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Fungicides and Their Effects on Animals

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1. Introduction

Fungicides are pesticides that specifically inhibit or kill fungi underlying diseases important to man. Understanding mechanisms of fungicide action and toxicity is important because humans and domesticated animals encounter these pesticides through a wide variety of applications. In agriculture, fungicides are used to protect tubers, fruits and vegetables during storage or are applied directly to ornamental plants, trees, field crops, cereals and turf grasses (Gupta & Aggarwal, 2007). In industry, numerous fungicides are used to protect products during shipment, suppress mildews that attack painted surfaces, preserve wood, control fungal growth in paper pulps, and protect household carpet and fabric (Osweiler et al., 1985). In veterinary medicine, fungicides are commonly an antibacterial/antiseptic treatment for foot rot disease but, some fungicides (e.g., copper sulphate), are also used a molluscicide to repel and kill slugs and snails, (Ortolani et al., 2004). Another example of dual use of fungicides is the treatment by the widely used agricultural fungicide thiabendazole against intestinal parasites in both human and veterinary medicine (Lorgue et al., 1996).

Each year, livestock are accidentally poisoned by fungicides applied to grains, potatoes, or other agricultural materials. Unfortunately, most toxicity data are from model laboratory animals (e.g., rats, mice, rabbits) and offer little information on livestock and pets. Therefore, it is valuable to be aware of several generalizations for fungicide toxicity. While these generalizations may serve as useful guidelines, always obtain detailed information for a specific fungicide wherever possible. In general, newer classes of fungicides have low-to-moderate toxicity (Gupta & Aggarwal, 2007). Because mechanisms of action and metabolic clearance differ among fungicides, specific reproductive, teratogenic, mutagenic, carcinogenic effects or patterns of organ toxicity may manifest according to the poison ingested (Hayes & Laws, 1990; U.S. Environmental Protection Agency, 1999). Additionally, some animals may be more susceptible to poisoning than others due to their physiology or behaviour. For example, some fungicides (e.g., copper sulphate, thiram, chlorothalonil and captan) have especially toxic effects on fish (Pimentel, 1971; Lorgue et al., 1996; Tomlin, 2000), and bees (Hardley & Kidd, 1983). In the past, each spring, wild birds (e.g., pigeons, pheasants) were poisoned by mercurial fungicides in fields sown with treated seeds (Bartik, 1981). The types of fungicides used in agriculture and food processing and storage range from those of relatively low toxicity to those, which can be lethal to animals. Guidelines for use and generally low toxicity make poisoning in animal uncommon. However, fungicides frequently used around the home constitute a major hazard to pets and livestock due to

accidents, carelessness, or deliberate misuse (Osweiler et al., 1985; Gupta & Aggarwal, 2007; Oruc et al., 2009). For example, fungicides have caused systemic poisoning in animals such as sheep (Garcia-Fernández et al., 1996; Ortolani et al., 2004; Oruc et al., 2009), poultry (Guitart et al., 1996 & 1999), and humans (Israeli et al., 1983; Kintz et al., 1997; Chodorowski, 2003; Kayacan et al., 2007; Calvert et al., 2008; Mortazavi & Jafari-Javid, 2009). Incorrect application and failure to use protective gear while applying fungicides are probably responsible for a disproportionate number of irritant injuries to skin and mucous membranes, as well as dermal sensitization. Fungicides are often used in combinations with other pesticides and carriers or solvents which, in combination, may be more toxic than estimated for any one of the compounds (Osweiler et al., 1985).

In France, Lorgue et al. (1996) reported that pesticides are the most common cause of animal poisoning (45.5%), with fungicides accounting for 6.1% of all pesticides. The two most commonly involved species are dogs and cattle. In 2003, 992 cases involving dogs and cats were confirmed as poisoning in France, and fungicides caused 2.8% of all poisonings (Barbier, 2005). Acute fungicide poisonings was 4.4% in 129 poisoning cases in Greece (Berny et al., 2009). In Italy, poisoning related with fungicides account was 8.1% of pesticides in pet poisonings (Caloni et al., 2004).

This chapter describes widely used fungicides and their toxicity in animals.

2. Toxicity category and LD_{50}/ LC_{50} values

Pesticides, including fungicides, are categorized on the basis of their relative acute toxicity (LD_{50} or LC_{50} values). Pesticides that are classified as highly toxic (Toxicity Category I) on the basis of either oral, dermal, or inhalation toxicity must have the signal words DANGER and POISON printed in red with a skull and crossbones symbol prominently displayed on the front panel of the package label. The acute (single dosage) oral LD_{50} for pesticide products in this group ranges from a trace amount to 50 mg/kg. Some pesticide products have just the signal word DANGER, which tells you nothing about the acute toxicity, just that the product can cause severe eye damage or severe skin irritation. Pesticide products considered moderately toxic (Toxicity Category II) must have the signal word WARNING displayed on the product label. In this category, the acute oral LD_{50} ranges from 50 to 500 mg/kg. Pesticide products classified as either slightly toxic or relatively nontoxic (Toxicity Categories III and IV) are required to have the signal word CAUTION on the pesticide label. Acute oral LD_{50} values in this group are greater than 500 mg/kg. Table 1 summarizes the LD_{50} and LC_{50} values for each route of exposure for the four toxicity categories and their associated signal word (Code of Federal Regulations, 2010).

LD_{50} is the dosage at which one-half of the test animals are killed. Usually rats are tested, although mice or rabbits may be used. LD_{50} is measured in milligrams of chemical being tested per kilogram of animal (mg/kg). One part per million (ppm) is equal to one mg/kg. LD_{50} is usually determined for the technical material rather than the formulated product. The higher the LD_{50}, the less toxic the material. LC_{50} is the lethal concentration at which 50% of test animals would be killed. Chemicals may be tested by mouth (oral), by skin (dermal), or inhalation. World Health Organisation (WHO) recommends standardized categories (levels of hazard) of major chemical classes of technical grade fungicides with representative examples of LD_{50} values in rats (Table 2) (International Programme on Chemical Safety, 2002; Gupta, P.K. & Aggarwal, M., 2007).

Routes of Exposure	Toxicity Category			
	I	II	III	IV
Oral LD$_{50}$	Up to and including 50 mg/kg	50-500 mg/kg	500-5,000 mg/kg	>5,000 mg/kg
Inhalation LC$_{50}$	Up to and including 0.2 mg/l	0.2-2 mg/l	2-20 mg/l	>20 mg/l
Dermal LD$_{50}$	Up to and including 200 mg/kg	200-2,000 mg/kg	2,000-20,000 mg/kg	>20,000 mg/kg
Eye Effects	Corrosive corneal opacity not reversible within 7 days	Corneal opacity reversible within 7 days; irritation persisting for 7 days	No corneal opacity; irritation reversible within 7 days	No irritation
Skin Effects	Corrosive	Severe irritation at 72 hours	Modarate irritation at 72 hours	Mild or slight irritation at 72 hours
Signal Word	DANGER POISON	WARNING	CAUTION	CAUTION

Table 1. Toxicity categories for active ingredients (Adapted from Code of Federal Regulations, 2010)

3. Fungicides

Below, structural classes of fungicide are listed in order of their adverse effects:
I.   Benzimidazoles
II.   Cadmium Compounds
III.   Carbamic Acid Derivates
    a.   Dithiocarbamates
    b.   Ethylene Bis Dithiocarbamates (EBDC Compounds)
IV.   Copper Compounds
V.   Halogenated Substituted Monocyclic Aromatics (Substituted Benzenes)
VI.   Organomercury Compounds
VII.   Phthalimides (Chloroalkylthiodicarboximides)

I. Benzimidazoles

The major benzimidazole fungicides include benomyl, carbendazim, fuberidazole and thiophanate-methyl and thiabendazole. Benomyl and carbendazim have low toxicity, whereas fuberidazole has moderate toxicity (Gupta & Aggarwal, 2007). Both benomyl and carbendazim are well absorbed after oral exposure (80-85%) but poorly absorbed after dermal exposure (1-2%) in rat, mice, hamster and dogs. The major pathway of clearance is the urinary elimination in rats and mice but in dogs the majority of the dose is eliminated via faeces. In animals, benomyl is converted into carbendazim through the loss of the n-butylcarbamyl side-chain prior to further metabolism (Gardiner et al., 1974).

Benomyl

Benomyl commonly used systemic fungicide is used for a wide range of diseases on fruits, nuts, vegetables, field crops, turf and ornamentals. Available commercially in the form of a wettable powder, 50% w/w. Chronic feeding in dogs at 2500 ppm results in impaired liver

Chemical class	Category	LD$_{50}$ (mg/kg, bw)	Chemical class	Category	LD$_{50}$ (mg/kg, bw)
Halogenated substituted monocyclic aromatics			Fuberidazole	II	336
Chlorothalonil	U	>10,000	*Conazoles*		
Tecnazene	U	>10,000	Cyproconazole	III	1020
Dicloran	U	4000	Diniconazole	III	639
HCB	Ia	[d]10,000	Etridiazole	III	2000
Quintozene	U	>10,000	Hexaconazole	U	2180
Dinocap	III	980	Penconazole	U	2120
Dichlorophen	III	1250	Triadimefon	III	602
PCP	Ib	[c]80	Triadimenol	III	900
Chloroneb	O	-	Azaconazole	II	308
			Bromuconazole	II	365
Chloroalkylthiodicarboximides					
Captan	U	9000	Propiconazole	II	1520
Captafol	Ia	5000	Tetraconazole (oil)	II	1031
Folpet	U	>10,000	Imazalil	II	320
Anilinopyrimidines			*Morpholines*		
Mepanipyrim	U	>5000	Dodemorph (liquid)	U	4500
Pyrimethanil	U	4150	Fenpropimorph (oil)	U	3515
Cyprodinil	III	>2000	Tridemorph	II	650
Carbamic acid derivatives			*Amides*		
Ferbam	U	>10,000	Fenhaxamid	U	>5000
Thiram	III	560	Benalaxyl	U	[c]4200
Ziram	III	1400	Metalaxy	III	670
Propamocarp	U	8600	Flutolanil	U	>10,000
Maneb	U	6750	Tolyfluanid	U	>5000
Mancozeb	U	>8000	Dichlofluanid	U	>5000
Zineb	U	>5000			
Nabam	II	395	*Others*		
Metiram	U	>10,000	Cycloheximide	O	-
Benzimidazoles			Fludioxonil	U	>5000
Benomyl	U	>10,000	Dimethomorph	U	>5000
Thiophanate-methyl	U	>6000	Trifloxystobin	U	>5000
Carbendazim	U	>10,000	Fenpyroximate	II	245
Thiabendazole	U	3330			

Ia: extremely hazardous; Ib: highly hazardous; II: moderately hazardous; III: slightly hazardous
U: unlike to present acute hazard in normal use; O: obsolete or discontinued; c: the variability is reflected in the prefix "c" and dermal in the prefix "d" before LD$_{50}$ values; bw: body weight.

Table 2. World Health Organisation hazardous classification oftechnical grade fungicides. Representative LD$_{50}$ values are provided for rats (Complied from IPCS, 2002; Gupta & Aggarwal, 2007).

function and cirrhosis. The chronic no-effect level in dogs was 500 ppm. Embryotoxic and teratogenic effects were seen in rats incubated with 125, 250 or 500 mg/kg (Osweiler et al., 1985). There is a very low toxicity in animals, but mildly toxic to fish (Lorgue et al., 1996). Although the molecule contains a carbamate grouping, benomyl is not a cholinesterase inhibitor. There is no specific treatment for benomyl poisoning in animals. Symptomatic treatment is applied to promote excretion (Lorgue et al., 1996).

Carbendazim

Carbendazim is also known as MCAB, BCM, or MCB. It is a systemic fungicide used on fruits, vegetables, field crops, ornamentals and turf (Osweiler et al., 1985). It has low toxicity and available commercially in the form of a wettable powder and concentrated suspensions (Lorgue et al., 1996). There is no specific treatment for carbendazim poisoning in animals. Symptomatic treatment is applied to promote excretion (Lorgue et al., 1996).

Fuberidazole

Fuberidazole is available as crystalline powder, and has moderate toxicity (Gupta & Aggarwal, 2007). Possible fuberidazole poisoning in young pheasants has been reported (Laing, 2001).

Thiophanate-methyl

Thiophanate-methyl is also referred to as TM. It is systemic fungicide used on fruits, vegetables, field crops and nuts (Osweiler et al., 1985). It has very low toxicity and is available commercially in the form of a wettable powder and concentrated suspensions. In rats, oral administration causes tremors, lacrimation, nasal discharge, tonic colonic convulsions. The compound causes reduced respiratory rate, prostration and mydriasis in dogs (Lorgue et al., 1996).

Thiabendazole

This is systemic fungicide used on fruits, trees and vegetables (Osweiler et al., 1985). It is also used as anthelmintic in veterinary and human medicine. Cattle are more sensitive than the other domestic animals for adverse effects of thiabendazole (Lorgue et al., 1996).

II. Cadmium Compounds

Cadmium salts have been used as systemic fungicide on turf and the bark of orchard trees. They were formulated as solution and emulsions. Cadmium chloride may contain 12.3% elemental cadmium. Cadmium succinate may contain 29% elemental cadmium (Osweiler et al., 1985). Cadmium sebacate is combined with thiram and potassium chromate as broad-spectrum fungicide. Cadmium chloride has also a mixture with thiram. In many countries, cadmium fungicides have been discontinued due to their toxic effects.

III. Carbamic Acid Derivates

The carbamic acid class of fungicides includes dithiocarbamates and ethylene bis dithiocarbamates (EBDC) compounds. In general, carbamic acid derivates have low or moderate acute toxicity by the oral, dermal and respiratory routes, except nabam (Gupta & Aggarwal, 2007). Carbamic acid derivate fungicides, such as EBDCs, are only partially absorbed, then rapidly metabolized and excreted with no evidence of long-term bioaccumulation. Absorption of oral doses is rapid and is excreted within 24 hour with about half eliminated in the urine and half in the faeces. Their common metabolite is ethylenethiourea, and only low-level residues of ethylenethiourea are found in tissues particularly in the thyroid (Gupta & Aggarwal, 2007).

a. Dithiocarbamates

Ferbam

Ferbam is ferric dimethyldithiocarbamate (Osweiler et al., 1985). It is formulated as flowable and wettable powders, and used widely on fruit and nut trees, apples, vegetables, tobacco,

and home gardens. In acute studies, ferbam has low acute toxicity (Toxicity Category III) via the oral and dermal routes, and moderate (Toxicity Category II) acute toxicity via the inhalation route of exposure. In longer-term studies, ferbam is toxic to the liver, kidneys, and lungs (U.S. Environmental Protection Agency, 2005a).

Thiram

The full chemical name for thiram is tetramethylthiuram disulphide. It is used as a fungicide, seed protectant, animal repellent, rubber accelerator, and bacteriostat in soap (Osweiler et al., 1985). At high doses it acts as a repellent to birds, rabbits, rodents, and deer in fields and orchards. Thiram is available as dust, wettable powder, water suspension formulations, and in mixtures with other fungicides. It has been used in the treatment of human scabies, as a sunscreen, and as a bacteriostat in medicated soaps and certain antiseptic sprays. Another important source of thiram for environmental contamination is the degradation of the two widely used ethylene bisdithiocarbamate fungicides, ferbam and ziram (Dalvi, 1988).

Thiram is moderately toxic by ingestion, but it is highly toxic if inhaled. Hepatotoxicity is one of many toxic effects of thiram in exposed workers and test animals. Typical symptoms include as liver enlargement and dysfunction, hepatitis, degenerative changes, and focal necrosis (Hasegawa et al., 1988; Maita et al. 1991). Clinical signs in thiram poisoning are anorexia, listless behavior, dyspnea, convulsions, and death due to cardiac arrest (Kaya & Bilgili, 1998). It is metabolized in the body to toxic metabolites dimethyldithiocarbamate and carbon disulfide. Although these compounds have been shown to inhibit hepatic microsomal enzymes (Dalvi & Deoras, 1986). Levels of thiram ranging from 100-500 ppm in the food rations of hens, quail and partridges inhibit egg laying (Lorgue et al., 1996). An outbreak of thiram poisoning on Spanish poultry farms was reported. Thiram-contaminated poultry feed caused soft egg shells, depressed growth and leg abnormalities in about 1 million birds. Corn was the source of the contamination that previously treated with thiram (Guitart et al., 1996). Thiram is toxic to fish, and LC_{50} (48 h) was found 0.1-0.2 mg/l in fish (Lorgue et al., 1996).

Ziram

Ziram is zinc dimethyldithiocarbamate, also known as methyl cymate (Osweiler et al., 1985). It is formulated as flowable and wettable powders, and used widely on fruit and nut trees, apples, vegetables, tobacco. Ziram is used in the United Kingdom as a bird and animal repellent (e.g. against bullfinches, rabbits, hares, deer). At levels of 500 ppm in the diet, ziram inhibits egg laying quail and partridges (Lorgue et al., 1996). Ziram is more toxic than ferbam and thiram in adult fowl (Rasul & Howell, 1974).

b. Ethylene Bis Dithiocarbamates (EBDC Compounds)

Mancozeb

Mancozeb contains zinc and manganese ethylene bis dithiocarbamate. While related to maneb and zineb it is a distinct chemical (Osweiler et al., 1985). It is formulated as a dust and as wettable and liquid flowable powders. Available in mixtures with other compounds (e.g. benaxyl, maneb, carbendazim or cymoxanil, zineb). The compound has low toxicity to animals, and is not toxic to fish (Lorgue et al., 1996).

Maneb

Maneb is manganese ethylene bis dithiocarbamate, and is extensively used in agriculture. It is available commercially in the form of wettable powders, for dusting, and as a soluble concentrate. It has low toxicity to animals, but toxic to fish (Lorgue et al., 1996).

Metiram

Metiram is a member of the ethylene bis dithiocarbamate group of fungicides, which includes the related active ingredients mancozeb and maneb. It is used on apples, potatoes, and ornamental plants (leatherleaf ferns) in nurseries and greenhouses. Thyroid effects observed in subchronic studies in rats include increased thyroid weights, increased thyroid stimulating hormone (TSH) and decreased T4 (serum thyroxin) values (U.S. Environmental Protection Agency, 2005b).

Nabam

Nabam is disodium ethylene-1,2 bis dithiocarbamate and toxic doses may result in nerve damage (Osweiler et al., 1985). It is used as soil fungicide, and available commercially in liquid form for mixing with water for irrigation (Lorgue et al., 1996).

Zineb

Zineb is zinc ethylene bis dithiocarbamate, and used for many edible crops. Available commercially in the form of wettable powders and for dry dusting, and also in combination with ferbam, mancozeb and maneb fungicides. It has low toxicity. In cases of zineb poisoning in sheep, the animals present with characteristic yellow, watery diarrhea (Lorgue et al., 1996).

IV. Copper Compounds

There are number of fungicides that contain copper. Copper acetate was the first commercial copper fungicide. Bordeaux mixture is an old fungicide that is mixture of hydrated lime and copper sulphate. Some formulations also may include lead arsenate. Copper carbonate is also known as malachite. Copper hydroxide is cupric hydroxide. Copper containing formulations are also used as wood preservatives. Copper naphthenate is used treat wood and fabrics. Copper compounds may contain basic sulphates, oxychlorides, or oxides. Copper oxides are both cuprous oxide and cupric oxide. Copper sulphate is used as a fungicide and algaecide (Osweiler et al., 1985). Poisonings related with copper containing fungicides are important to livestock (Oruc et. al., 2009) and pets (Albo & Nebbia, 2004) especially sheep due to contaminated forage and feeds, and careless (Oruc et. al., 2009).

Copper sulphate

Copper sulphate is also known as bluestone, blue vitriol, blue copperas. The chemical name is cupric sulphate pentahydrate (Osweiler et al., 1985). It is used to control bacterial and fungal disease of fruit, vegetable, nut and field crops. Some of the disease that is controlled by this fungicide includes mildew, life spots, blights and apple scab. It is used in combination with lime and water as a protective fungicide, referred to as Bordeaux mixture, for leaf application and seed treatment. It is also used as an algaecide, an herbicide in irrigation and municipal water treatment systems, and as molluscicide, a material used to repel and kill slugs and snails (U.S. Environmental Protection Agency, 1986). Copper sulphate is available in dust, wettable powders, and fluid concentrates form.

Copper sulphate lead to acute or chronic copper poisoning in animals. Sheep are affected most often, although other species are also susceptible to copper (Cu) overdose. Chronic Cu toxicosis occurs in sheep when animals are fed diets over weeks or months that are marginally high in copper content (15–20 mg/kg, dry weight) with low concentrations of molybdenum (Zervas et al., 1990; Lorgue et al., 1996). Systemic poisonings have been reported in sheep (Ortolani et al., 2003; Ortolani et al., 2004; Roubies et al., 2008; Oruc et. al.,

2009). Poisonings with copper sulphate are also reported in dog and cats. For both species, fungicides account for nearly one-fourth of the calls of the agrochemical class and the majority of these (43% for dogs and 52% for cats) are related to the accidental ingestion of copper sulphate (Albo & Nebbia, 2004). Rabbits can also be poisoned with copper sulphate (Vinlove et al., 1992).

Clinical features of acute poisonings includes salivation, vomiting, watery diarrhoea that is grey-green in colour and often haemorrhagic, painful, severe colic and gastrointestinal effects. Neurological effects include convulsions, followed by paralysis, and decubitus. Death may occur within several hours to several days after ingestion. There is no specific antidote. Symptomatic care include gastrointestinal demulcents, adsorbents (activated vegetable charcoal), cardiorespiratory stimulants and treatments to control convulsions (xylazine, diazepam), if necessary. Laboratory investigation of copper carries out in contents of the stomach and/or intestine (Lorgue et al., 1996). In chronic poisonings, sheep and cattle are most affected species, and copper is hepatotoxic. Clinical signs are bright yellow mucous membranes, yellow-coloured skin, haematuria, bloody nasal discharge, anaemia, anorexia, occasional convulsions, edema of the head and neck (presenting several hours before the onset of jaundice). In general, death occurs within a few hours of presentation of these symptoms (Lorgue et al., 1996; Oruc et. al., 2009). Once jaundice is evident, treatment is unlikely to be effective. Before jaundice, dimercaprol (BAL), 2-4 mg/kg, by intramuscular route, twice in the first 24 hours, then two to four times in the next 48 hours should be administered. Another treatment includes EDTA (sodium calcium edentate 25% w/v), 40-50 mg/kg by intravenous route, given in one to two doses daily for 2-3 days. Ammonium molybdenate (50-500 mg/day per animal) and sodium thiosulphate (0.3-1 g/day per animal) may be administrated orally in the diet for 10 to 15 days. Laboratory investigations show accumulation in liver, kidney, feeds, and hay (Lorgue et al., 1996).

Copper sulphate less threat to birds than to other animals (Tucker & Crabtree, 1970). It is also toxic to fish and other aquatic invertebrates, such as crab, shrimp and oysters as well as earthworms in soil (Clayton & Clayton, 1981). Bees are endangered by strong, water-based compounds, such as a Bordeaux mixture of copper sulphate, lime and water (Hartley & Kidd, 1983).

V. Halogenated Substituted Monocyclic Aromatics (Substituted Benzenes)

This class of chemicals includes such as chloroneb, chlorothalonil, dicloran, hexachlorobenzene and pentachlorophenol.

Chloroneb

Chloroneb is used for seed treatment and on foliage, and is supplied as wettable powder for treatment of soil and seed. It has a low toxicity (Gupta & Aggarwal, 2007).

Chlorothalonil

Chlorothalonil is tetrachloroisophthalonitrile and is widely used in both agriculture and the household. Chlorothalonil's acute toxicity through ingestion is low; however, chlorothalonil is much more toxic when inhaled. In laboratory tests, chlorothalonil causes kidney damage, mild anaemia, liver damage, embryo loss during pregnancy, oxidative DNA damage (damage to the cell's genetic material), and cancers of the kidney and forestomach. Most of these effects have been observed in several test species. It is classified as a "probable human carcinogen" by the U.S. Environmental Protection Agency (Cox, 1997). It causes irreversible and severe ocular lesion in rabbits. Signs of toxicity include decreased body weight and

decreased haematological parameters and increased absolute kidney weight (Gupta & Aggarwal, 2007). Absorption of chlorothalonil from the gastrointestinal tract is of the order of 30-32% of the administered dose. At least 80% of the administered dose is excreted in faeces within 96 hour. Highest concentrations are observed in the kidneys, approximately 0.1% of the dose (Parsons, 2001).

Chlorothalonil is very highly toxic to fish, and concentrations as low as 2 parts per billion (ppb) can cause gill damage and anaemia. It is also toxic to shrimp, frogs, beneficial microorganisms, and earthworms. In plants it causes a variety of effects, including reductions in yield. Chlorothalonil is contaminated with the carcinogen hexachlorobenzene. Its major breakdown product is about thirty times more acutely toxic than chlorothalonil itself and is more persistent in soil (Cox, 1997).

Dicloran

Dicloran (DCNA) is pre- and post-harvest fungicide formulated as a dust, wettable powder and liquid. The major pre-harvest crop uses include celery and lettuce; the major post-harvest use is on sweet potatoes. It has a low acute toxicity in mammals by oral basis, and the target organs for dicloran include the kidney, liver, spleen and hematopoietic system, particularly red blood cells. Dicloran is toxic to birds, but has low toxicity effects for fish and aquatic invertebrates (U.S. Environmental Protection Agency, 2006).

Hexachlorobenzene

Principal formulations of hexachlorobenzene are dust and powders. In animals, liver enlargement is accompanied by changes in the drug-metabolizing enzymes, neurological changes, reduced weight gain, immunosuppression, teratogenic and carcinogenic effects (Renner, 1981). It possesses all the properties of chemical stability, slow degradation and biotrasformation, environmental persistence, bioaccumulation in adipose tissue and organs containing a high content of lipid membranes (Ecobichon, 2001).

Pentachlorophenol

Pentachlorophenol or its salts have been used as herbicides, bactericides, fungicides, molluscacides and insecticides, and it is also referred to as penta or PCP. The majority (90%) of pentachlorophenol is used as a wood preservative. Pentachlorophenol in high doses to pregnant animals is embriyotoxic and fetotoxic, but is not teratogenic (Osweiler et al., 1985).

Pentachlorophenol acts at the cellular level to uncouple oxidative phosphorylation, the target enzyme being Na^+, K^+-ATPase. Oxygen consumption is increased, while adenosine triphosphatase (ATP) formation is decreased. This leads to depletion of energy reserves (Eaton & Gallagher, 1997).

Pentachlorophenol is rapidly absorbed from the skin, digestive tract and lung. It is irritating to mucous membranes, the respiratory tract and the skin. In mild intoxications there is muscular weakness, anorexia and lethargy. Moderate toxicities results in accelerated respiration, hyperpyrexia, hyperglycaemia, glycosuria, sweating, and dehydration. Lethal intoxications result in the previous symptoms plus cardiac and muscular collapse and death with a rapid onset of rigor mortis (Osweiler et al., 1985; Sanli, 2002). Chronic toxicity results in anaemia. Acute lethal intoxications occur with blood levels of 100 ppm. There is no specific treatment. It has been suggested and, in some human cases, successful to use large volumes of balanced fluids to help flush the pentachlorophenol through the kidney (Osweiler et al., 1985).

VI. Organomercury Compounds

Mercury exists in a variety of organic and inorganic forms. The replacement of commercial mercurial compounds, including antiseptics (eg, mercurochrome), diuretics, and fungicides by other agents has decreased the likelihood of mercurial toxicosis; however, the possibility of exposure to environmental sources of organic methylmercury still exists (Aiello & Mays, 1998). Adverse effects of organic mercury are important to animal and human healthy. Inorganic mercury is converted to the organic alkyl forms, methylmercury and ethylmercury, by microorganisms in the sediment of rivers, lakes, and seas. Marine organisms (e.g., bivalves and fish) accumulate the most toxic form, methylmercury, and shellfish and fish must be monitored for contamination. There are reports of commercial cat food causing severe neurologic disturbances in cats fed an exclusive tuna diet for 7-11 months. The organic mercurials are absorbed via all routes and bioaccumulate in the brain and to some extent in the kidneys and muscle. Aryl mercurials (eg, phenylmercury fungicide) are slightly less toxic and less prone to bioaccumulation. Animals poisoned by organic mercury exhibit CNS stimulation and locomotor abnormalities after a lengthy latent period (weeks). Signs may include blindness, excitation, abnormal behavior and chewing, incoordination, and convulsions. Cats show hindleg rigidity, hypermetria, cerebellar ataxia, and tremors. Mercury is also a mutagen, teratogen, and a carcinogen, and is embryocidal. Differential diagnoses include conditions with tremors and ataxia as predominant signs, such as ingestion of other metals and insecticides and cerebellar lesions due to trauma or feline parvovirus (Aiello & Mays, 1998).

The mechanism of mercurial fungicides is to inhibit sulfhydryl group of enzymes involved in the transfer of amino acids across the blood brain barrier and then interfere with protein synthesis. Organomercurials can also release some mercury ions in the body, but their toxicity is not believed to be a primary action of mercury ions (Sandhu &Brar, 2000).

The first known cases of human poisoning from methylmercury-contaminated fish were reported in Japan, on the island of Kyushu, around Minamata Bay. Between 1953 and 1970, more than 121 poisonings were reported in this area, with 46 deaths recorded (Eyl, 1971).

By the mid-1970s, dietary toxicity thresholds and adverse effects of methylmercury were described for game birds and mink, and considerable information on mercury concentrations in tissues of wildlife had been generated in field biomonitoring studies (Thompson, 1996).

The aryl organomercurials, methyl or ethyl mercury chloride are poorly excreted and tend to accumulate in muscle, brain and other tissues, while the aryl organomercurials, phenyl mercury is more readily excreted via the kidney and less likely to accumulate in brain and muscles (Gupta & Aggarwal, 2007).

Neurologic signs may be irreversible once they develop. Chelating therapy with dimercaprol (3 mg/kg body wt, intramuscular, every 4 hr for the first 2 days, four times on the third day, and two times for the next 10 days or until recovery is complete) has been beneficial. When available, the water soluble, less toxic analogy of dimercaprol is the chelator of choice for organic mercury poisoning. Penicillamine (15-50 mg/kg, peros) may be used only after the gut is free of ingested mercury and renal function has been established (Aiello & Mays, 1998).

VII. Phthalimides (Chloroalkylthiodicarboximides)

This class of chemicals contains broad-spectrum fungicides such as captan, captafol and folpet. They are usually non-toxic to mammals (Gupta & Aggarwal, 2007).

Captan

Captan is a chloroalkylthio fungicide that belongs to the dicarboximide chemical family. Captan is used on a variety of crops as post-harvest fruit dips and seed treatment. It is also

used for indoor non-food uses and ornamental sites. Captan can be formulated as an emulsifiable concentrate, flowable concentrate, ready-to-use liquid, liquid soluble concentrate, solid, water dispersible granules, wettable powder, and dust (U.S. Environmental Protection Agency, 1999). Available also in combination with other fungicides (Lorgue et al., 1996).

Sheep and cattle are susceptible to captan poisoning. Sheep died after a single 250 mg/kg oral dose of captan. Signs of overexposure to captan include hypothermia, listlessness, depression, diarrhea, weight loss, anorexia, and increased water consumption in animals (Edwards et al., 1991; Lorgue et al., 1996).

Captan is rapidly degraded to 1,2,3,6-tetrahydrophthalimide (THPI) and thiophosgene in the stomach before reaching the duodenum. THPI has a half-life of 1-4 and thiophosgene is detoxified by reaction with cysteine or glutathione and is rapidly excreted. No captan is detected in blood or urine. Therefore, this compounds or even thiophosgene would survive long enough to reach systemic targets such as the liver, uterus and testes. Due to rapid elimination, meat, milk or eggs from livestock/poultry would be devoid of the parent materials (Kriger & Thongsinthusak, 1993).

Captan is highly to very highly toxic to fish such as bluegill sunfish, fathead minnow, brook trout, coho salmon, harlequin fish and brown trout. Captan is relatively non-toxic to honey bees, with a contact LD50 of >10 μg/bee (U.S. Environmental Protection Agency, 1999).

There is no specific treatment for captan poisoning in animals. Symptomatic treatment is applied (Lorgue et al., 1996; Sener, 2000).

Captafol

Captafol is used on fruits, vegetables, cereals and as a seed protectant. It is also used as wood preservative (Osweiler et al., 1985). Captafol is available in the form of concentrated suspensions. Cattle and fish are susceptible to captafol poisoning (Lorgue et al., 1996).

Folpet

The other name is "folpel" that used in France (Lorgue et al., 1996). It is used on fruits, vegetables and ornamental plants. It is also used in paints and plastics for fungal control (Osweiler et al., 1985). Folpet is formulated as a wettable powder or as a concentrated suspension. Although it has low toxicity, the most affected animals are cattle and poultry (Lorgue et al., 1996).

4. Conclusion

Fungicides vary enormously in their potential for causing toxic effects in animals. The main hazard to animals from fungicides is likely to arise from their use in agriculture and garden. Fungicides can lead to acute or chronic poisoning in animals, although fungicides have low to moderate toxicity for animals. Some livestock poisoning cases result from accidental overdosing or careless use of fungicide for treatment in the animals. In general, there is no specific treatment for fungicides poisoning in domesticated animals and humans. Some fungicides also have adverse effects on wildlife, such as birds, honey bees, fish and aquatic invertebrates. Fungicides are currently and, undoubtedly, will continue to be widely used in agriculture. Therefore, we should use fungicides on plants, seeds and trees carefully (i.e., according to manufacturer instructions and wearing appropriate protective gear) and we should monitor our agricultural products and domesticated animal foods for fungicide contamination.
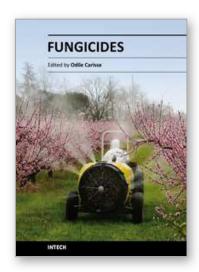
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Plant and plant products are affected by a large number of plant pathogens among which fungal pathogens. These diseases play a major role in the current deficit of food supply worldwide. Various control strategies were developed to reduce the negative 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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