Review Article

SOME TOXICOLOGICAL HEALTH HAZARDS OF MANCOZEB: REVIEW ARTICLE

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ABSTRACT

Fungicides are pesticides that specifically, in agriculture, used to protect fruits and vegetables during storage or are applied directly to ornamental plants, trees, field crops, cereals and turf grasses. Mancozeb (MZ), a broad spectrum dithiocarbamate fungicide used in Egypt, is one of the most frequently utilized pesticides in homes, agricultural, and industrial settings worldwide. The main mechanism of mancozeb toxicity is the creation of reactive oxygen species and the activation of oxidative stress, which leads to mitochondria dysfunction, apoptotic pathways activation and increase lipid peroxidation that are implicated in the pathophysiology of numerous diseases and has been linked to acute and chronic exposure to such dithiocarbamates pesticides. The purpose of this review article is to highlight on MZ regarding chemical structure, environmental fate, ways of human exposure, mechanism of toxicity and some of its potential health hazards. So, it is important to recommend the presence of an applicable access of information for farmers and workers about proper use or the precautions needed when handling pesticides or at least using the simplest hygienic and protective measures, also, attention to sanitary environmental work place is required to avoid take-home mechanism of toxicity. Also, widespread public education regarding the health hazards of dithiocarbamates pesticides is essential.

Keywords: Fungicides, dithiocarbamate, Mancozeb, Environmental.

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INTRODUCTION

Pesticides are important chemical or biological substances that prevent or eliminate pests. The term “pesticides” encompasses a large number of compounds, such as fungicides, insecticides, herbicides, rodenticides, plant growth regulators and others, according to the pest target (Silva et al., 2022).

The use of pesticides has risen steadily over time as it is still considered the most effective method to lessen pests and promote crop growth. However, pesticides can potentially be hazardous to both humans and wildlife. The use of pesticides has been linked to an increased risk of cancer, cardiovascular illness, and birth problems. According to the World Health Organization, 3 million workers in developing countries suffer from severe pesticide poisoning every year, and 18,000 of them eventually die. People who use pesticides in agricultural and occupational settings run a significant risk of direct exposure. However, the general population can also be indirectly exposed to pesticides and the byproducts of their breakdown at low levels through water, food, air and dust (Sule et al., 2022).

Pesticides can be classified based on the chemical structure into organochlorines, organophosphates, bipyridyls, morpholines, triazines, carbamates, pyrethroids and dithiocarbamates (Martins et al., 2021).

Dithiocarbamate pesticides, which were first employed in agriculture in the 1950s, are utilized as fungicides, insecticides, and herbicides. These pesticides are used in industrial and commercial settings as biocides and accelerating agent. Therapeutically they are used for the alcohol aversion (Bansal, 2022).

The first dithiocarbamate to be introduced as a fungicide was tetramethylthiuram disulphide, known as Thiram, followed by more potent substances, such as Ferbam and Ziram. Disodium ethylene bisdithiocarbamate (Nabam) was the first ethylene bisdithiocarbamate (EBDC) to be used. It was unstable in solid form, which made its practical handling difficult. Shortly after Nabam introduction in the market, it was discovered that zinc sulphate had a stabilizing effect on the liquid. The reaction product between zinc sulphate and Nabam was zinc ethylene bisdithiocarbamate (Zineb). Later, manganese was used instead of zinc forming manganese ethylene
bisdithiocarbamate (Maneb), which was more active than Nabam or Zineb. The zinc ion complex of Maneb (Mancozeb), which is a mixture of Maneb and Zineb, was registered in 1962 and quickly became the most popular EBDC (Cocco, 2022).

Route of Exposure:

1) Occupational Exposure:-

Occupational exposures to pesticides may occur in people working in greenhouses and open fields in agriculture, workers in the pesticide industry, and exterminators for house pests (Damalas and Eleftherohorinos, 2011).

Agricultural operators are mainly exposed to pesticides during the preparation and use of the spray solution. Due to spills and splashes, direct spray contact, or even drift, they are potentially exposed to pesticides via two routes of exposure; dermal absorption and respiratory inhalation (Damalas and Abdollahzadeh, 2016; El-Nahhal and El-Nahhal, 2021).

2) Non-Occupational Exposure:-

The pesticide contamination of food and water is the main way that the general population is exposed to pesticides. The pesticides are bioaccumulated in the vegetables and fruits through plant uptake from contaminated soil, irrigation by the pesticide-contaminated water and spraying of the pesticides on agricultural plants for pest management (El-Nahhal and El-Nahhal, 2021; Bansal, 2022).

Children may come into contact with pesticides through ingesting contaminated food and drink, playing with contaminated clothing and equipment, interacting with pesticide-treated animals and plants in rural and household gardens, and receiving head lice treatment in schools (Pascale and Laborde, 2020).

Mancozeb

Mancozeb (MZ) is a manganese/zinc ethylene-bisdithiocarbamate (Mn/Zn-EBDC) fungicide that is commonly used in agriculture for controlling a wide range of fungal infections of vegetables and ornamental plants. Its wide application in agriculture is due to the reported low acute toxicity and short persistence in the environment (Saber and El-Aziz, 2016; Saber et al., 2019).

Chemical and Physical Properties: -

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) (Joshi et al., 2005).

**Chemical Name:**

[[1,2-ethanediylbis-[carbamodithioato]][(2-)] manganese, in combination with [[1,2- ethanediylbis-[carbamodithioato]]-(2-)]zinc. (Xu, 2000)

Mancozeb is a powder of greyish-yellow colour. Usually, it is stable as long as there are proper storage conditions but if there is increase in moisture and temperature, it undergoes decomposition (Baligar and Kaliwal, 2001).

As MZ has a very low vapour pressure, it has a minimal potential for volatilization into the air. MZ has a low water solubility yet it is rapidly hydrolyzed in water throughout a wide pH range with a half-life of fewer than two days (Xu, 2000; Belpoggi et al., 2002).

**Mechanism of Action:**

The Fungicide Resistance Action Committee places MZ in the mode-of-action group M. (Multi-Site Action). Mancozeb is considered a fungicide that, when exposed to water, breaks down to yield ethylene bisisothiocyanate sulphide (EBIS), which is then converted to ethylene bisisothiocyanate (EBI) by ultraviolet radiation. Both EBIS and EBI are likely to be the active toxicants, interfering with sulphydryl-group-containing enzymes. At least six different biochemical pathways within the fungal cell cytoplasm are thought to be inhibited or interfered with by this catastrophic disturbance of essential enzyme functions (Gullino et al., 2010).

**Environmental Fate of Mancozeb:**

Mancozeb degrades quickly in soil. In three months, it decreased to undetectable levels in nonsterile soils. At an average temperature of 230 ± 0.60°C, the metabolism of MZ was studied in nonsterile and sterile silt loam soil under aerobic and sequential aerobic/anaerobic conditions. Ethyleneurea (EU) was produced via the intermediates EBIS and Ethylenethiourea (ETU) in both sterilized and unsterilized soils. Under anaerobic circumstances, a small quantity of EU was further degraded to 2- imidazoline and other unknown chemicals. EU is formed through both biological and chemical factors. In non-sterile aerobic and anaerobic soils, MZ had half-lives of less than 2 days and 8 days, respectively (Xu, 2000).

Another environmental fate of mancozeb is hydrolysis, MZ
hydrolyzes fast over a wide pH range; under sterile and dark conditions, hydrolysis half-lives at pH 5, 7, and 9 varied from 1-1.5 days at 250°C. pH affects the degradates and their relative quantities. Its hydrolysis results in production of EBIS, ETU, and EU (Xu, 2000).

Due to its rapid hydrolysis, MZ has a limited soil persistence and adsorption capability, but ETU, the most major metabolite of MZ, is permeable to the soil and can contaminate groundwater. Residues have been found regularly in fruit and vegetables, and it has been demonstrated that a large amount of ETU is formed when contaminated crops are cooked (Belpoggi et al., 2002).

Toxicokinetics of Mancozeb:

Mancozeb, as a dithiocarbamate compound, can be absorbed via the skin, the mucous membranes, and the respiratory and gastrointestinal tracts (Houeto et al., 1995).

The metabolic pathway of MZ in mammals produces a significant number of species among which ETU is the most relevant, representing about 15–48% of the total metabolites excreted in urine. ETU is also a by-product in the synthesis of EBDTC and therefore it is present in trace quantities in all commercial EBDTC formulations. In addition, ETU may also be produced during storage, or cooking of food contaminated with EBDTC residues (Colosio et al., 2002).

Mechanism of Toxicity of Mancozeb:

The main mechanism of MZ toxicity is induction of oxidative stress and production of reactive oxygen species (ROS). It reduces antioxidant enzymes activities, total antioxidant capacity and glutathione content. MZ can also lead to mitochondria dysfunction, apoptotic pathways activation and increase lipid peroxidation (Liu et al., 2017; Mohammadi-Sardoo et al., 2018).

Toxicological Effects of Mancozeb:

Mancozeb and its metabolites are widely distributed in the environment and have harmful effects when ingested, inhaled, or absorbed through the skin by non-target creatures. Agricultural workers are exposed during seed treatments and foliar applications, and the general population is harmed through the food chain. In human and experimental animals, short- and long-term exposures to MZ have been linked to neurotoxic, developmental impairment,
immunotoxic, and carcinogenic consequences (Bindali and Kaliwal, 2002; Kwon et al., 2018).

Despite its modest acute toxicity, MZ has been demonstrated to have harmful effects on the gonads, and chromosomes of bone marrow cells in male rats and mice. Mancozeb exposure results in normocytic anemia, a considerable fall in blood glucose and globulin levels, and severe pathological alterations in the liver, kidney, spleen, and heart, which showed congestion with modest enlargement, and a few petechial haemorrhages in the brain (Baligar and Kaliwal, 2001).

1) Reproductive Effects: -

According to Sakr et al. (2009), mancozeb-treated animals had a considerable fall in testosterone level. Seminiferous tubule diameters and germinal epithelium heights were both drastically reduced. Furthermore, tests of treated animals revealed that spermatogenesis was inhibited, as evidenced by a decrease in the number of distinct spermatogenic cells. Degeneration of spermatogenic cells, destruction of Leydig cells and blood vessels congestion were all observed histologically. These findings suggested that MZ had an effect on testicular function.

Bindali and Kaliwal (2002) reported that the oral administration of MZ impacts ovarian growth, vaginal cyclicity and development of follicles in the experimental animals. It also affects the biochemical constituents of ovary and uterus.

Mancozeb, as an endocrine disruptor pesticide, may have a deleterious impact on female rats reproductive competence as it can cause poor fecundity, spontaneous abortion, preeclampsia, endometriosis, menstrual cycle irregularities and polycystic ovarian syndrome. Also, MZ exposure is considered a risk factor for maternal death, and foetal abnormalities (Bianchi et al., 2020).

2) Hepatotoxic Effects: -

Mancozeb-treated rats showed a variety of histopathological alterations in the liver such as vascular congestion, leucocytic infiltration, vacuolization of hepatocyte cytoplasm and pyknosis. There were also marked increase in the level of alanine aminotransferase and aspartate aminotransferase enzymes in serum, increase in the lipid peroxidation marker malondialdehyde and decrease in the antioxidant enzyme level in serum and superoxide dismutase activity (Sakr and Saber, 2007).
Mancozeb exposure can result in hepatic structural changes and cellular dysfunction as it causes oxidative stress and deoxyribonucleic acid (DNA) damage in hepatocytes through the formation of ROS and the suppression of the antioxidant defense system (Hashem et al., 2018).

3) Neurological Effects:

Saber and El-Aziz (2016) noted that the brain of rats treated with mancozeb showed a marked elevation in the level of glutamate and gammaaminobutyric acid. That rise in brain glutamate level may be due to glutamate uptake inhibition. There was also marked increase in lipid peroxidation, protein carbonyl content and nitric oxide level. A marked decrease in glutathione level and glutathione peroxidase, glutathione reductase and glutathione-S-transferase activity also has been recorded. Furthermore, MZ raised inducible nitric oxide synthase immunohistochemistry expression in the cerebral cortex.

According to Li et al. (2013), MZ has been linked to neurotoxicity and neurodegenerative diseases in humans, including manganism and parkinsonism. That link between MZ exposure and parkinsonism is due to the ability of MZ to cause neurodegenerative changes in both dopaminergic and γ -aminobutyric acid (GABA)-ergic neurons. Mancozeb also has been linked to ROS generation, modifications to the antioxidant defense mechanisms, all of which may contribute to neuronal toxicity. Fatigue, nausea, headaches and impaired vision are all symptoms of MZ neurotoxicity, but if high doses exposure occurred, exposed people may develop convulsions, slurred speech, confusion and other severe symptoms.

4) Haematological Effects:

According to Kotb et al. (2019), MZ treated animals showed significant decrease in both white and red blood cells values. Whereas hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration values showed significant increase. MZ induced alterations in hematological indices may be a defensive mechanism against MZ toxicity through stimulation of leucopoiesis.

5) Immunological Effects:

According to Corsini et al. (2005), study on farmers’ immune profiles after exposure to MZ, the blood cells counts results showed decrease in eosinophil percentage and
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compared to controls, post-exposure samples had a higher white blood cell count. Exposure to MZ had no effect on the immunoglobulin serum levels, except immunoglobulin E which showed significant drop in its level. MZ exposure had no effect on complement fraction or autoantibody levels in the blood. Regarding lymphocyte subsets, post-exposure samples showed a substantial rise in the absolute number of CD3+ and CD4+ cells compared to controls. After exposure, both the absolute number and percentage of CD19+ cells increased. The proportion of cells that express the interleukin 2 receptor's alpha subunit, or CD25 percent, was significantly lower in the post-exposure group as compared to controls. In the workers' samples collected following exposure, natural killer cells, as well as their percentage and absolute number, exhibited a minor but substantial increase as compared to baseline.

6) Carcinogenic Effects:-

Mancozeb can be regarded as a multipotent carcinogen that can cause many tumours in various sites in treated animals. From the age of 8 weeks to 104 weeks, animals treated with MZ in food showed a significant increase in the overall number of malignant tumours as well as tumours at other sites, such as malignant mammary tumours, osteosarcomas of the bones of the head, and ear canal carcinomas, hepato-carcinoma and pancreatic malignant tumors (Belpoggi et al., 2002).

7) Teratogenic Effects:-

Mancozeb-treated pregnant rats showed fetal and maternal developmental toxicity manifested as decreased dams and fetal body weight, increase in post-implantation loss and increased fetal external, visceral and skeletal abnormalities. MZ induced different teratological effects, such as significant irregular distribution of implantation sites, increase resorption and number of dead fetuses and less ossification of most parts of skull and legs as well as complete loss of ossification in digits and caudal vertebrae (Belonovskaya et al., 2010; Nahas and Abbas, 2015).

CONCLUSIONS AND RECOMMENDATIONS:

Dithiocarbamates pesticides occasionally used indiscriminately in large amounts causing environmental pollution, and therefore, are a cause of concern. Mancozeb, a broad spectrum dithiocarbamate fungicide used in Egypt, is one of the most frequently
utilized pesticides in homes, agricultural, and industrial settings worldwide. The main mechanism of MZ toxicity is induction of oxidative stress and production of reactive oxygen species. MZ can also lead to mitochondria dysfunction, apoptotic pathways activation and increase lipid peroxidation. It has been demonstrated that acute, long-term, and developmental dithiocarbamates pesticide exposure all cause oxidative stress, which is known to have a role in the pathogenesis of various diseases. So, we recommend increase awareness of farmers and workers towards the proper dealing and handling of such pesticide products. Attention to sanitary environmental work place is required to avoid take-home mechanism of toxicity. Widespread public education regarding the health hazards of dithiocarbamates pesticides is essential.

REFERENCES


health hazards. *Environmental Health Perspectives*, 103(6), 568-573.


**Pascale, A. and Laborde, A. (2020):** Impact of pesticide exposure in
childhood. Reviews on environmental health, 35(3), 221-227.


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بعض المخاطر السمية الصحية للمانكوزيب: بحث مقالي

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مبيدات الفطريات هي مبيدات حشرية تستخدم على وجه التحديد، في الزراعة، لحماية الفواكه والخضروات أثناء التخزين أو يتم تطبيقها مباشرة على نباتات الزينة والأشجار والمحاصيل الحقلية والحبوب والأعشاب. المانكوزيب، مبيد فطري واسع المجال يستخدم في مصر، هو واحد من أكثر المبيدات استخداما في التطبيقات المنزلية والزراعية والصناعية في جميع أنحاء العالم. الآلية الرئيسية لسمية المانكوزيب هي تحريض الإجهاد التأكسدي وإنتاج أنواع الأكسجين التفاعلي التي تؤدي إلى خلل في الmitoكوندريا، وتنشيط مسارات موت الخلايا المبرمج وزيادة بيروكسيد الدهون تتسبب في العديد من الأمراض، وقد تم وصفها في التعرض الحاد والمزمن لمبيدات الآفات ثنائية الكربامات. الغرض من هذا البحث المقالي هو جمع المعلومات عن المانكوزيب فيما يتعلق بالتركيب الكيميائي والمصير البيئي وأليات السمية وبعض المخاطر الصحية المحتملة للمانكوزيب. لذلك، من أهم التوصيات اخذ الاحتياطات اللازمة للمزارعين والعمال عند التعامل مع مبيدات الآفات أو على الأقل استخدام أبسط التدابير الصحية والوقائية لضمان الاستثمار السليم، والاهتمام يمكن العمل البيئي لتجنب نقل السمية المنزلية للمبيد، والتنفيذ العام على نطاق واسع فيما يتعلق بالمخاطر الصحية لمبيدات الآفات ثنائية الكربامات.