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Introduction and Toxicology of Fungicides

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1. Introduction

Fungicides are either chemicals or biological agents that inhibit the growth of fungi or fungal spores. Modern fungicides do not kill fungi, they simply inhibit growth for a period of days or weeks. Fungi can cause serious damage in agriculture, resulting in critical losses of yield, quality and profit. Fungicides are used both in agriculture and to fight fungal infections in animals. Chemicals used to control oomycetes, which are not fungi, are also referred to as fungicides as oomycetes use the same mechanisms as fungi to infect plants (Latijnhouwers et al., 2000).

Fungicides can either be contact, translaminar or systemic. Contact fungicides are not taken up into the plant tissue, & only protect the plant where the spray is deposited; translaminar fungicides redistribute the fungicide from the upper, sprayed leaf surface to the lower, unsprayed surface; systemic fungicides are taken up & redistributed through the xylem vessels to the upper parts of the plant. New leaf growth is protected for a short period.

Most fungicides that can be bought retail are sold in a liquid form. The most common active ingredient is sulfur, present at 0.08% in weaker concentrates, and as high as 0.5% for more potent fungicides. Fungicides in powdered form are usually around 90% sulfur and are very toxic. Other active ingredients in fungicides include neem oil, rosemary oil, jojoba oil, and the bacterium *Bacillus subtilis*.

Fungicide residues have been found on food for human consumption, mostly from postharvest treatments (Brooks & Roberts, 1999).

Some fungicides are dangerous to human health, such as vinclozolin, which has now been removed from use (Hrelia, 1996), FCX and DFB that are used as pesticides to control pests and they have many side effects on natural non-target organisms (Rouabhi et al., 2009). In this chapter, we will develop the fungicides and their toxicity on biological and ecological systems.

2. Classification of fungicides

Different authors have differing classification systems according to chemical structure, which somewhat complicates and confuses both the presentation and the discussion of fungicides. Several classification systems based on structure appear more of a web organization than a rationalized listing. In addition to classification by chemical structural grouping, fungicides can be categorized agriculturally and horticulturally according to the

mode of application (use). According to the origin of fungicides, we can classify them in two major groups of fungicides

1. Biologically based fungicides (biofungicides): Contain living microorganisms (bacteria, fungi) that are antagonistic to the pathogens that cause turf disease. Examples: Ecoguard contains *Bacillus licheniformis*; Bio-Trek 22G contains *Trichoderma harzianum*. In the case of a biofungicide, the Latin name of the microbe that it contains is the generic name of the fungicide.
2. Chemically based fungicides: Synthesized from organic and inorganic chemicals, most of the fungicides that are sold throughout the world are chemically-based. They can be recognized according to similarities in three groups:

2.1 Chemical structure

There are 29 generic names (active ingredients) associated with turf grass fungicides, shown in the table1.

1.	propiconazole	2.	triadimefon
3.	myclobutanil	4.	fenarimol
5.	triticonazole	6.	tetraconazole
7.	fluoxastrobin	8.	trifloxystrobin
9.	azoxystrobin	10.	pyraclostrobin
11.	flutolanil	12.	boscalid
13.	polyoxin D	14.	thiophanate-methyl
15.	iprodione	16.	vinclozolin
17.	mefenoxam	18.	propamocarb
19.	fosetyl aluminum	20.	phosphonate
21.	quintozene	22.	chloroneb
23.	ethazole	24.	mancozeb
25.	thiram	26.	hydrogen dioxide
27.	chlorothalonil	28.	fludioxonil
29.	cyazofamid	30.	Biofungicides

Table 1. Fungicides generic names according to their chemical structure (Burpee, 2006).

These 29 names represent 16 groups that have similar chemical structures (table 2). It is important to know which fungicides are chemically related to one another. For example, you should know that azoxystrobin, trifloxistrobin, and pyraclostrobin are chemically related to each other. However, they differ chemically from a fungicide, such as propiconazole, which is in a different chemical group. Because (i) all fungicides in a chemical group generally, control the same diseases. For example, the strobilurin fungicides provide good to excellent control of anthracnose, brown patch, gray leaf spot and summer patch. If you have purchased one strobilurin fungicide for control of these diseases, it is probably not necessary to purchase another. (ii) Since all fungicides in a chemical group control the same diseases, it does not make sense to tank-mix fungicides that represent a common chemical group in order to expand the scope of control. For example, to control anthracnose and dollar spot, tank-mixing two strobilurin fungicides will not work well because the strobilurins provide poor to weak control of dollar spot. (iii) If a pathogen develops resistance to one fungicide in a chemical group, the pathogen is usually resistant to all fungicides in that particular group. In Georgia,

the fungi that cause dollar spot, Pythium blight and anthracnose have developed resistance to fungicides in one or more chemical groups.

Generic Names	Chemical Group	
propiconazole triadimefon myclobutanil triticonazole tetraconazole	triazoles	DMI (demethylation Inhibitors fungicides)
fenarimol	pyrimidines	
fluoxastrobin trifloxystrobin azoxystrobin pyraclostrobin	strobilurins	
polyoxin D	polyoxins	
thiophanate-methyl	benzimidazoles	
iprodione vinclozolin	dicarboxamides	
mefenoxam	phenylamides	
propamocarb	carbamates	
fosetyl aluminum phosphonate	phosphonates	
mancozeb thiram	dithiocarbamates	
quintozene chloroneb ethazole	aromatic hydrocarbons	
hydrogen dioxide	peroxides	
chlorothalonil	nitriles	
fludioxonil	phenylpyrolles	
cyanofamid	cyanoimidazole	
flutolanil boscalid	carboxamides	
Ecoguard Sonata Soilguard	Biofungicides	

Table 2. Chemical groups of fungicides according the Generic names (Burpee, 2006).

2.2 Topical activity

Fungicides can be placed into one of four groups based topical activity:

2.2.1 Contact fungicides

Contact fungicides act only on plant surfaces. They are not absorbed by leaves, stems or roots and cannot inhibit fungal development inside plants. Example: dithiocarbamates, nitriles, aromatic hydrocarbons, peroxides, phenylpyrolles, cyanoimidazoles.

2.2.2 Localized penetrants

Localized penetrant fungicides are absorbed by leaves and move short distances within a treated leaf, they do not move from one leaf to another and they are not absorbed by roots. These fungicides inhibit fungi on treated plant surfaces and inside treated leaves. Example: dicarboximides, strobilurins (except azoxystrobin and fluoxastrobin)

2.2.3 Acropetal penetrants

Acropetal penetrants can penetrate plants through roots, shoots and leaves. These fungicides are absorbed by the xylem and move upward (acropetally) in plants. Acropetal penetrants inhibit fungi on and in treated plant surfaces and inside plant parts that lie above the treated surface. Example: benzimidazoles, triazoles, pyrimidines, carboximides, acylalanines, plus the strobilurins azoxystrobin and fluoxastrobin.

2.2.4 Systemic fungicides

Systemic fungicides are the only fungicides that are absorbed into xylem and phloem and moves up and down in plants. These fungicides inhibit fungi on and in treated plant surfaces and inside plant parts that lie above or below the treated surfaces. Example: phosphonates.

2.3 Mode of action

The body or thallus of most fungi exists as microscopic tubes called hyphae (Fig. 1)

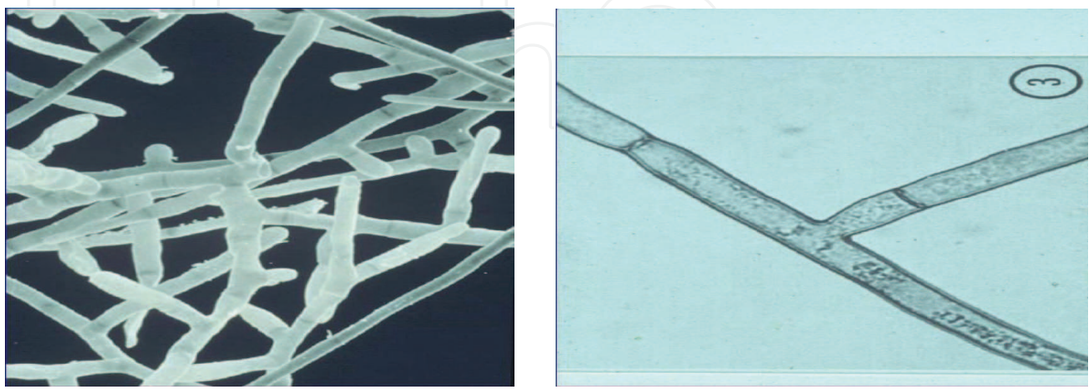

Fig. 1. Hyphae of a fungi (Burpee, 2006)

A fungal cell contains many of the same organelles as other eukaryotes (Fig.2).

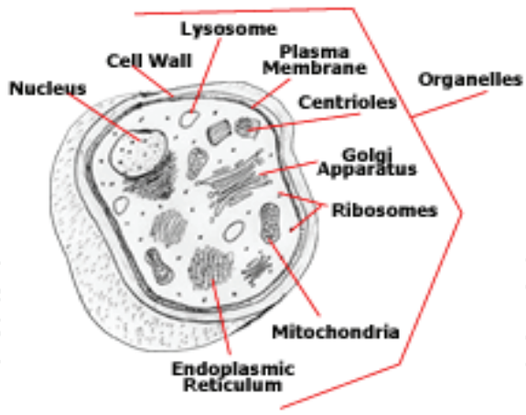

Fig. 2. Fungal cell with organelles (Foster and Smith, 2010)

Fungicides can be divided into 2 groups based on mode of action in fungal cells:

a. **Site-specific inhibitors:** Site-specific inhibitors target individual sites within the fungal cell (Fig. 3).

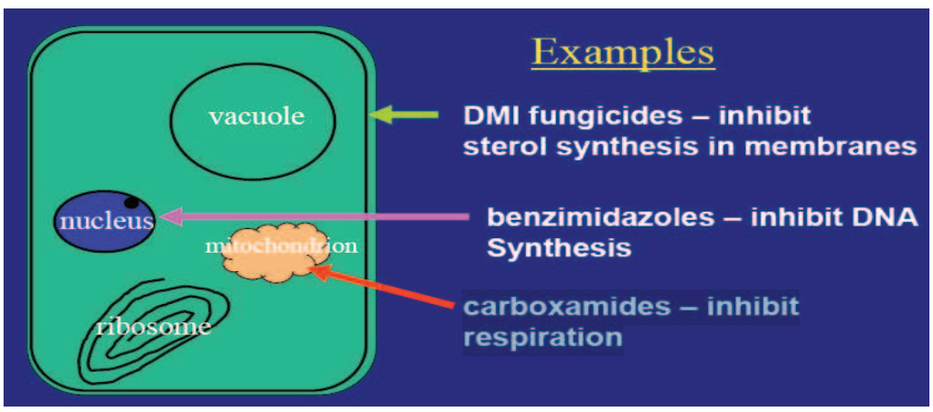

Fig. 3. Site-Specific Inhibitors. DMI: demethylation inhibitors fungicides (Burpee, 2006).

b. **Multi-site inhibitors**

Multisite inhibitors target many different sites in each fungal cell (fig. 4)

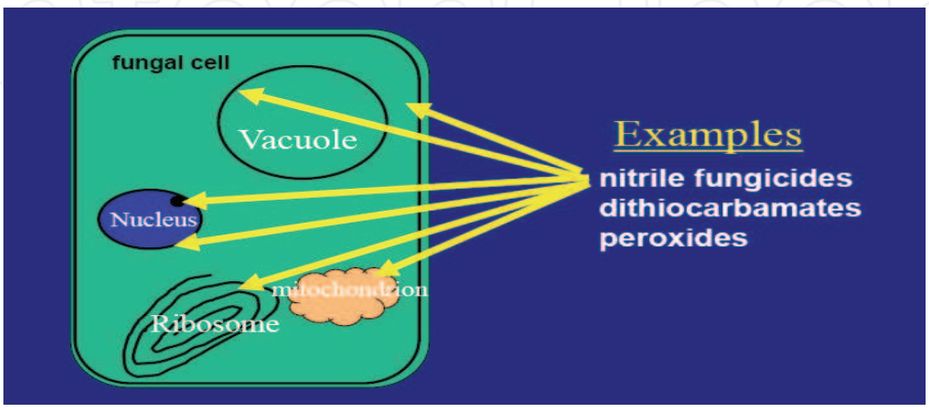

Fig. 4. Multi-site Inhibitors (Burpee, 2006).

3. Toxicology of fungicides

In general, fungicides are of low to moderate mammalian toxicology, although they are believed to have a higher overall incidence than other pesticides to cause developmental toxicology and oncogenesis (Costa, 1997). It has, for example, been estimated that more than 80 per cent of all oncogenic risk from the use of pesticides comes from a few fungicides (NAS, 1987). However, fungicides usually are responsible for only a small proportion of pesticide-related deaths, and account for only about 5 per cent or less of human pesticide exposures reported to Poison Control Centers (Blondell, 1997; Hayes and Vaughn, 1977; Litovitz et al., 1994). It has been noted that since fungi differ significantly in morphology and physiology from other forms of life, they may be successfully combated by compounds of low toxicity to other organisms, notably mammals (Edwards et al., 1991). However, since the mechanism of injury to pathogenic fungi may be different to that for injury to mammalian systems, it is possible that the two properties may co-exist in a given fungicide molecule (Marrs and Ballantyne, 2004).

It has been noted (Phillips, 2001) that the ideal fungicide should have the following characteristics: (a) low mammalian toxicity, (b) low ecotoxicity, (c) low phytotoxicity, (d) high penetration rates for spores and mycelia, and (e) limited biodegradation on the plant surface. Many fungicides combine several of these characteristics but few approach optimum for all of them.

3.1 Triazoles

This chemical family of fungicides, introduced in the 1980s, consists of numerous members: difenoconazole, fenbuconazole, myclobutanil, propiconazole, tebuconazole, tetraconazole, triadimefon, and triticonazole. They are important tools against diseases of turfgrasses, vegetables, citrus, field crops and ornamental plants. Homeowner products are available for use as well, and may be readily obtained at garden and nursery retail centers. They are applied as foliar sprays and seed treatments, but are diverse in use, as they may be applied as protectant or curative treatments. If applied as a curative treatment, triazole applications must be made early in the fungal infection process. Once the fungus begins to produce spores on an infected plant, the triazoles are not effective. Although the triazoles do not have the degree of systemic movement of many herbicides, they are xylem-mobile. They are readily taken up by leaves and move within the leaf. The triazoles are very specific in their mode of action – they inhibit the biosynthesis of sterol, a critical component for the integrity of fungal cell membranes. Because their site of action is very specific, there are resistance concerns (Fishel, 2005).

3.1.1 Toxicology

By the oral route of exposure, these triazoles would be considered as having low toxicity. Inhalation of dusts can cause irritation of the nose, lungs, and throat. For mycobutanil, in animals, effects were reported on the following organs: testes, adrenal gland, kidney, and thyroid. Mycobutanil did not cause cancer or birth defects; only doses that caused significant toxicity to parent animals caused reproductive effects on laboratory animals. Increased incidence of liver tumors at extremely high doses was reported in laboratory studies involving male mice who had been exposed to propiconazole or tebuconazole. There were no reproductive, developmental or chronic effects reported with either propiconazole or tebuconazole. Additionally, tebuconazole is considered to not cause any mutagenic or

genotoxic effects; however, EPA has classified it as a "possible human carcinogen" because of the liver effects seen with mice. The main concern with triadimefon is its potential to cause birth defects, although data suggest that in humans such effects would occur only at moderate to high doses of exposure. Ecologically, the main concern with the triazoles is with fish and other aquatic organisms. Their labels will carry statements expressing this concern in the Environmental Hazards section. Of this pesticide family, only difenoconazole is considered to be highly toxic to fish. Most of the triazoles are considered to be practically nontoxic to birds and bees. Mammalian toxicities for the triazole fungicides are shown in Table 3. Table 4 lists the toxicities to wildlife by the common name of the pesticide (Fishel, 2005).

Common name	Rat oral LD 50	Rabbit dermal LD50
Difenoconazole	1,453	2,010
Fenbuconazole	>2,000	>5,000 (rat)
Mycobutanil	1,600	>5,000 (rat)
Propiconazole	1,517	>4,000
Tebuconazole	1,700	>2,000
Triadimefon	569	2,000
Triticonazole	>2,000	>2,000

Table 3. Triazole fungicide mammalian toxicities (mg/kg of body weight).

Common name	Bird acute oral LD 50 (mg/kg)*	Fish (ppm)**	Bee***
Difenoconazole	PNT	HT	PNT
Fenbuconazole	ST	PNT	PNT
Mycobutanil	PNT	MT	PNT
Propiconazole	PNT	MT	PNT
Tebuconazole	PNT	MT	PNT
Triadimefon	PNT – ST	ST	PNT
Triticonazole	PNT	ST	PNT

Table 4. Triazole fungicide wildlife toxicity ranges.

*Bird LD 50: Practically nontoxic (PNT) = >2,000; slightly toxic (ST) = 501 – 2,000; moderately toxic (MT) = 51 – 500; highly toxic (HT) = 10 – 50; very highly toxic (VHT) =<10.

**Fish LC 50: PNT = >100; ST = 10 – 100; MT = 1 – 10; HT = 0.1–1 ; VHT = <0.1.

***Bee: HT = highly toxic (kills upon contact as well as residues); MT = moderately toxic (kills if applied over bees); PNT = relatively nontoxic (relatively few precautions necessary).

3.1.1.1 Toxicology of an Example of the family "Cyproconazole"

The primary dissipation routes of Cyproconazole (Fig. 5) in surface soil are microbial degradation and plant uptake. Soil photolysis (breakdown by sunlight) and volatilization are not significant routes of degradation. The major breakdown product (degradate, metabolite) of cyproconazole is further broken down to intermediate metabolites, carbon dioxide and bound material. There has been no evidence that Cyproconazole accumulates in the soil.

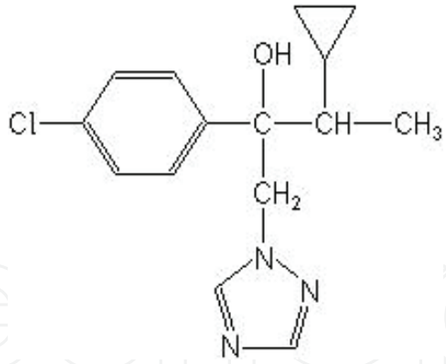

Fig. 5. Cyproconazole

Toxicology

Cyproconazole is of low risk to birds, mammals, bees and other non-target terrestrial organisms. Cyproconazole is moderately to slightly toxic to most aquatic organisms, and because of the low use rates the exposure potential is low and hence poses minimal risk of adverse effects (Envirofacts, 2005).

Oral LD50s are 1020mg/kg for male rats, 1333 mg/kg for female rats, 200 mg for male mice, and 218 mg/kg for female mice. The percutaneous rabbit LD50 is >2000 mg/kg. The rat 4-h inhalation is LC50 > 5.65 mg/L. The major plant residue is Cyproconazole. There is moderately rapid soil degradation; DT50 is about 3 months. Avian acute oral LD50 for Japanese quail is 150 mg/kg. Eight-day dietary LC50s are 816mg/kg (diet) for Japanese quail and 1197 mg/kg (diet) for mallard duck. Aquatic organism 96-h LC50 toxicity values include 18.9 mg=L for carp, 19 mg/L for trout, and 21 mg/L for bluegill sunfish. In Daphnia the 48-h LC50 is 26 mg/L. For bees, the contact LD50 is >0.1 mg/bee and the peroral LD50 is >1mg/bee (Marrs and Ballantyne, 2004).

Plants absorb cyproconazole and rapidly degrade it to multiple metabolites. Studies have shown that cyproconazole residues may exist at harvest, but the levels are insignificant and well under the safety margins for human and environmental risks as established by regulatory authorities in many countries, including the US EPA (Envirofacts, 2005).

3.2 Aromatics hydrocarbons fungicides

Major fungicides in this group include chlorothalonil, tecnazine, chloroneb, dichloran, hexachlorobenzene, quintozene, pentachlorophenol, and sodium pentachlorophenate. Many of these are, or metabolized to, uncouplers of oxidative phosphorylation. This can lead to excessive heat production, hyperpyrexia, liver damage, and corneal opacities.

3.2.1 Toxicology of an example of the family "Chloroneb"

Chloroneb (Fig. 6) is a broad spectrum systemic fungicide taken up by the roots, and used on various fruit and vegetable crops as a wet or dry application powder or dust. Mechanism of fungal toxicity may be related to inhibition of DNA polymerization (Phillips, 2001). Principal use in Soil systemic and supplemental seed treatment forseedling diseases of beans, sugar beets, turf and soybeans. Excellent against damping-off (Harding, 1979-80). Used for the treatment of turfgrass to control snow mold (Typhula) and Pythium blight (Meister et al., 1994).

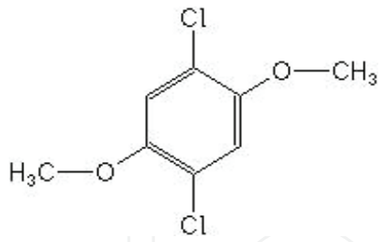

Fig. 6. Chloroneb

Toxicology

a. **Acute Toxicity**

Dermal: LD50 = >5000 mg/kg (rabbit). A 50% aqueous suspension of the 65% caused no irritation to guinea-pigs and repeated applications did not result in skin sensitization (Worthing, 1979).

Oral: LD50 = >11,000 mg/kg (rat) (Wothing, 1979)

b. **Environmental considerations**

Hazardous to fish and wildlife. Nonphytotoxic when used as directed. Does not leach from the soil (Harding, 1979-80). The material was not toxic to bluegill Sunfish at 4,200 ppm in the 48-hour exposure.

3.3 Dithiocarbamate fungicides

The dithiocarbamate fungicides: ferbam, mancozeb, maneb, nabam, thiram, zineb and ziram were evaluated at the Joint FAO/WHO Meeting in 1967. Although the biochemical data were limited, temporary acceptable daily intakes (ADI's) were established for all of these compounds, but it was pointed out that these ADI's are to be applicable to the parent compounds only (FAO/WHO, 1968).

3.3.1 Toxicology of an example of the family "Thiram"

Thiram (fig. 7) is a dimethyl dithiocarbamate compound used as a fungicide to prevent crop damage in the field and to protect harvested crops from deterioration in storage or transport. Thiram is also used as a seed protectant and to protect fruit, vegetable, ornamental, and turf crops from a variety of fungal diseases. In addition, it is used as an animal repellent to protect fruit trees and ornamentals from damage by rabbits, rodents, and deer. Thiram is available as dust, flowable, wettable powder, water dispersible granules, and water suspension formulations, and in mixtures with other fungicides. Thiram has been used in the treatment of human scabies, as a sunscreen, and as a bactericide applied directly to the skin or incorporated into soap.

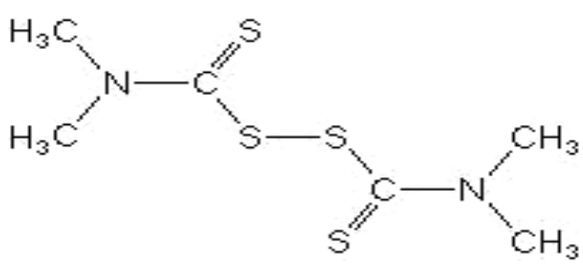

Fig. 7. Thiram.

Toxicology

a. **Acute Toxicity**

Thiram is slightly toxic by ingestion and inhalation, but it is moderately toxic by dermal absorption. Acute exposure in humans may cause headaches, dizziness, fatigue, nausea, diarrhea, and other gastrointestinal complaints. In rats and mice, large doses of thiram produced muscle incoordination, hyperactivity followed by inactivity, loss of muscular tone, labored breathing, and convulsions. Most animals died within 2 to 7 days. Thiram is irritating to the eyes, skin, and respiratory tract. It is a skin sensitizer. Symptoms of acute inhalation exposure to thiram include itching, scratchy throat, hoarseness, sneezing, coughing, inflammation of the nose or throat, bronchitis, dizzines, headache, fatigue, nausea, diarrhea, and other gastrointestinal complaints. Persons with chronic respiratory or skin disease are at increased risk from exposure to thiram (U.S. National Library of Medicine, 1995). Ingestion of thiram and alcohol together may cause stomach pains, nausea, vomiting, headache, slight fever, and possible dermatitis. Workers exposed to thiram during application or mixing operations within 24 hours of moderate alcohol consumption have been hospitalized with symptoms. The 4-hour inhalation LC50 for thiram is greater than 500 mg/L in rats. Reported oral LD50 values for thiram are 620 to over 1900 mg/kg in rats; 1500 to 2000 mg/kg in mice; and 210 mg/kg in rabbits (Edwards et al., 1991; Kidd and James, 1991). The dermal LD50 is greater than 1000 mg/kg in rabbits (U.S. National Library of Medicine, 1995) and in rats (Edwards et al., 1991; Kidd and James, 1991).

b. **Chronic toxicity**

Symptoms of chronic exposure to thiram in humans include drowsiness, confusion, loss of sex drive, incoordination, slurred speech, and weakness, in addition to those due to acute exposure. Repeated or prolonged exposure to thiram can also cause allergic reactions such as dermatitis, watery eyes, sensitivity to light, and conjunctivitis (Edwards et al., 1991). Except for the occurrence of allergic reactions, harmful chronic effects from thiram have been observed in test animals only at very high doses. In one study, a dietary dose of 125 mg/kg/day thiram was fatal to all rats within 17 weeks. Oral doses of about 49 mg/kg/day to rats for 2 years produced weakness, muscle incoordination, and paralysis of the hind legs. Rats fed 52 to 67 mg/kg/day for 80 weeks exhibited hair loss, and paralysis and atrophy of the hind legs. Symptoms of muscle incoordination and paralysis from thiram poisoning have been shown to be associated with degeneration of nerves in the lower lumbar and pelvic regions. Day-old white leghorn chicks fed 30 and 60 ppm for 6 weeks exhibited bone malformations. At doses of about 10% of the LD50 for 15 days, thiram reduced blood platelet and white blood cell counts, suppressed blood formation, and slowed blood coagulation in rabbits (Edwards et al., 1991).

c. **Organ toxicity**

Studies have shown evidence of damage to the liver by thiram in the form of decreased liver enzyme activity and increased liver weight (Edwards et al., 1991). Thiram may also cause damage to the nervous system, blood, and kidneys (U.S. National Library of Medicine, 1995).

d. **Ecological effects**

Effects on birds: Thiram is practically nontoxic to birds. The reported dietary LC50 of thiram in Japanese quail is greater than 5000 ppm (Hill and Camardese, 1986). Reported dietary LC50 values in pheasants and mallard ducks are 2800 ppm and 673 ppm, respectively (Hudson et al., 1984). The LD50 for the compound in red-winged blackbirds is greater than 100 mg/kg (Kidd and James, 1991).

Effects on aquatic organisms: Thiram is highly toxic to fish (U.S. National Library of Medicine, 1995). The LC50 for the compound is 0.23 mg/L in bluegill sunfish, 0.13 mg/L in trout, and 4 mg/L in carp (Mayer and Ellersieck, 1986). Thiram is not expected to bioconcentrate in aquatic organisms (Howard, 1989).

3.4 Benzimidazoles fungicides

This class is confused since the individual classes are closely related. Sometimes, however, the benzimidazoles are classified separately but in an overlapping manner, creating confusion. They are nitrogen heterocyclic compounds, with parent structures of thiabendazole and/or benzimidazole. Included in this overall group are benomyl, thiabendazole, thiophanate, thiophanate–methyl, mebendazole, carbedazim, imazalil, and fuberidazole. Benomyl, carbendazim, thiophanate, and thiophanate–methyl are sometimes referred to (and classified) as benzimidazoles carbamates. Many of these fungicides inhibit mitochondrial fumarate reductase, reduce glucose transport, and uncouple oxidative phosphorylation. Inhibition of microtubule polymerization by binding to ┐-tubulin is a primary action, and specific high affinity binding to host α-tubulin occurs at significantly lower concentrations than mammalian protein binding (Phillips, 2001).

3.4.1 Toxicology of an example of the family “Benomyl”

Benomyl was first reported as a fungicide in 1968 and introduced onto the UK market in 1971 by the US Company Du Pont (Tomlin, 1994). It is a systemic benzimidazole fungicide that is selectively toxic to microorganisms and to invertebrates, especially earthworms (Extoxnet, 1994).

Benomyl and its main metabolite carbendazim bind to microtubules (an essential structure of all cells) and therefore interfere with cell functions such as cell division and intracellular transportation. The selective toxicity of benomyl as a fungicide is possibly due to its heightened effect on fungal rather than mammalian microtubules (WHO/PCS, 1994).

Benomyl is used as a pre-harvest systemic fungicide, and as a post-harvest dip or dust. It combats a wide range of fungal diseases of arable and vegetable crops, apples, soft fruit, nuts, ornamentals, mushrooms, lettuce, tomatoes and turf. It is also available widely for amenity and amateur garden use (Whitehead, 1996).

Toxicology

a. **Acute Toxicity**

Benomyl is of such a low acute toxicity to mammals that it has been impossible or impractical to administer doses large enough to establish an LD50. It therefore has an arbitrary LD50 that is 'greater than 10,000 mg/kg/day for rats'. However, skin irritation may occur with workers exposed to benomyl (Extoxnet, 1994). It is a mild to moderate eye irritant and is a skin sensitizer. Florists, mushroom pickers and flower growers have reported allergic reactions to benomyl (MAFF, 1992).

In 1992, benomyl exposure caused adverse occupational health effects (headaches, diarrhoea and sexual dysfunction) in agricultural workers in Florida (Agrow, 1992).

b. **Chronic toxicity**

In a laboratory study, dogs fed benomyl in their diets for three months developed no major toxic effects but did show evidence of altered liver function at the highest dose (150 mg/kg). With longer exposure, more severe liver damage occurred including cirrhosis after two years (Extoxnet, 1994).

c. **Carcinogenic effects**

The US Environmental Protection Agency classified benomyl as a possible human carcinogen (Office of Pesticide Programs, 1996). There is an element of doubt in this classification because carcinogenic studies have produced conflicting results. A two year experimental mouse study has shown it probably caused an increase in liver tumors. The Ministry of Agriculture Fisheries and Food (MAFF) takes the view that this was bought about by the hepatoxic effect of benomyl (MAFF, 1992).

d. **Reproductive effects**

Tests on laboratory animals have shown benomyl can have an effect on reproduction. In one rat study, where the mothers were fed 1,000 mg/kg/day for four months, the offspring showed a decrease in viability and fertility (WHO, 1993). In studies to investigate the effects of benomyl on male reproductive performance, fertility was reduced at all dose levels tested. In another study, a no-effect level of 15mg/kg/day was established based on testicular abnormalities (MAFF, 1992).

Permanent reductions occurred in the size of testes and male accessory glands in 100 day-old offspring from female laboratory rats receiving 31.2 mg benomyl/kg body weight per day. Rats developed a reduced sperm activity following acute inhalation exposure, acute and sub-chronic oral exposure. The same effect occurred in dogs following a single four-hour inhalation exposure (MAFF, 1992).

e. **Environment**

Benomyl binds strongly to soil and does not dissolve in water largely. When applied to turf, it has a half-life of three to six months, and when applied to bare soil the half-life is six to 12 months (Extoxnet, 1994).

3.5 Piperazines fungicides

3.5.1 Triforine toxicology

Triforine (fig. 8) is a piperazine derivative used as a systemic fungicide with protectant, eradicant and curative characteristics. It is used for control of powdery mildew, rusts, black rot and scab on cereals, fruit, ornamentals, and vegetables (Royal Society of Chemistry, 1983; Worthing, 1983). Triforine is also active against storage diseases of fruit and suppresses red spider mite activity (Worthing, 1983). Because of its low hazard to beneficial insects, triforine may be used in Integrated Pest Management (IPM) programs. Triforine comes in emulsifiable concentrates, liquid seed treatments, and wettable powder formulations. Triforine is miscible with common insecticides and herbicides in the recommended manner of use (Royal Society of Chemistry, 1983).

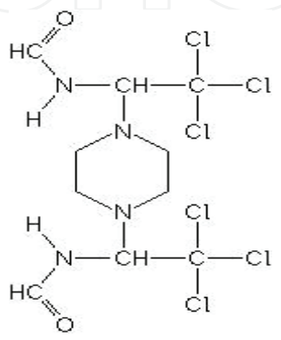

Fig. 8. Triforine

Toxicological effects

a. **Acute toxicity**

Triforine and the formulated product Saprol have a low acute and dermal toxicity and have a moderate acute inhalation toxicity. The acute oral LD50 for triforine in rats is greater than 16,000 mg/kg body weight. The acute percutaneous LD50 for rats is greater than 10,000 mg/kg. Acute dermal LD50 for rats is greater than 10,000 mg/kg body weight. The one-hour acute inhalation LC50 for triforine in rats is greater than 4.5 mg/l air (Worthing, 1983). This compound is rapidly absorbed and metabolized by the rat (OHS Database, 1994). The acute oral LD50 for the formulated product Saprol in rats is 5,273 mg/kg body weight. The acute dermal LD50 for Saprol in rats is 4,186 mg/kg body weight. The acute inhalation LC50 for Saprol in rats is greater than 5,288 mg/m3. Saprol is considered an irritant to the skin. The acute oral LD50 for triforine in mice is greater than 6,000 mg/kg; and greater than 2,000 mg/kg in dogs. The acute dermal LD50 for rabbits is greater than 10,000 mg/kg body weight (Thomson, 1990).

b. **Chronic toxicity**

In two-year feeding studies, the No-effect-level (NEL) for triforine in dogs was 100 mg/kg diet and 625 mg/kg diet for rats (Worthing, 1983).

Reproductive Effects

A decreased number of fetuses and an increased number of resorptions were observed in a study of pregnant rats fed triforine at a dietary level of 1,600 mg/kg (OHS Database, 1994). The formulated product Saprol does not affect reproduction and development. In another developmental study, rabbits were fed doses of 0, 5, 25 and 125 mg/kg/day of triforine. The maternal No-observable-effect-level (NOEL) was 5 mg/kg/day; the maternal Lowest-effect-level (LEL) was 25 mg/kg/day, rabbits exhibited reduced food intake and loss of body weight. The fetotoxic NOEL was 5 mg/kg/day; the fetotoxic LEL was 25 mg/kg/day, decreased average relative weight was observed (U.S Environmental Protection Agency, 1993).

Teratogenic Effects

In a developmental study, rabbits were fed doses of 0, 5, 25 and 125 mg/kg/day of triforine. The teratogenic NOEL was greater than 125 mg/kg/day. The formulated product Saprol is not considered a teratogen (U.S Environmental Protection Agency, 1993).

Mutagenic Effects

The formulated product Saprol is not considered a mutagen.

Carcinogenic Effects

In short and long-term studies of the formulated product Saprol, no irreversible or carcinogenic effects were observed.

c. **Ecological effects**

Effects on Birds

The acute oral LD50 for triforine in bobwhite quail is greater than 5,000 mg/kg (Worthing, 1983). The formulated product Saprol is practically non-toxic to birds by acute oral exposure and only slightly toxic by dietary exposure. The acute oral LD50 for Saprol in bobwhite quail is greater than 5,000 mg/kg. The dietary LC50 for bobwhite quail is 1,850 ppm in the diet. Mallard ducks had a dietary LC50 of greater than 4,640 ppm in the diet.

Effects on Aquatic Organisms

At 50 mg/l in water, there are no signs of poisoning in *Lebistes reticulatus*. Rainbow trout and bluegill sunfish tolerate 1,000 mg/l in water for 96 hours without symptoms (Royal Society of Chemistry, 1983). The 96- hour LC50 for rainbow trout and bluegill sunfish is greater than 1,000 mg/l (Worthing, 1983). The formulated product Saprol is of low hazard to fish and aquatic invertebrates. Both rainbow trout and bluegill sunfish had a 96-hour LC50 of greater than 500 mg/l. The aquatic invertebrate *Daphnia* (water flea) had a 48-hour EC50 of greater than 25 mg/l. Saprol was also noted to be of low hazard to *Scenedesmus subspicatus* (aquatic algae). The 96-hour EC50 was greater than 380 mg/l.

Effects on Other Animals (Nontarget species)

No toxic effect was observed in honeybees at less than or equal to 1,000 mg/kg diet (Worthing, 1983). Triforine and the formulated product Saprol are considered of low hazard to honeybees and to the predatory mite *Typhlodromus pyrii*. It is also of low hazard to earthworms at recommended dose rates (Meister et al., 1994).

3.6 Aliphatic aldehydes Fungicides

Several aliphatic aldehydes are used as fungicides, amongst them formaldehyde and formaldehyde releasers, which have been considered in detail elsewhere (Feinman, 1988).

3.6.1 Toxicology of Acrolein

Acrolein reacts with SH groups. It is formulated as a liquid (fig. 9).

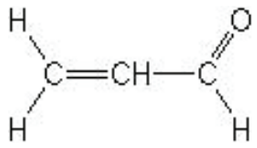

Fig. 9. Acrolein.

Toxicology

a. **Acute toxicity**

The rat oral LD50 is 29mg=kg and the mouse oral LD50 is 13.9mg=kg (males) and 17.7mg=kg (females). The percutaneous rabbit LD50 is 231mg=kg. By inhalation the rat 1-h LC50 is 65mg=m3 (males) and 60mg=m3 (females): the rat 4-h LC50 is 18.5mg=m3 (males) and 22mg=m3 (females). The rat 30-min LC50 is 131 ppm and the 10-min LC50 is 355 ppm (Ballantyne et al., 1989).

b. **Short-term and subchronic toxicology**

Hamsters, rats, and rabbits were exposed to acrolein vapor at 0, 0.4, 1.4, and 4.9 ppm for 6 h/day for 5 days/week for 13 weeks. At 4.9 ppm there was mortality, ocular and nasal irritation, depression of growth, and inflammation, necrosis, hyperplasia, and metaplasia of the respiratory tract epithelium. A no-effect concentration was not established for the rat (Feron et al., 1978).

c. **Chronic toxicology**

Sprague-Dawley rats were given acrolein by gavage at daily dosages of 0, 0.05, 0.5, and 2.5mg/kg up to 102 weeks. The only effects noted were decreased serum creatinine kinase and increased early cumulative mortality. There were no significant increases in neoplastic or non-neoplastic histopathology (Parent et al., 1992a).

Carcinogenicity

Given by intraperitoneal injection to male Fischer 344 rats, Acrolein had an initiating activity for urinary bladder carcinogenesis (Cohen et al., 1992).

Reproductive toxicology

Male and female rats were incubated and given 70 daily doses of Acrolein at 0, 1, 3, or 6mk=kg. The F0 generation was assigned to a 21-day period of co-habitation and dosing of females continued through co-habitation, gestation, and lactation. F1 generation pups were similarly treated. In general, reproductive indices were unaffected, with the exception of reduced pup weights in the F1 generation at the high dose. Gastric lesions were consistently found in the high dose and some mid-dose animals; erosions of the glandular mucosa and hyperplasia=hyperkeratosis of the fore stomach were the most frequent lesions. Relative to the controls, mortality and body weight gain decreases were noted for high dosage animals (Parent et al., 1992b).

3.7 Biological Fungicides (Biofungicides)

Biofungicides are microorganisms (microbial pesticides) and naturally occurring substances that control diseases (biochemical pesticides) that are approved for organic production. Biofungicides are widely used by organic vegetable growers to control selected foliar and soilborne diseases of vegetable crops (see Table 5). Biofungicides can be applied as a stand-alone treatment to control a target disease, provided the application is made before the disease starts (Francis and Keinath, 2010). In the case of a biofungicide, the Latin name of the microbe that it contains is the generic name of the fungicide.

3.6.1 Toxicology of EcoGuard

EcoGuard is a concentrated suspension of spores of Bacillus licheniformis SB3086 that has been found effective as a natural inhibitor of a variety of agronomically important fungal diseases - particularly dollar spot and anthracnose. EcoGuard allows you to control the disease and significantly improve overall turf quality at the same time. The activity of EcoGuard is due to the synthesis of powerful anti-fungal compounds that inhibit fungal growth. As a primary benefit, EcoGuard can be used just like other fungicides. As a secondary benefit, when EcoGuard is integrated with conventional turf management practices, you will see a noticeable and often dramatic improvement in the health and vigor of your turf. In addition, the turf will also recover more quickly from diseases with improved color and increased density in the damaged areas (Novozymes Biologicals Inc., 2007).

B. licheniformis SB3086 is a naturally occurring, ubiquitous bacterium originally isolated from United States farm soil. Consequently, the United States Environmental Protection Agency (USEPA) required limited data for federal registration of EcoGuardTM Biofungicide. The data from acute toxicity/pathogenicity studies on the active ingredient indicate that Bacillus licheniformis SB3086 is not toxic, infective or pathogenic via the oral or inhalation routes of exposure (tested at 1 x 108 Colony Forming Units (CFU) per animal), or via intravenous injection (tested at 1x10' CFU/animal). The end product was not very acutely toxic via oral, dermal, or inhalation routes of exposure. It was also not irritating to the eyes (tested on rabbits) or a dermal sensitizer (tested on guinea pigs), but was a slight dermal irritant (tested on rabbits).

Product	Active Ingredient	Disease	Treatment Site
Ballad	*Bacillus pumilus*	Several (Foliar)	Foliar
Bio-Save	*Pseudomonas syringe*	Post-harvest	Irish and sweet potatoes in storage
Contans	*Coniothyrium minitans*	White Mold	Soil applied
Kodiak	*Bacillus subtilis*	*Pythium, Rhizoctonia, Fusarium*	Seed treatment, beans only
Mycostop	*Streptomyces griseoviridis*	Several	Greenhouse; Soil applied
Regalia	Plant extract	Powdery mildew	Foliar
RootShield Granules, RootShield WP	*Trichoderma harzianum*	*Pythium, Rhizoctonia, Fusarium*	Soil applied
Serenade	*Bacillus subtilis*	Powdery mildew, other foliar diseases	Foliar
T22-HC	*Trichoderma harzianum*	*Pythium, Rhizoctonia, Fusarium*	Soil applied
Surround	Kaolin	Powdery mildew	Foliar
Trilogy	Neem Oil	Powdery mildew	Foliar
Actinovate AG	*Streptomyces lydicus*	*Fusarium, Rhizoctonia, Pythium, Phytophthora*	Soil applied Foliar
SoilGard	*Gliocladium virens*	Damping off	Greenhouse-transplants, soil applied

Table 5. List of biofungicides (biological) used to control selected vegetable crop diseases (Francis and Keinath, 2010)

The USEPA waived the requirement for subchronic, chronic, developmental, reproductive toxicity, genotoxicity and oncogenicity studies for federal registration of EcoGuardTM Biofungicide. Instead, the USEPA used reports from the scientific literature to evaluate this product. The data from these reports suggest that *B. licheniformis* is occasionally associated

with infections in individuals who have significant preexisting health problems such as severe immune system depression, cancer or trauma. In addition, it has been associated with reproductive failures (spontaneous abortions and inflammation of the placenta) in cattle, sheep and swine, usually in association with the ingestion of moldy hay. A search of the toxicological literature did not find any additional significant information on *B. licheniformis*.
A quantitative worker risk assessment was not provided in the registration package. However, *B. licheniformis* has been used in various industrial fermentation processes for a number of years and, according to the registrant, no pathogenicity, toxicity or hypersensitivity has been reported among these workers. Given the use pattern of the EcoGuardTM product, exposure of applicators would likely be less than that of fermentation workers. Also, the product label requires applicators and other handlers to wear a long-sleeved shirt, long pants, and shoes plus socks. In addition, handlers must also use a non-powered air purifying NIOSH approved respirator.
The limited toxicity data required to support the federal registration of EcoGuardTM Biofungicide indicate that this product is not very toxic following acute exposures. The active ingredient B. licheniformis also appears to have a low degree of pathogenicity and infectivity to animals and humans. Although there are no animal study data on longer-term exposure, significant risks to workers or the general public from EcoGuardTM use are not expected given the use pattern and the required personal protective equipment. The required personal protective equipment also should protect against the slight dermal irritation that EcoGuardTM may cause.

Ecological Risk

B. licheniformis SB3086 is not toxic, infective, or pathogenic to mammals when administered orally, by inhalation, direct tracheal injection, dermally, and by intravenous injection. A significant decrease in weight gain in young mallard ducks was observed when administered EcoGuardTM formulation at a rate of approximately 1.0 ml/kg body weight. The effect was attributed to formulation ingredients other than the active ingredients. B. licheniformis SB3086 appears not to be toxic, infective, or pathogenic to mallards; there were no mortalities.
The 30-day EcoGuardTM rainbow trout LC50 is greater than 1.1 xl06 CFU/ml which is roughly I I 7X (times) the expected environmental concentration (EEC) when the maximum application rate is applied directly to the surface of six-inch deep water body. The daphnia No Observable Adverse Effect Concentration (NOAEC) is 120X the EEC. There was no sign of infection or pathogenicity in either study.
The EcoGuardTM formulation had no effect on honeybee larva when exposed to *B. licheniformis* SB3086 at 1.6 x106 CFU/ml, roughly 2/3 full strength formulation, in their diet. No adverse behavioral or developmental abnormalities were observed in emerged adult honeybees that had been exposed as larva. All marine/estuarine organism and nontarget plant testing was waived by the USEPA.
Bacillus licheniformis is a ubiquitous soil organism. While numbers of *B. licheniformis* in soil are unknown and likely vary from soil to soil, the total number of Bacillus organisms is estimated to be 10' CFU/g soil. The added soil density of *B. licheniformis* from the proposed use rates would be 0.42% to 1.5%. This is a very small proportion of the naturally occurring bacilli in soil and is not expected to add substantially to the effects of the normally occurring Bacillus populations. No adverse effects to fish or wildlife resources are expected from use of EcoGuardTM Biofungicide when used as labeled. There are reports in the literature of B.

licheniformis being a sporadic mammal pathogen. *B. licheniformis* diseases appear to be limited to cows, sheep, and swine as very unusual events associated with the ingestion of moldy hay. Wild ruminants exposure to the combination of conditions seemingly implicated in livestock disease should be minimal. The IBA contained in EcoGuardTM poses no risk to fish or wildlife resources: The IBA concentration in EcoGuardTM is very low, application at the maximum label rate results in an IBA application rate of roughly 30 milligrams/acre (Serafini, 2003).

4. Conclusion

It is to note that this study showed a less or more toxicity of all category of chemical fungicides, contrarily, to biofungicides that showed a little or note side effects on human and ecosystems.

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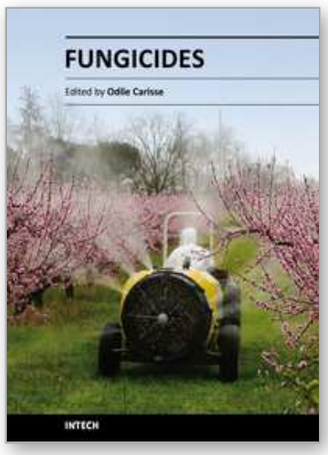

Fungicides

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Plant and plant products are affected by a large number of plant pathogens among which fungal pathogens. These diseases play a major role in the current deficit of food supply worldwide. Various control strategies were developed to reduce the negative effects of diseases on food, fiber, and forest crops products. For the past fifty years fungicides have played a major role in the increased productivity of several crops in most parts of the world. Although fungicide treatments are a key component of disease management, the emergence of resistance, their introduction into the environment and their toxic effect on human, animal, non-target microorganisms and beneficial organisms has become an important factor in limiting the durability of fungicide effectiveness and usefulness. This book contains 25 chapters on various aspects of fungicide science from efficacy to resistance, toxicology and development of new fungicides that provides a comprehensive and authoritative account for the role of fungicides in modern agriculture.

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