of nutrients such as amino acids (qv) (35),

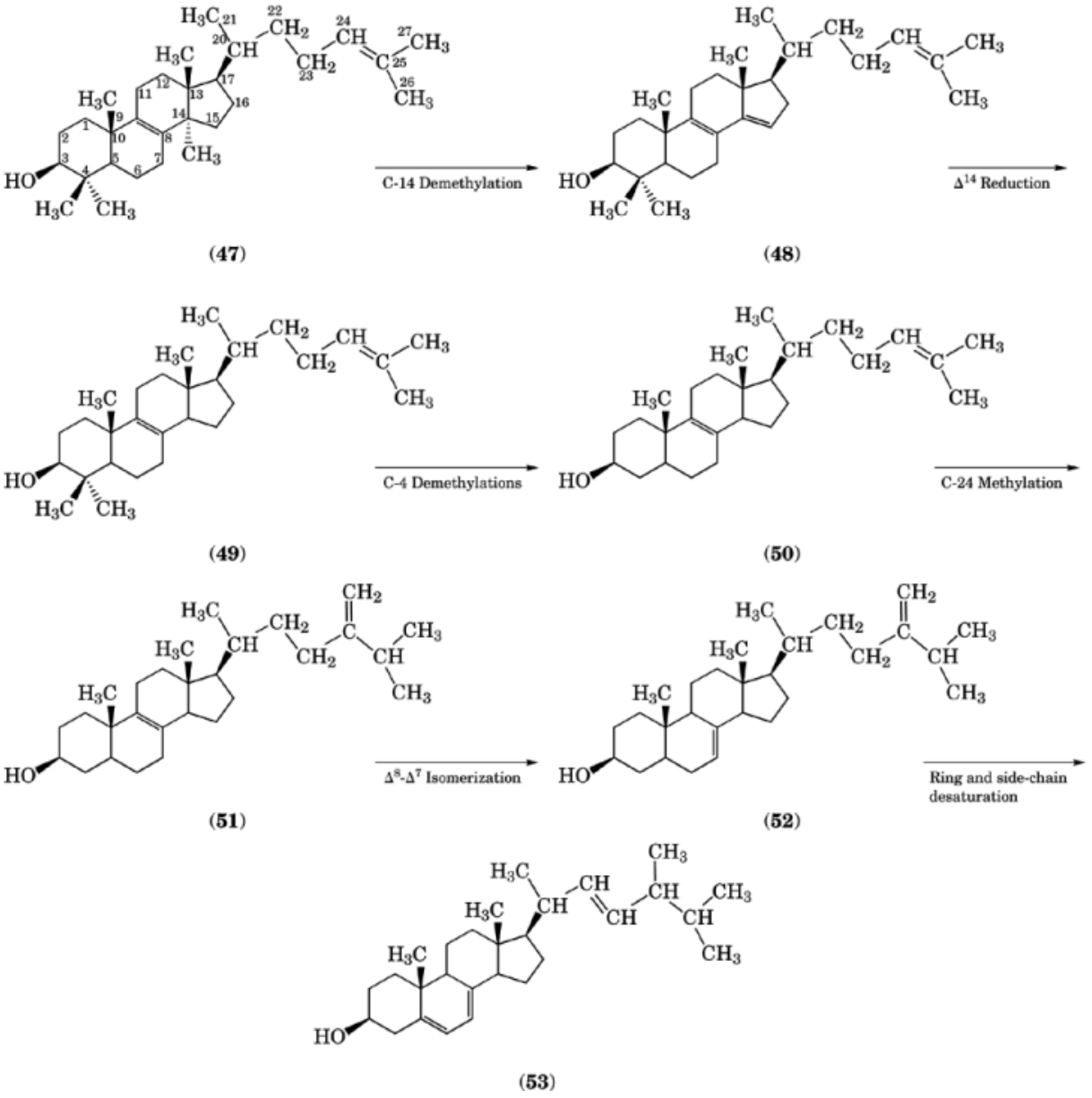


Fig. 5. Ergosterol biosynthesis pathway.

and the activity of membrane-located enzymes. Finally, ergosterol and related fungal sterols may also serve as precursors for steroid hormones necessary for sexual reproduction events in fungi and, possibly, other biological processes (36).

Although sterol biosynthesis-inhibiting compounds have been used since the 1950s to control human fungal diseases, the success and impact of agricultural fungicides with target sites in ergosterol biosynthesis

has, since the late 1960s, revolutionized the control of plant diseases (37). The impact of these new classes of inhibitors has been particularly marked against Ascomycetes, Deuteromycetes, and Basidomycetes.

2.3.1. C-14 Demethylation Inhibitors

Piperazines, pyridines, pyrimidines, and azoles all inhibit the C-14 demethylation step catalyzed by the cytochrome P450-dependent 14α-demethylase (Fig. 5). The only apparent common feature of the various demethylation inhibitors is the presence of a heterocycle containing at least one nitrogen atom. Basic amines, pyridines, and azoles have long been known to exhibit a strong affinity for various cytochrome-P450 monoxygenases and may act by the hydrophobic substituents of the various compounds binding to the site on the demethylase normally occupied by lanosterol (**47**). This binding positions the basic nitrogen of the essential heterocycle such that it blocks the binding of oxygen to the cytochrome P-450 cofactor, which is a prerequisite for demethylation (38–40).

The earliest commercial fungicides recognized to inhibit ergosterol formation in fungi were the piperazines, eg, triforine [26644-46-2] (**54**); pyridines, eg, buthiobate [51308-54-4] (**55**); and the pyrimidine carbinols, represented by triarimol [26766-27-8] (**56**), fenarimol [60168-88-9] (**57**), and nuarimol [63284-71-9] (**58**) (Fig. 6). Imidazoles, also very active, were among the earliest azoles developed. Imazalil [35554-44-0] (**59**) is effective against a wide variety of fruit, vegetable, and cereal diseases. It is used primarily as a seed or post-harvest treatment. Prochloraz [67747-09-5] (**60**) has found a niche in the control of eyespot (*Pseudocerosporella herpotrichoides*), glume blotch (*Septoria nodorum*), and leaf blotch (*Septoria tritici*) diseases of cereals, whereas triflumizole [99387-89-0] (**61**), a more recent example, is primarily used in controlling fruit diseases.

Probably the most important fungicides in this group are the triazoles which have in common a 1,2,4-triazole group attached through the 1-nitrogen to a large lipophillic group (Fig. 7). The most important members of this family are triadimefon [43121-43-3] (**62**), introduced in 1973 as a highly active compound against powdery mildews (*Erysiphe graminis*) and rusts of cereals; propiconazole [60207-90-1] (**63**), introduced in 1979 with an extremely broad spectrum of cereal disease activity; tebuconazole [107534-96-3] (**64**); cyproconazole [113096-99-4] (**65**); and tetraconazole [112281-77-3] (**66**), all highly efficacious, broad-spectrum fungicides recently introduced for use on both cereals and top fruit. Some of the more unusual structures in this class are flusilazole [85509-19-9] (**67**), which incorporates a silicon atom; myclobutanil [88671-89-0] (**68**), with a nitrile; flutriafol [76674-21-0] (**69**), which mimics the pyrimidine carbinols; and imibenconazole [86598-92-7] (**70**), which incorporates an imine in the alkyl chain. Additional structures of commercialized azoles have been outlined in detail in a number of publications (41, 42).

The almost exclusive use of triazoles for cereal powdery mildew control up to the mid-1980s has resulted in a shift in *Erysiphe* populations toward reduced sensitivity or resistance to this class of fungicides. However, use has continued because field performance of most triazoles has remained adequate (43). Decreased azole sensitivity in the *Septoria* population to azoles has also been noted.

2.3.2. Δ^{14}-Reduction and Δ^{8}–Δ^{7}-Isomerization Inhibitors

Only one group of compounds that act as inhibitors for both the Δ^{14}-reduction and Δ^{8}–Δ^{7}-isomerization steps (Fig. 6), the morpholines, have been developed as commercial agricultural fungicides. The earliest compounds of this class, dodemorph [1593-77-7] (**71**) and tridemorph [81412-43-3] (**72**), were first introduced in the 1960s. These were followed in 1979 by fenpropimorph [67306-03-0] (**73**) and fenpropidin [67306-00-7] (**74**), which are especially active, both as eradicants and protectants, against the Ascomycete (particularly powdery mildews) and, to a lesser extent, Basidiomycete (eg, rusts) diseases of cereals and ornamentals. The Δ^{8}–Δ^{7} isomerase step (**49**) to (**52**) in Figure 5, was initially proposed as the primary target of the morpholines following accumulation, in tridimorph-treated fungi, of such sterols as fecosterol (**51**) (44). However, specific morpholines also inhibit the Δ^{14}-reduction step, (**48**) to (**49**), to a greater or lesser extent (45). Although laboratory resistance to morpholines

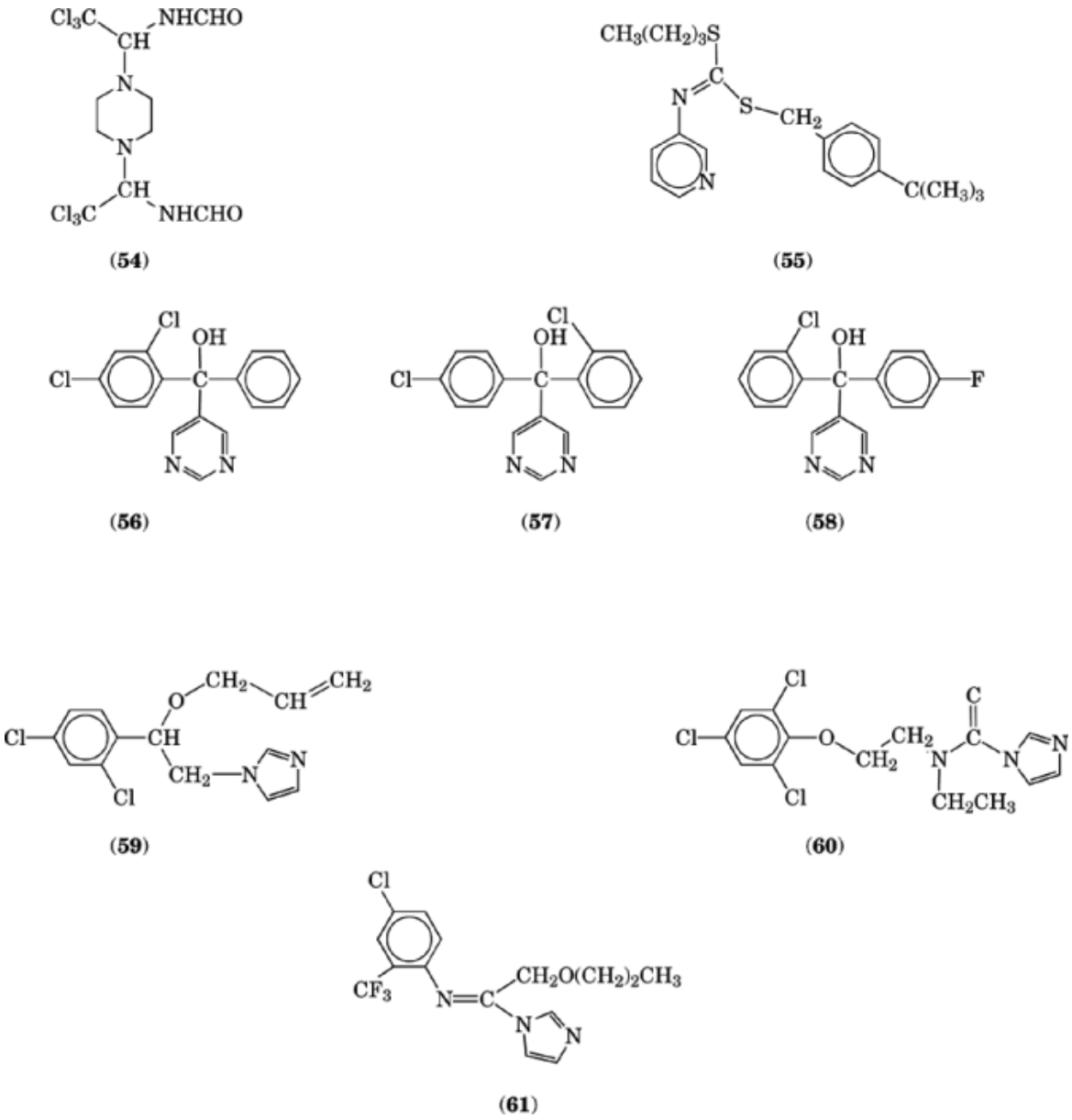


Fig. 6. C-14 demethylation inhibitors.

has been reported in several fungi (46, 47), significant resistance problems have not yet surfaced in the field (43, 48), and these compounds are widely used particularly for cereals.

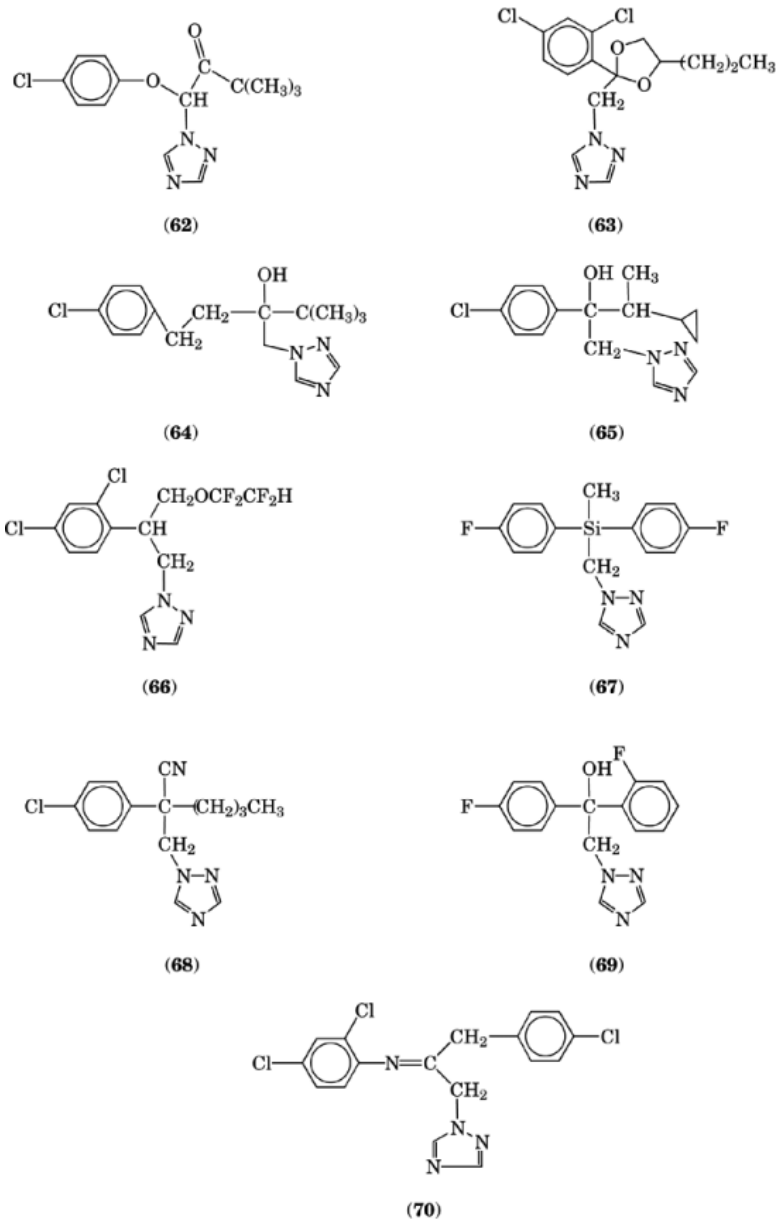
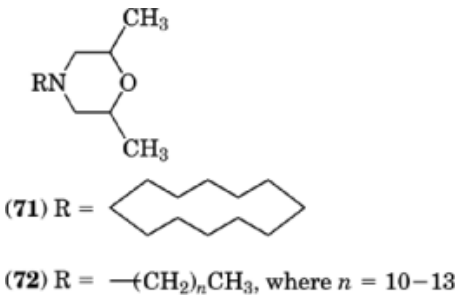
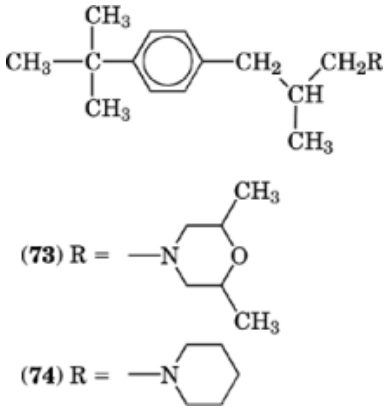


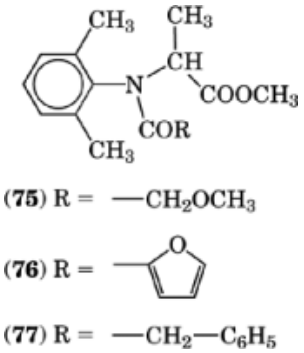
Fig. 7. Triazole C-14 demethylation inhibitors.

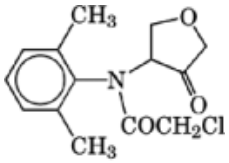




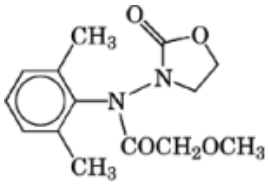
2.4. RNA Biosynthesis Inhibitors

Phenylamides and hydroxypyrimidines function as RNA biosynthesis inhibitors. The phenylamide fugincides are comprised of the acylalanines, eg, metalaxyl [137414-52-9] (**75**), furalaxyl [57646-30-7] (**76**), and benalaxyl [71626-11-4] (**77**); the butyrolactones, eg, ofurace [58810-48-3] (**78**); and the oxazolidinones, eg, oxadixyl [77732-09-3] (**79**). These compounds are readily taken up by roots and foliage, and have good activity against the oomycetes including grape downy mildew and potato late blight. Studies of phenylamides on various steps in the infection process indicate little effect on the release, mobility, encystment, and germination of zoospores of these oomycete pathogens or on host penetration and primary haustorium (the specialized fungal structure which absorbs nutrients from the plant host) formation (49). Studies using other *Phytophthora* species firmly established RNA-polymerase I as the primary biochemical target of the phenylamides (50, 51). As a consequence of interference with this enzyme target new ribosome formation is inhibited and protein synthesis becomes impaired, leading to fungal growth inhibition. Inhibition of RNA biosynthesis leads to accumulation of nucleoside triphosphate precursors which promote fungal β-(1,3)-glucan synthetase, and thus stimulate the biosynthesis of key cell wall constituents resulting in inhibition of cell growth. After repeated and exclusive use of metalaxyl in the field against late blight of potato, resistance to all the phenylamides rapidly developed (52, 53) and strategies involving combination sprays and mixtures with other fungicides have been developed to address this problem.

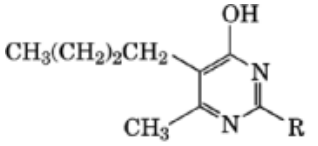




(**78**)

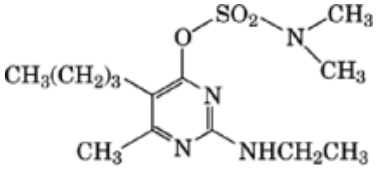


(**79**)



(**80**) R = —$NHCH_2CH_3$

(**81**) R = —$N(CH_3)_2$

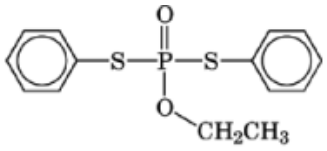


(**82**)

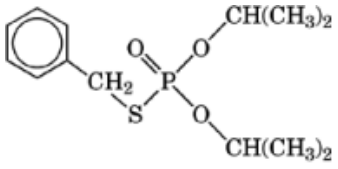
The 4-hydroxypyrimidine derivatives, eg, ethirimol [23947-60-6] (**80**), dimethirimol [5221-53-4] (**81**), and bupirimate [41483-43-6] (**82**), have a selective and systemic activity against powdery mildews of cereals, field vegetables, and ornamentals, both as foliar and seed treatment compounds. These interfere with several stages of the infection process of powdery mildew, but particularly with appressorium formation (54) and germ tube extension. Biochemically, ethirimol (**80**) may interfere with purine metabolism. Reversal experiments showed that ethirimol was antagonized by metabolites such as adenine, adenosine, guanine, and folic acid (55). Later studies have shown that the target enzyme is adenosine deaminase, which appears to be inhibited specifically in powdery mildews (55). Powdery mildews do not synthesize purines *de novo* and it is believed that adenosine deaminase is essential to these fungi for utilization of purines acquired from the host during the infection process. Kinetin (6-fufuryladenine) and isopentenyladenine have also been observed to inhibit appressorium formation, and ethirimol-resistant isolates of barley powdery mildew exhibit cross-resistance to these growth regulators (see Growth regulators, plants) (56). Resistance problems were encountered in the field shortly after introduction of the hydroxypyrimidines, and use of these compounds has been restricted to cereal seed treatment and greenhouse applications.

2.5. Phospholipid Biosynthesis Inhibitors

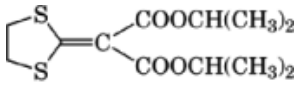
The organophosphate compounds ediphenphos [17109-49-8] (**83**) and iprobenphos [26087-47-8] (**84**) represent a class of fungicides that target a site in the lipid biosynthesis pathway (57). The structurally unrelated compound isoprothiolane [50512-35-1] (**85**), introduced in 1975, appears to have the same mechanism of action despite the absence of a phosphorus atom. All three are readily taken up by both roots and leaves of rice, subsequently translocated to control rice blast (*Pyricularia oryzae*), and appear to be more toxic to mycelium growth and sporulation of rice blast than to spore germination or appressorium formation (58, 59). The biochemical mode of action has been identified as the inhibition of methyl transfer to phosphatidyl ethanolamine (59, 60) in phosphatidyl choline biosynthesis, resulting in membrane disruption. After 10 years of field usage strains of rice blast resistant to iprobenphos (**85**) have emerged.



(**83**)



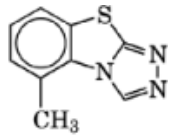
(**84**)



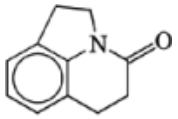
(**85**)

2.6. Melanin Biosynthesis Inhibitors

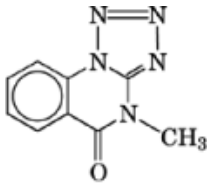
The discovery in 1969 of tricyclazole [41814-78-2] (**86**) and its protectant activity against rice blast led to understanding of the importance of melanin inhibition as a means of controlling this pathogen (61). Since then other compounds of differing structures have been shown to similarly inhibit melanin formation, eg, pyroquilon [57369-32-1] (**87**) and the experimental compound PP389 [89342-33-5] (**88**). Melanization of the appressorial walls of the rice blast fungus is essential for the development of infection hyphae and successful penetration of the leaf (62, 63). Appressoria formed in the presence of tricyclazole are devoid of melanin and this reduces the mechanical strength of the infection peg and prevents leaf penetration (64, 65). Biochemical studies have indicated that these compounds inhibit the polyketide pathway of melanin biosynthesis at two sites (66, 67). No evidence of rice blast resistance to tricyclazole has been observed in the field.



(**86**)



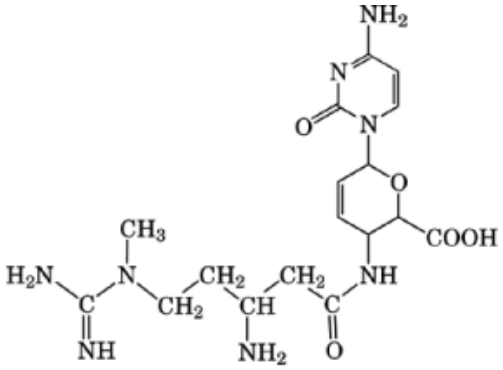
(**87**)



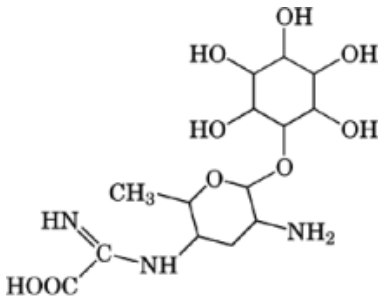
(**88**)

2.7. Fungal Protein Biosynthesis Inhibitors

Two fermentation products have been shown to be very effective against rice blast. The first, blasticidin S [2079-00-7] (**89**), is produced by *Streptomyces grieschromogens*. The second, kasugamycin [6980-18-3] (**90**), is a water-soluble base obtained from *Streptomyces kasugaensis*. Both have been used to control rice blast in Japan since 1965 as protectant and curative rice blasticides. They inhibit the growth of the rice blast fungus at levels of 5–10 μg/mL and primarily work by inhibiting protein biosynthesis. These compounds exert this effect by binding respectively to the larger, 60S, and smaller, 30S, subunits of fungal ribosomes (68–71). Resistance has been observed to both compounds in fields where they have been extensively used.



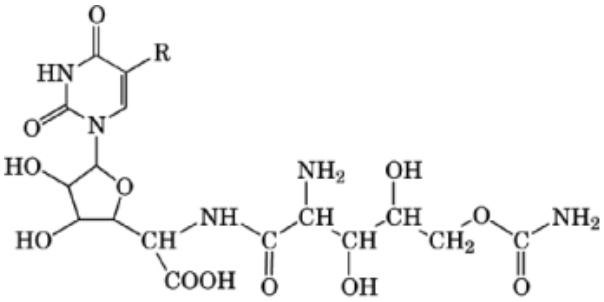
(**89**)



(**90**)

2.8. Cell Wall Biosynthesis Inhibitors

Polyoxin B [19396-06-6] (**91**) and polyoxin D [22976-86-9] (**92**), both from Streptomyces cacaoi var. asoensis, are closely related antibiotics (qv) that act as highly selective inhibitors of fungi containing chitin in their walls. For this reason the polyoxins are not active against Oomycetes that contain cellulose as the principal cell wall constituent. The mode of action of the polyoxins has been determined to be the inhibition of chitin synthase (chitin UDP-*N*-acetylglucosaminyl transferase), which is localized in the plasma membrane of growing hyphae (72–74). These nucleoside antibiotics show structural similarities to UDP-*N*-acetylglucosamine with which they compete for the chitin synthase active site (75).

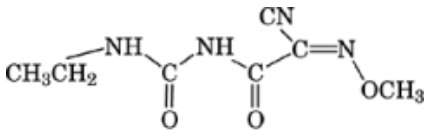


(**91**) R = CH_2OH
(**92**) R = COOH

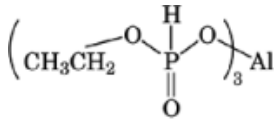
2.9. Incompletely Elucidated Modes of Action

A number of compounds have been successfully used as agricultural fungicides but their modes of action have yet to be completely understood. Cymoxanil [57966-95-7] (**93**) is a systemic compound that shows curative and protectant activity against the oomycetes, notably grape downy mildew and potato late blight (76). It has been shown to interfere with RNA and protein synthesis in some fungi but it is not clear whether cymoxanil or some metabolite is the active moiety (77). Fosetyl-Al [39148-24-8] (**94**) is also highly active against the oomycetes, especially grape downy mildew and a variety of other diseases (78). It can be applied as a foliar spray, root drench, or by stem injection, and translocates in both the xylem and phloem systems of the plant. Though several lines of evidence indicate that fosetyl-Al (**94**) has a direct action on target pathogens (79, 80), treatment of tobacco plants with fosetyl-Al increased the synthesis of the natural phytoalexin capsidiol. It is possible

that accumulation of capsidiol in tobacco and of other phytoalexins such as stilbenes and flavonoids in grape is associated with its activity (79, 80).



(93)



(94)

2.10. Resistance to Fungicides

Development of fungicide resistance continues to be one of the primary problems in plant disease control. Resistance can be defined as a stable inheritable adjustment by a fungus to a fungicide that results in less than normal sensitivity to that fungicide (81). In the case of the protectant fungicides, because these are generally multisite inhibitors (with the possible exception of dicarboximides), fungi have little chance, in the short term, of developing resistance. By contrast, systemic fungicides frequently are single-site inhibitors and thus carry a greater potential for resistance to develop. Mutation of a single gene can result in a modified target site with reduced affinity to the fungicide. When under selection pressure by the fungicide, buildup of a residual resistant population occurs and, in the extreme case, may result in the failure of disease control.

Well over 100 plant pathogens have become resistant to various fungicides under field conditions. Failure of the acyl alanines, benzimidazoles, thiophanates, carboxanilides, dicarboximides, hydroxypyrimidines, some organophosphates, and most of the antibiotics has occurred. In other cases, a moderate decrease in sensitivity without a rapid loss of disease control has been observed as in the case of sterol biosynthesis inhibitors (triazoles, pyrimidines, and imidazoles) and organophosphates. The most effective approach is to use fungicides having different modes of action in combination, either as mixtures or in alteration, possibly utilizing both specific site and multisite inhibitors. Because of resistance problems great importance is attached to chemistries that inhibit novel fungal enzyme targets.

2.11. Economic Aspects

Growers regard the use of fungicides as part of their broad crop management strategy, in both planning and implementation. The conventional approach to crop production and pesticide use has been via economically justified maximum yield responses, and has led to applications being either made routinely or targeted to specific risks, with a wide range of frequency of applications. Within a particular market segment the pricing of fungicide products from the various manufacturers is extremely uniform and tends to be dictated at least in part by the cost of established products that have stood the test of time balanced against the needs of the grower to demonstrate a clear cost-benefit advantage from their use. As of 1993, fungicide costs for some of the key market segments ranged from $26 per treatment equivalent to $76 per season for European cereals, $25 per treatment or $150 per season for pome fruit to $18–42 per treatment or $110–250 per season for the prevention of grape downy mildew. These three markets together generated sales of $1.7 billion at the manufacturers' level.

Newer fungicides, in order to retain cost-effectiveness, need to be very highly active, which also serves to achieve efficacy in the field at low dose rates thus keeping environmental pollution problems as small as possible. More in-depth knowledge of fungal biochemistry and the molecular events involved in host/pathogen interactions should facilitate the identification of novel fungal targets for use in a biorational approach to fungicide discovery, through the application of computer-aided molecular design (CAMD) approaches to the molecular modeling (qv) of the target to design new fungicides (82). Recombinant DNA technologies are expected to play an escalating role in the validation of such biorational targets (see Genetic engineering).

Government regulations for the registration and utilization of all plant protection agents require exhaustive studies on topics such as mammalian toxicology, effects on various forms of wildlife (eg, fish toxicity), soil leachability, and residue levels in crops, soil, and water. It is also required that compounds persist in the environment only as long as is necessary to control crop diseases before being biodegraded. As a consequence, some previously registered fungicides have been withdrawn from the market.

BIBLIOGRAPHY

"Fungicides, Agricultural" in *ECT* 1st ed., Vol. 6, pp. 984–991, by J. C. Horsfall, Connecticut Agricultural Experiment Station; in *ECT* 2nd ed., Vol. 10, pp. 220–228, by D. C. Torgeson, Boyce Thompson Institute for Plant Research; in *ECT* 3rd ed., Vol. 11, pp. 490–498, by E. J. Butterfield and D. C. Torgeson, Boyce Thompson Institute for Plant Research.

Cited Publications

1. *Reference Volume of the Agrochemical Service*, County NatWest WoodMac Securities Ltd., London, 1992, 48–69.
2. A. P. Sinha, K. Singh, and A. N. Mukhopadhyay, *Soil Fungicides*, Vols. **I** & **II**, CRC Press, Inc., Boca Raton, Fla., 1988.
3. J. W. Eckert, in H. R. Siegel and H. D. Sisler, eds., *Antifungal Compounds*, Vol. **1**, Marcel Dekker, Inc., New York, 1977, 290–352.
4. H. Buchenauer, in G. Haug and H. Hoffmann, eds., *Chemistry of Plant Protection*, Vol. **6**, Springer-Verlag, Berlin, 1990, 221–226.
5. W. Forsyth, *A Treatise on the Culture and Management of Fruit Trees*, Nichols & Son, London, 1802.
6. A. Millardet, *J. Agr. Prat.* **49**, 801–805 (1885), English trans. F. J. Schneiderhan, *Phytopathol. Classics* **3**, 18–25 (1933).
7. Ref. 4, p. 222.
8. S. E. A. McCallen, in D. C. Torgeson, ed., *Fungicides, an Advanced Treatise*, Vol. **1**, Academic Press, Inc., New York, 1967, 1–37.
9. Ref. 4, 240–241.
10. U.S. Pat. 1,972,961 (1934), W. H. Tisdale and I. Williams (to E. I. du Pont de Nemours & Co., Inc.)
11. Ref. 4, p. 223.
12. R. J. Lukens and H. D. Sisler, *Phytopathology* **48**, 235 (1958).
13. M. R. Siegel, *Pestic. Biochem. Physiol.* **1**, 225 (1971).
14. *Chem. Week* **136**(23), 40 (1985).
15. T. Kato, in I. Miyamoto and P. C. Kearney, eds., *Pesticide Chemistry*, Vol. **3**, Pergamon Press, Oxford, U.K., 1983, p. 153.
16. H. Lyr, in H. Lyr, ed., *Modern Selective Fungicides—Properties, Application and Mechanism of Action*, Gustav Fischer Verlag, Jena, Germany, 1987, p. 75.
17. E. H. Pommer and G. Lorenz, in Ref. 15, p. 91.
18. H. Sisler, in C. J. Delp, ed., *Fungicide Resistance in North America*, APS Press, St. Paul, Minn., 1988, p. 52.
19. B. von Schmeling and M. Kulka, *Science* **152**, 659 (1966).
20. D. E. Mathre, *Phytopathology* **60**, 671 (1970); N. N. Ragsdale and H. D. Sisler, *Phytopathology* **60**, 1422 (1970).
21. D. E. Mathre, *Pestic. Biochem. Physiol.* **1**, 216 (1971).
22. J. T. Ulrich and D. E. Mathre, *J. Bacteriol* **110**, 628 (1972).
23. S. G. Georgopoulos, E. Alexandri, and M. Chrysayi, *J. Bacteriol* **110**, 809 (1972).
24. S. G. Georgopoulos, M. Chrysayi, and G. A. White, *Pestic. Biochem. Physiol.* **5**, 543 (1975).

25. I. A. U. N. Gunatilleke, H. N. Arst, and C. Scazzochio, *Aspergillus nidulans, Genet. Res. Cambridge* **26**, 297 (1975).
26. J. P. R. Keon, G. A. White, and J. A. Hargreaves, *Current Genetics* **19**, 475–481 (1991).
27. L. V. Edington and G. L. Barron, *Phytopathology* **57**, 1256 (1967).
28. G. A. White and S. G. Georgopoulos, *Pestic. Biochem Physiol.* **25**, 188 (1986).
29. T. Staron and C. Allard, *Phytiat–Phytopharm.* **13**, 163 (1964).
30. H. Lyr, *Plant Disease* **1**, 239 (1977).
31. P. Leroux and B. Besselat, *Phytoma–Defense des Cultures* **359**, 25 (1984).
32. H. Ishii, H. Yanase, and J. Dekker, *Meded. Fac. Landbouwwet. Rijksuniv. Gent.* **49**(2a), 163 (1984).
33. M. Fujimura and co-workers, in M. B. Green, H. M. LeBaron, and W. K. Moberg, eds., *Managing Resistance to Agrochemicals*, American Chemical Society, Washington, D.C., 1990, p. 224.
34. D. Berg and M. Plempel, eds., *Sterol Biosynthesis Inhibitors—Pharmaceutical and Agrochemical Aspects*, Ellis Horwood, Chichester, 1988.
35. J. F. Ryley, R. G. Wilson, and K. J. Barrett-Bee, *J. Med. Vet. Mycol.* **22**, 53 (1984).
36. W. Köller in W. Köller, ed., *Target Sites of Fungicide Action*, CRC Press, Inc., Boca Raton, Fla., 1992, 139–141.
37. K. H. Kuck and H. Scheinpflug, in G. Haug and H. Hoffmann, eds., *Chemistry of Plant Protection*, Vol. **1**, Springer-Verlag, Berlin, 1986, 65–96.
38. Y. Yoshida, in M. R. McGinnis, ed., *Current Topics in Medical Mycology*, Vol. **2**, Springer-Verlag, New York, 1988, p. 388.
39. H. Vanden Bossche, in Ref. 40, Vol. **1**, 1985, p. 313.
40. H. Vanden Bossche, in Ref. 36, p. 79.
41. C. R. Worthing and R. J. Hance, eds., *The Pesticide Manual*, 9th eds., British Crop Protection Council, Farnham, U.K., 1991.
42. W. Kramer, in Ref. 39, 25–64.
43. M. A. De Waard, in I. Denholm, A. L. Devonshire, and D. W. Hollomon, eds., *Resistance 91: Achievements and Developments in Combating Pesticide Resistance*, Elsevier Applied Science, London, 1992, 48–60.
44. T. Kabo, M. Shoami, and Y. Kaurase, *J. Pestic. Sci.* **5**, 69 (1980).
45. R. I. Baloch and E. I. Mercer, *Phytochemistry* **26**, 663 (1987).
46. A. Keerkenaar, in R. A. Fromtling, ed., *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*, J. R. Prouse, Science Publishers, Barcelona, Spain, 1987, p. 523.
47. E. I. Mercer, in Ref. 36, p. 120.
48. W. Köller, in D. Pimentel, ed., *Handbook of Pest Management in Agriculture*, Vol. **3**, 2nd ed., CRC Press, Boca Raton, Fla., 1991, p. 679.
49. T. Staub, H. Dahmen, and F. J. Schwinn, *Z. Pfl. Krankh. Pfl. Schutz* **87**, 83 (1980).
50. L. C. Davidse, A. E. Hoffman, and G. C. M. Velthuis, *Mycology* **7**, 344 (1983).
51. R. Wollgiehn and co-workers, *Z. Allgem. Mikrobiologie* **24**, 269 (1984).
52. F. J. Schwinn, in D. C. Erwin, S. Bartnicki-Garcia, and P. H. Tsao, eds., *Phytophthora: Its Biology, Taxonomy, Ecology*, American Phytopathic Society, St. Paul, Minn., 1983, p. 327.
53. L. C. Davidse, O. C. M. Gerritsma, and A. E. Hoffman, *Phytotiatrie-Phytopharmacie* **30**, 235 (1981).
54. D. W. Hollomon, in N. R. McFarlane, ed., *Crop Protection Agents*, Academic Press, Inc., London, 1977, p. 505.
55. D. W. Hollomon, *Pestic. Biochem. Physiol.* **10**, 181 (1979).
56. J. Dekker, *Nature* **197**, 1027 (1963).
57. Ref. 7, 253–254.
58. S. H. Ou, *Plant Disease* **64**, 439 (1980).
59. O. Kodama, K. Yamashita, and T. Akatsuka, *Agric. Biol. Chem.* **44**, 1015 (1980).
60. M. Yoshida, S. Moriya, and Y. Uesugi, *J. Pestic. Sci.* **9**, 703 (1984).
61. J. D. Froyd and co-workers, *Phytopathology* **66**, 1135 (1976).
62. C. P. Woloshuk, H. D. Sisler, and E. L. Vigil, *Physiol. Plant Pathol.* **22**, 245 (1983).
63. P. M. Wolkow, H. D. Sisler, and E. L. Vigil, *Physiol. Plant Pathol.* **23**, 55 (1983).
64. C. P. Woloshuk and H. D. Sisler, *J. Pestic. Sci.* **7**, 161 (1982).
65. S. Inoue, T. Vematsu, and T. Kato, *J. Pestic. Sci.* **9**, 689 (1984).
66. C. P. Woloshuk and co-workers, *Pestic. Biochem. Physiol.* **14**, 256.
67. M. H. Wheeler, *Exp. Mycol.* **6**, 171 (1982).
68. H. Yamaguchi, C. Yamamoto, and N. Tanaka, *J. Biochem (Tokyo)* **57**, 667 (1965).

69. Ref. 3, p. 399.
70. N. Tanaka, in N. Tanaka, *Antibiotics*, Vol. **3**, Springer-Verlag, New York, 1975, p. 340.
71. B. Poldermans, N. Goosen, and P. H. van Knippenberg, *J. Biol. Chem.* **254**, 9085 (1979).
72. A. Endo and T. Misato, *Biochem. Biophys. Res. Commun.* **37**, 718 (1969).
73. S. Bartnicki-Garcia and E. Lippman, *J. Gen. Microbiol.* **71**, 301 (1972).
74. B. Bowers, G. Levin, and E. Cabib, *J. Bacteriol.* **119**, 564 (1974).
75. K. Endo and co-workers, *Nipon Nogei Kakatu Kaishi* **44**, 356 (1970).
76. H. L. Klopping and C. J. Delp, *J. Agric. Food Chem.* **28**, 467 (1980).
77. R. Fritz, D. Despreaux, and P. Leroux, *Tag.-Ber., 222, Akad. Landwirtsch.-Wiss, DDR, Berlin*, 65 (1984).
78. T. Staub and H. Hubele, in R. Wegler, ed., *Chemie der Pflazenschutz und Schädlings-bekämpfungsmittle*, Vol. **6**, Springer-Verlag, Berlin, 1981, p. 389.
79. O. Langcake, *Phil. Trans. Royal Soc. London Ser. B* **295**, 83 (1981).
80. D. I. Guest, *Physiol. Plant Pathol.* **25**, 125 (1984).
81. J. Dekker, in Ref. 15, 39–52.
82. A. Dearing, in H. Frehse, ed., *Proceedings 7th International Congress of Pesticide Chemistry (IUPC) Hamburg 1990*, VCH Verlagsgesellschaft, Weinheim, Germany, 1991, 61–72.

General References

83. D. C. Torgeson, ed., *Fungicides: An Advanced Treatise*, Vols. **1** & **2**, Academic Press, Inc., New York, 1967.
84. N. N. Melnikov, in F. A. Gunther and J. D. Gunther, eds., *Residue Reviews* Vol. **36**, Springer-Verlag, Berlin, 1971.
85. R. W. Marsh, ed., *Systemic Fungicides*, 2nd ed., Longman, London, 1977.
86. M. R. Siegel and H. D. Sisler, eds., *Antifungal Compounds*, Vols. **1** & **2**, Marcel Dekker, Inc., New York, 1977.
87. J. Dekker and S. G. Georgopoulos, eds., *Fungicide Resistance in Crop Protection*, Centre for Agricultural Publishing and Documentation, Wageningen, the Netherlands, 1982.
88. T. H. Staub and A. Hubele, in R. Wegler, ed., *Chemie der Pflanzenschutz-und Schädlings-bekämpfungsmittel*, Vol. **6**, Springer-Verlag, Berlin, 1981.
89. G. Haug and H. Hoffman, eds., *Chemistry of Plant Protection, Vol. 1: Sterol Biosynthesis Inhibitors and Anti-Feeding Compounds*, Springer-Verlag, Berlin, 1986.
90. H. Buchenauer, in G. Haug and H. Hoffmann, eds., *Chemistry of Plant Protection*, Vol. **6**, Springer-Verlag, Berlin, 1990.
91. H. Frehse, ed., *Pesticide Chemistry: Advances in International Research, Development and Legislation, Proceedings of the 7th International Congress of Pesticide Chemistry (IUPAC)*, Hamburg, 1990, VCH Verlagsgesellschaft, Weinheim, Germany, 1991.
92. C. R. Worthing and R. J. Hance, eds., *The Pesticide Manual*, 9th ed., The British Crop Protection Council, Farnham, U.K., 1991.
93. W. Köller, ed., *Target Sites of Fungicide Action*, CRC Press, Boca Raton, Fla., 1992.
94. I. Denholm, A. L. Devonshire, and D. W. Holloman, eds., *Resistance 91: Achievements and Developments in Combating Pesticide Resistance*, Elsevier Applied Science, London, 1992.

BARRY A. DREIKORN
W. JOHN OWEN
DowElanco

Related Articles

Genetic engineering; Growth regulators, plants