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A Review on Toxicological Effects of Fungicides.

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ABSTRACT

Today, humans and wildlife are constantly exposed to thousands of chemical residues, through air, food and water. Fungicides have been used widely in order to control fungal diseases and increase crop production. However, the regular use of fungicides can potentially pose a risk to the environment and public health. Fungicides can be classified by chemical group, general mode of action, specific mode of action, or by physical properties once in the plant. These are found to be teratogenic, carcinogenic, mutagenic, reproductive toxicant as well as show harmful effects on ecology including non target plants and animals. This review deals with structure, uses and adverse effects of fungicides on different systems, thus indicates limited use of fungicides to improve the quality of life for human welfare.

Keywords: Fungicides; environment; carcinogenic; reproductive toxicant; adverse effects

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INTRODUCTION

Pesticides are a diverse group of chemical compounds and consist of insecticides, herbicides, molluscicides, namaticides, rodenticides and fungicides [1]. Pesticides have contributed to dramatic increases worldwide in crop yields and have helped to limit the spread of disease but pesticides also have harmful effects and can injure human health as well as the environment. The range of these adverse health effects including acute and persistent injure to the nervous system, lung damage, injure to the reproductive organs [2-7] and dysfunction of the immune and endocrine system [8-10], birth defects and cancer [11-15].

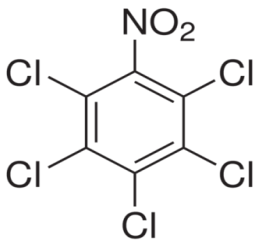
Adverse Effects of Fungicides

The discussion of fungicide related adverse effects proceeds in the following order-

- Substituted Benzenes
- Thiocarbamates
- Ethylene Bis Dithiocarbamates
- Thiopthalimides
- Copper compounds
- Organomercury compounds
- Organotin compounds
- Cadmium compounds
- Organic fungicides

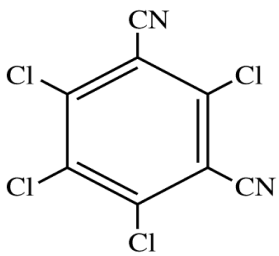
Substituted benzenes

The substituted benzene pesticides are a group of fungicides with a wide range of uses. Applications are made as treatments to seed, soil, and the foliage of vegetables and field crops, flowers, bulbs, and turfgrass. Some of the members of this pesticide family, such as pentachloronitrobenzene (PCNB), have been in use since the 1930s. PCNB is used to treat seed and soil at planting, and for selected foliage applications. Skin has caused sensitization in some tested volunteers. One case of conjunctivitis and keratitis occured following eye contamination.



Pentachloronitrobenzene

The widely used fungicide, chlorothalonil, first became available in 1964 and has proven to be very useful in applications as a broad-spectrum foliage-protecting fungicide. Chorothalonil has caused irritation of skin and mucous membranes of the eye and respiratory tract on contact. Cases of allergic contact dermatitis have also been reported. There is one report of immediate anaphylactic reaction by skin contact [16]. Diabetic ketoacidosis has been reported following high occupational exposure of chlorothalonil [17].



Chorothalonil

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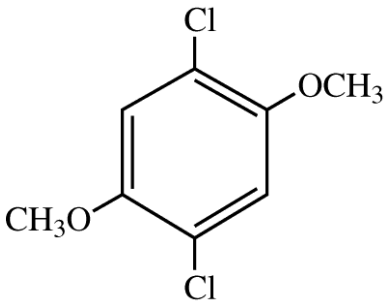
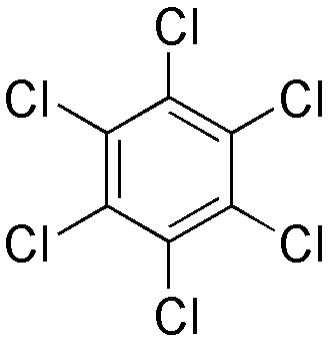
Another member of this group, chloroneb, is used for treatment of seed and turf. Chloroneb exhibits oral toxicity in mammals. It is moderately irritating to skin and mucous membranes [18].



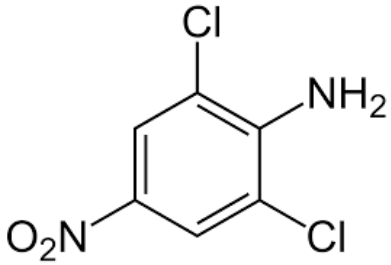
Chloroneb

One member of this group, hexachlorobenzene, is a seed protectant fungicide caused toxic porphyria resembling porphyria cutanea tarda (impaired haemoglobin synthesis). It has been discontinued for use in the United States. Hexachlorobenzene (HCB) is one of the highly toxic and persistent compounds that are released unintentionally through various man-made chemicals [19]. It was shown to cause adverse health effects to Turkish farm dwellers in the 1950s, and some infants who were being nursed by exposed mothers died. Product formulations of the substituted benzenes include wettable powders, dusts, water-dispersible granules, emulsifiable concentrates, and granules [20]. During the period 1955-1959, approximately 4000 people in southeast Anatolia developed porphyria due to the ingestion of hexachlorobenzene (HCB), a fungicide added to wheat seedlings. These HCB exposures subsequently led to the development of bullae on sun-exposed areas, hyperpigmentation, hypertrichosis, and porphyrinuria. The condition was called kara yara or "black sore." Many of the breast-fed children under the age of 2 years whose mothers had ingested HCB-treated grain died from a disease known as pembe yara or pink sore [21].



Hexachlorobenzene

Dicloran is broad spectrum fungicide widely used to protect perishable produce. Dicloran is registered for use in Florida as a broad-spectrum fungicide used to protect perishable produce. Doses of dicloran given to laboratory animals cause liver injury, corneal opacities, pyrexia and possibly methemo-globinemia [22].



Dicloran

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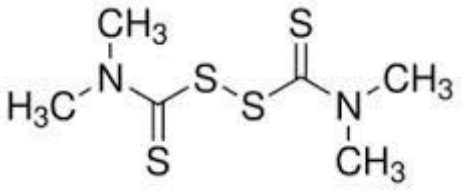
Thiocarbamates

They are used to protect seeds, seedlings, ornamentals, turf, vegetables, fruits and apples. Few exhibit weak anticholinesterase activity. Metam-sodium can be very irritating to the skin. It decomposes in water yields methyl isothiocyanate, a gas that is extremely irritating to respiratory mucous membranes, to the eyes and to the lungs. Inhalation of this fungicide may cause pulmonary edema (severe respiratory distress, coughing of bloody, frothy sputum). Many investigators have reported that dithiocarbamates exhibit the characteristics of endocrine disruptors and can disrupt steroidogenesis by inhibiting enzyme activities [23-25,14]. Thiram is irritating to human skin, eyes and respiratory mucous membranes. Contact dermatitis has occured in occupationally exposed workers. Few individuals have experienced sensitization to thiram. Thiram, at high doses causes hyperactivity, ataxia, loss of muscle tone, dyspnea and convolusions [26].



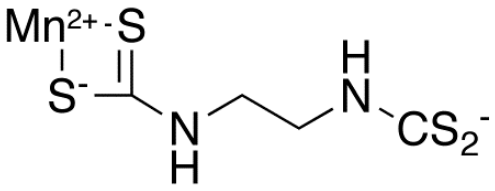
Thiram

Toxic and some tumorigenic effects have been observed in different animal species exposed to thiram [27,28], numerous tests indicate that it is genotoxic [29,30] and effects on cartilaginous tissues in vivo and in vitro [31-33]. Thiram might have a chronic toxicity to mammals that can be shown affecting their growth [34]. Clinical signs in thiram poisoning are anorexia, listless behavior, dyspnea, convulsions, and death due to cardiac arrest [35].

Ethylene bisthiocarbamates (EBDC) compounds

Maneb, Zineb and Mancozeb fungicides have apparently been responsible for some cases of chronic skin disease in occupationally exposed workers.

Maneb exposure has been reported in one person who developed acute renal failure and was treated with hemodialysis [36]. One report suggests parkinson's disease like abnormalities in maneb exposed persons [37,38].



Maneb

Zineb [ethylene bis(dithiocarbamate)zinc] is a widely used foliar fungicide and is registered for use on a large number of fruits, vegetables and field crops, as well as on a large number of ornamental plants and for the treatment of many seeds. Zineb is also registered for use as a fungicide in paints and for mold control on fabrics, leather, linen, painted surfaces, surfaces to be painted and paper, plastic and wood surfaces [39]. Trigathy *et al*. [40] reported zineb as a positive genotoxic agent in somatic and germ cells of *Drosophila*. While Chernov and Khitsenko [41] observed an increased incidence of lung tumors after its oral administration to C57BL mice.

Dose-dependent increase in the number of abnormal cells and chromatid-type and chromosome-type aberrations, as well as in the total number of aberrations was noticed in zineb-containing *in vitro* cultures of human lymphocytes [42,43]. In cases of zineb poisoning in sheep, the animals present with characteristic yellow, watery diarrhea [44].

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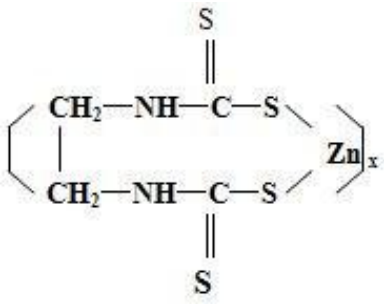
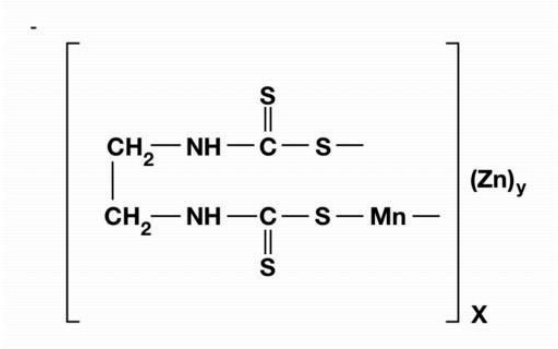


Zineb

Mancozeb, an Inorganic-Zinc dithiocarbamate, is a typical fungicide with a carbamate structure where sulphurs replace both oxygens in the amide functional group. It is chemically identified as ethylenebisdithiocarbamate (EBDC). The poisoning caused with EBDC compounds cause symptoms of irritation of skin, eyes and respiratory tract, skin sensitization; chronic skin disease has also been observed in occupationally exposed workers. Mancozeb exposure is associated with pathomorphological changes in liver, brain and kidney. It has produced significant enzymatic changes in the activities of various enzymes [45]. Inhibition of implantation by Mancozeb due to hormonal imbalance or its toxic effects has been studied [46].



Mancozeb

In female, it has been reported that direct exposure to mancozeb leads to ovarian hypertrophy and disruption of estrous cycle in hemiovarictomized albino rat and this may be due to a direct effect on the ovary or the hypothalamus-hypophysial-ovarian axis. Baligar and Kaliwal [47] found that mancozeb decrease the number of healthy follicles and increase of the number of atretic follicles due to hormonal imbalance or its direct toxic effect. In addition, mancozeb induced a significant decrease in the number of ovulated eggs and caused a significant decrease of fertilizability related to a reduction in the formation of male and female pronuclei [48].

Mancozeb is a widely used fungicide with low reported toxicity in mammals. In mice, mancozeb induces embryo apoptosis, affects oocyte meiotic spindle morphology and impairs fertilization rate even when used at very low concentrations. Paro et al. [49] evaluated the toxic effects of mancozeb on the mouse and human ovarian somatic granulosa cells. Results revealed that mancozeb affects the somatic cells of the mammalian ovarian follicles by inducing a premalignant-like status, and that such damage occurs to the same extent in both mouse and human GC. These results further substantiate the concept that mancozeb should be regarded as a reproductive toxicant. Patel et al. [50] revealed that mancozeb exhibited weak mutagenic response at tested dosage.

In our laboratory, mancozeb administration brought about marked reduction in epididymis and testicular sperm counts in exposed males. Pre- and post-fertility test showed 80% negative results after treatment. A significant reduction in the testicular glycogen and sialic acid was observed whereas a significant increase in the protein and cholesterol content of testis was noticed. In addition, acid phosphatase enzyme activity increased significantly while alkaline phosphatase activity showed a sharp decline. Mancozeb also suppressed testosterone level significantly [51].

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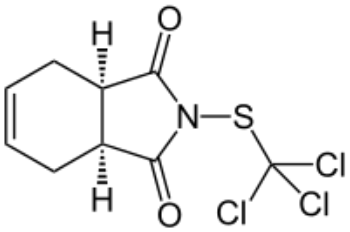
Thiopthalimides

Captan, captafol and folpet, all of these fungicides are irritating to the skin eyes and respiratory tract, dermal sensitization may occur.

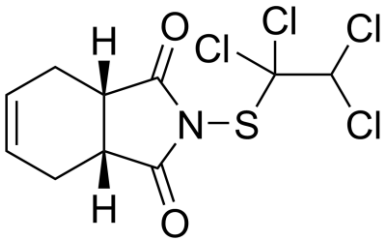
Captan is used on a variety of crops as post-harvest fruit dips and seed treatment. It is also used for indoor non-food uses and ornamental sites. Captan can be formulated as an emulsifiable concentrate, flowable concentrate, ready-to-use liquid, liquid soluble concentrate, solid, water dispersible granules, wettable powder, and dust. There is strong evidence that captan can cause cancer in female mice and male rats at high doses [52].

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 [53,44].



Captan

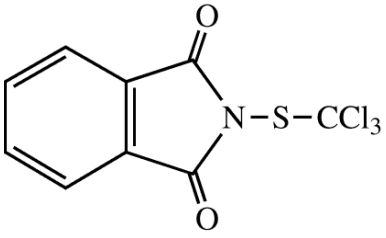
Captafol is used on fruits, vegetables, cereals and as a seed protectant. It is also used as wood preservative. Captafol is available in the form of concentrated suspensions. Captafol appears to have been responsible for several episodes of occupational contact dermatitis. Cattle and fish are susceptible to captafol poisoning [44].



Captafol

Folpet is used to control diseases on many fruit, ornamental and vegetable crops. It has also been shown to produce cancer in test animals [52]. Although it has low toxicity, the most affected animals are cattle and poultry [44].

Folpet produces duodenal glandular tumors in mice. At sufficiently high, prolonged dietary doses, folpet irritates the mouse duodenum, resulting in cytotoxicity with consequent regenerative proliferation and ultimately tumor development [54].



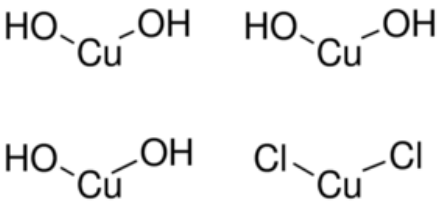
Folpet

Copper compounds

Today many commercial copper containing fungicides are available in the market. These are irritating to the skin, respiratory tract and particularly to the eyes. The organic copper compounds exhibit the greatest systemic toxicity in laboratory animals. Early signs and symptoms of copper poisoning include a metallic taste, nausea, vomiting and epigastric pain. In more severe poisonings, the gastrointestinal irritation will worsen with hemetemesis and metanotic stools. Jaundice and hepatomegaly are common. Hemolysis can occur, resulting in circulatory collapse and shock. Acute renal failure with oliguria can also occur. Shock is a primary cause of death early in the course and renal failure and hepatic failure contribute to death more than 24 hours after poisoning [55,56].

Fytolan is one of the broad spectrum copper based fungicide. It controls wide range of fungal and bacterial diseases on fruits, vegetables and ornamental plants, so being used widely for crop protection. But copper released from fytolan are found to be very toxic for crops. Unfortunately the rampant and indiscriminate usage, further lack of safe handling, illiteracy and insufficient scientific knowledge of these chemicals makes them potential environmental contaminants, which cause severe harmful effects in many organisms, including man. Of all the toxicological hazards arising from these chemical least is known about its risks on blood and its components. In our laboratory investigation a significant decrease in total erythrocyte count, haemoglobin content and haematocrit value were observed, however increase in the total leukocyte count was noticed in fytolan administered rats. The level of blood sugar and blood urea was increased significantly when exposed to fytolan. Protein content was found to be increased significantly after oral administration of fytolan. Significant increases in triglyceride and phospholipid level were noticed in higher doses exposed rats. In serum, total cholesterol, HDL, LDL and VLDL

cholesterol were found to be significantly elevated compared to control [1].



Fytolan

Organomercury fungicides

Methyl mercury, metho-xyethyl mercury compounds, phenyl mercuric compounds- These fungicides have been used chiefly as seed protectants. The mercurial fungicides are among the most toxic pesticides ever developed, for both chronic and acute hazards. Epidemics of severe, often fatal neurologic disease have occurred when indigent residents of less developed countries consumed methyl mercury treated grain intended for planting of crops [57,58]. Poisoning has also occured from eating meat from animals fed mercury treated seeds [59].

Early symptoms of poisoning are metallic taste in the mouth, numbness and tingling of the digits and face, tremor, headache, fatigue, emotional lability, and difficulty in thinking. Manifestations of more severe poisoning are in coordination, slurred speech, loss of position sense, hearing loss, constriction of visual fields, spasticity or rigidity of muscle movements and deterioration of mental capacity. Many poisonings caused by ingestion of organic mercurials have terminated fatally and large percentage of survivors has suffered severe permanent neurologic damage [57,58].

Phenyl-mercuric acetate had been used to prevent fungal growth in latex paint. There have been reports of acrodynia in persons exposed to mercury vapour from use of interior latex paint. Symptoms include fever, erythema and desquamation of hands and feet, muscular weakness, leg cramps and personality changes [60].

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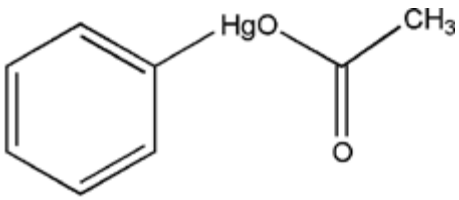
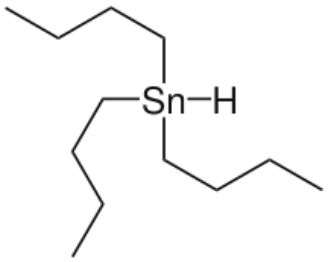


Phenyl-mercuric acetate

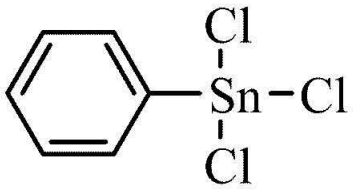
Organotin Compounds

These fungicides are used to control blights on field crops and orchard trees. Tributyltin used as fungicides and antifouling agents on ships. These fungicides are irritating to the eyes and respiratory tract. Manifestations of toxicity are due principally to effects on the central nervous system, headache, nausea, vomiting, dizziness and sometimes convulsions and loss of consciousness. Photophobia and mental disturbances occur. Elevation of blood sugar, sufficient to cause glycosuria, has occured in some cases.



Tributyltin

Phenyltin fungicides caused cerebral edema, neurologic damage and death in severely poisoned individuals who were exposed dermally [61].



Phenyltin

Cadmium Compounds

Cadmium containing fungicides have been used to treat fungal disease affecting turf and the bark of orchard trees. Cadmium containing fungicides are very irritating to the respiratory and gastrointestinal tract. A more severe form of toxicity includes chemical pneumonitis and associated with labored breathing, chest pain and sometimes fatal hemorrhagic pulmonary edema [62].

Ingested cadmium fungicide causes nausea, vomiting, diarrhoea, abdominal pain and tenesmus. Relatively small inhaled and ingested doses produce serious symptoms. Protracted absorption of cadmium has led to renal damage (proteinuria and azotemia), anemia, liver injury (Jaundice), and defective bone structure (Pathologic fractures) in chronically exposed persons. Prolonged inhalation of cadmium dust has contributed to chronic obstructive pulmonary disease.

Cadmium chloride may contain 12.3% elemental cadmium. Cadmium succinate may contain 29% elemental cadmium. Cadmium sebacate is combined with thiram and potassium chromate as broad spectrum fungicide [63].

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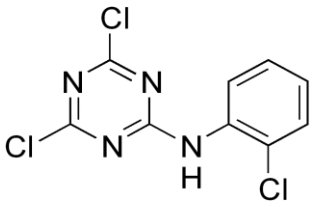
Organic fungicides

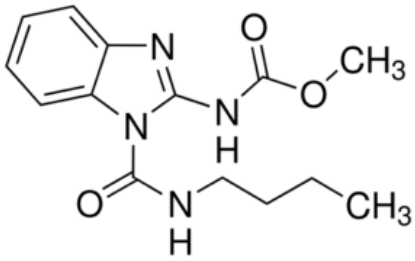
Some modern organic fungicides are widely used. Anilazine is supplied as wettable and flowable powders. It is used on vegetables, cereals, coffee, ornamentals and turf. It has caused skin irritation in exposed workers. Acute oral and dermal toxicity in laboratory animals is low.



Anilazine

Benomyl [methyl 1-(butylcarbamoyl)-2-benzimidazole carbarnate] is a classic benzimidazole carbamate fungicide and nematocide that has been used for many years on a variety of food crops, ornamental plants, trees and grasses [64]. This chemical and its primary metabolite, carbendazim, are microtubule poisons that are relatively nontoxic to all mammalian organs, except for the male reproductive system.

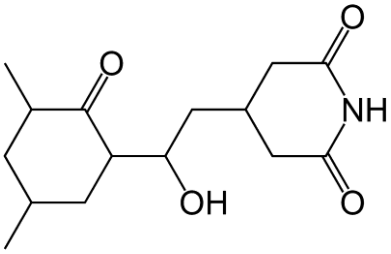
Benomyl administered male Japanese Quails show a significant decrease in relative weight and size of testes. Microscopically, seminiferous tubules of testes exhibit a decreased number of spermatocytes, necrotid spermatids and syncytial cell formation [65]. Adult rats fed benomyl for 70 days showed significant depressions in sperm count, testicular weight and had lowered fertility indexes [66]. Similar effects were elicited in rats given benomyl during or after puberty [67]. In another study in rats, the testes were the most affected sites at relatively low doses of benomyl. Male rats had decreased sperm counts, decreased testicular weights and lower fertility rates [53].



Benomyl

Benomyl metabolized into carbendazim and disrupts the production of sperm and damages testicular development in adult rats, probably partly through disrupting the assembling of cells in tissue which is the same way as benomyl works as a fungicide [68,69].

Cycloheximide is a product of fungal culture, effective against fungal diseases of ornamentals and grasses. It is selectively toxic to rats much less toxic to dogs and monkeys. Cycloheximide (CHX)-induced liver injury in rats has been characterized by hepatocellular apoptosis and necrosis [70].



Cycloheximide

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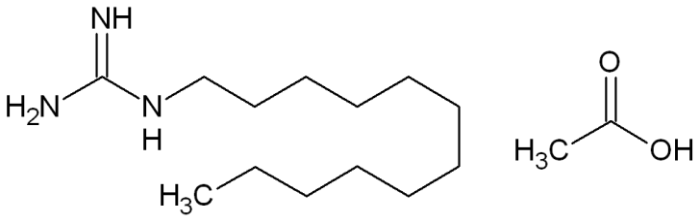
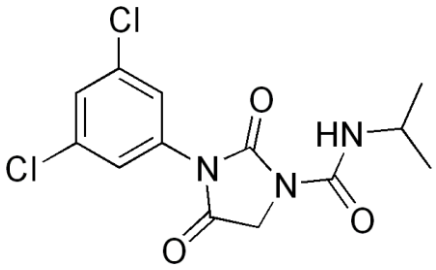
Dodine is commonly applied to berries, nuts, peaches, apples, pears and to trees afflicted with leaf blight. Dodine was slightly toxic to mice and rats when given orally. The clinical signs in rats included abnormal defaecation, various discoloured areas due to discharge or excretion, hypoactivity, prolapsed penis, and impaired muscle coordination. On necropsy, distension of the stomach and/or intestines and abnormal abdominal adhesions were observed. Dodine was not toxic to rats or rabbits when applied dermally, but it was severely toxic to rats exposed by inhalation. The clinical signs included exaggerated breathing, immobility, lethargy, unsteady gait, cold to touch, and piloerection. Dodine was extremely irritating to the eyes and slightly irritating to the skin of rabbits in one study and severely irritating in another study. It was not a skin sensitizer in guinea-pigs [71].



Dodine

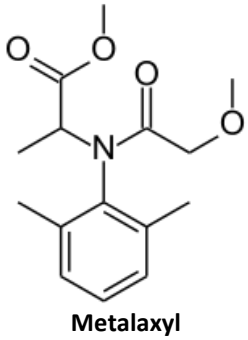
The chemical induced a significant reduction of the protein content and in sucrase activity in the jejunum. Morphological alterations included a significant decrease in crypt height and in villus length and depth. The intestinal modifications observed in animals after Dodine administration may explain the observed loss in body weight and diarrhea [72].

Iprodione is used as a seed dressing, exhibits low acute oral and dermal toxicity in laboratory animals. The toxic mechanism of iprodione has not been fully clarified yet and this compound is classified sometimes as antiandrogenic [73] sometimes as androgenic agent [74]. According to Galli et al. [75] it is clear that iprodione and its metabolite compete with the endogenous hormones in all the tested species, exerting antiandrogenic effects.



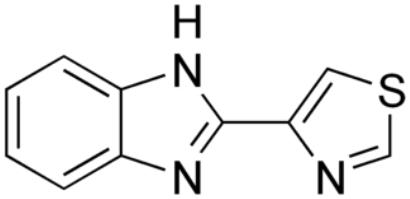
Iprodione

Metalaxyl is used to control soil-borne fungal disease on fruit trees, hops, soybeans, peanuts, ornamentals and grasses. Metalaxyl exhibits low acute oral, dermal and reproductive toxicity in laboratory animals [76]. Recent studies proved that metalaxyl induced many histopathological alterations in the liver such as congestion of blood vessels, leucocytic infiltration, cytoplasmic vacuolization of the hepatocytes and necrosis [77].



Metalaxyl

Thiabendazole is widely used as an agricultural fungicide. Blood enzyme tests may indicate liver injury. Persons with liver and kidney disease may be unusually vulnerable to toxic effects. Imazalil (IMA) is a widely used imidazole fungicide and therefore a food contaminant. Studies shows that coingestion of IMA-contaminated food and CYP3A4 or CYP1A1-metabolizable drugs could lead to drug toxicological interactions, with possible adverse effects for human health [78].



Thiabendazole

CONCLUSION

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. This review suggested the limited use of such toxic fungicides to improve the quality of life for human welfare. Thus, the people need to be educated for vigilant use of these pesticides.

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