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Systemic effects of the pesticide mancozeb – A literature review

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Abstract. – OBJECTIVE: The purpose of this literature review is to document what has already been scientifically published about the pesticide Mancozeb and its potential systemic complications.

MATERIALS AND METHODS: Data were collected during the months of July, August and September 2020, from the Medline and PubMed databases, in the Portuguese, English and Spanish, covering articles written in the last 20 years. Twenty-one studies were selected for analysis.

RESULTS: The results found in this review study, indicate that Mancozeb is potentially damaging to health, appearing as an increase in ethylethiourea (ETU) dosages in most studies.

CONCLUSIONS: About the widespread use of Mancozeb, the studies found show that this fungicide is a potential cause of several health problems, mainly hepatic, renal and genotoxic, demonstrating with an increase in ETU dosages, as well as liver enzymes in most studies, corroborating the idea that the deliberate use of the product can induce potential systemic complications, and is a public health problem.

Key Words:
Mancozeb, Systemic damage, Toxicity, Chronic exposure.

Introduction

Agribusiness in Brazil represents 22% of the country's total Gross Domestic Product (GDP). The jobs created by this sector correspond to 32% of those currently existing, and the sector corresponds to 44% of the total value of Brazilian exports[1]. Brazil consumes about 20% of all agricultural pesticides sold worldwide, and this consumption has increased very significantly in recent years[2]. In the last decade, the pesticide market in the country grew by 190%, which placed it first in the world ranking of consumption since 2008, and the south region accounts for approximately 30% of this consumption[3].

The intensive and progressive use of several classes of agricultural inputs in farming has raised a number of concerns about their adverse effects and consequences in humans, animals and on the environment[4].

According to World Bank data, every year 355,000 people die of involuntary poisoning by pesticides[5]. As informed by the International Labor Organization (ILO) and the World Health Organization (WHO), approximately 70 thousand workers in developing countries die from acute and chronic poisoning by pesticides and another 7 million develop a non-fatal disease. Although pesticide poisonings are reported as events that must be compulsorily notified, estimates showed that only 20% of the cases are in fact recorded[6]. This is a major reason of concern, especially for the epidemiological sector; with a great amount of hidden information, we shall never know the reality faced by our country and cannot avoid what will become a public health problem.

Pesticides were developed aiming to avoid the invasion of crops by pests and to protect public health[7]. Outstanding among the most used classes of pesticides are the fungicides which are which are much used to prevent or eradicate fungal infections in plants or seeds.

Byproducts of carbamic acid, including the Ethylenebisdithiocarbamates (EBDCs), are fungicides that have been widely used around the

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world since the 1940s[8,9]. Among the EBDCs, are: Mancozeb, Maneb, Zineb and Methyran[10,11]. These compounds are organic salts of manganese, zinc or zinc and sodium, insoluble in water and in organic solvents, unstable in alkaline or acid medium in the presence of oxygen, and also in biological systems[12,13]. In Brazil, Mancozeb appears among the 10 most sold active ingredients[2].

Mancozeb, according to literature, is classified as a low toxicity product, however it proved to have adverse effects on humans[14] and in different animal models[15,16]. The metabolic decomposition of EBDCs results in the formation of carbon disulfide, ethylethiourea (ETU), manganese and zinc, and biological monitoring has shown to be an important tool to evaluate exposure to these pesticides[17,18].

The experimental and epidemiological evidence of the main adverse effects resulting from exposure to pesticides played an important role in evaluating the EBDCs in experimental studies with these compounds[19].

The objective of this literature review is to document what has already been scientifically published on the pesticide Mancozeb and its potential systemic complications.

Materials and Methods

The present study was performed through a literature review on the use of Mancozeb. First the titles and abstracts of the publications found in the search were analyzed, the abstracts then have been selected and read in detail. Data were collected during the months of July, August and September 2020, in the Medline and PubMed electronic databases, in the Portuguese, English and Spanish languages. Four descriptors and their combinations in English were used for the search, as follows: Mancozeb; systemic damage; genotoxicity; monitoring (*mancozeb; systemic damage; genotoxicity; biological monitoring*).

The inclusion criteria adopted were publications whose topics were the discussion of the use of the pesticide Mancozeb in clinical and experimental studies between the years 2000 and 2020. Review articles and articles that were not available in full for reading were excluded. By listing the pre-selected articles, three researchers, independently, screened the studies that were in duplicate, excluded and potentially eligible for review, by reading the titles and abstracts.

Seventy articles were retrieved (PubMed: 33; Medline: 37) through electronic searches. Initially, 49 articles were excluded because they did not fit the inclusion criteria by reading the title and abstract or because they were duplicated in the databases. Thus, 21 studies were selected for full analysis of the article.

Results

In the present systematic integrative review, a total of 21 articles that met the previously established inclusion criteria were analyzed and an overview of the articles evaluated will be presented below.

The tables designed demonstrate the characteristics of the studies included in the integrated review, such as author, place where the research was performed, year of the study, sample, instruments used to evaluate it, and also the results of the studies performed. Table I shows the studies performed in humans. Table II covers the same data, but for studies performed in animals.

Discussion

Mancozeb and its Potential Systemic Damage

Several studies[20-22] analyzed the consequences of human exposure to Mancozeb. Colossio et al[20] investigated exposure to Mancozeb in 13 vineyard workers exposed and in 13 vineyard workers who have not been occupationally exposed (control group) to pesticides. The baseline results of the urinary ETU were lower than the analytic limit of detection for all controls (0.5 mg; g creatinine) and for ten workers, when the dosage determined was previous to exposure (range 0.5-3.4 mg/g creatinine). However, at the dosage determined at the end of the shift of vineyard workers exposed, urinary ETU significantly increased compared to the baseline levels. Urinary ETU at the final shift was positively correlated to the skin exposure to Mancozeb determined both on the vineyard workers' clothes and on their skin[20]. Another study performed by Colosio et al[21] defined the reference values for ETU in the population in northern Italy, and sought to identify the sources of exposure, selecting 95 healthy individuals (29 women and 66 men, living in north Italy, and not exposed occupationally to the

Table I. Studies on humans.

Characteristics of the studies used in the review Studies in humans					
Author (year)	**Country**	**No.**	**Group**	**Method**	**Results**
Fustinoni, 2008[17]	Italy	496 people	Control Group: 248 individuals not exposed to EBDCs Exposed Group 1: 55 greenhouse workers Exposed Group 2: 51 potato farmers; Exposed Group 3: 48 vineyard workers; Exposed Group 4: 42 flower growers; Exposed Group 5: 52 farmers who used Zineb	(Lab 1) High Performance Liquid Chromatogrpahy (HPLC) + UV detector; (Lab 2) Gas Chromatography + mass spectrometry	T0: Control Group: 1.3 ± 1.5 Exposed group: 1.8 ± 5.3 (between exp. from T0 and T30 p<0.001 T30: Control group: ~0.5 µg/g creatinine Exposed Group 1: 49.6 µg/g creatinine Exposed Group 2: 7.5 µg/g creatinine Exposed Group 3: 11.8 µg/g creatinine Exposed Group 4: 0.9 µg/g creatinine Exposed Group 5: 23 µg/g creatinine
Colosio, 2002[20]	Italy	26 winegrowers	Control Group: 13 not exposed vineyard workers Exposed Group: 13 exposed vineyard workers	HPLC	Control Group (Pre-exposure) < 0.5 µg/g creatinine Exposed group (Pre-exposure) 0.5 (0.5-3.4) µg/g creatinine (12% exposed) x Exposed Group (Post-exposure) 2.5 (0.5-95.1) µg/g creatinine (p=0.008)
Colosio, 2006[21]	Italy	95 healthy individuals	Individuals not exposed occupationally to the EBDCs	Gas Chromatography + Mass spectrometry	39 samples: ETU below the limit of detection (40% individuals) 56 samples: concentrations of ETU in the range from 0.5 to 11.6 µg / g of creatinine (60% individuals)
Colosio, 2007[22]	Italy	93 vineyard workers	Control Group: 45 individuals who had not been occupationally exposed to Mancozeb Exposed group: 48 vineyard workers exposed intermittently to Mancozeb	Gas chromatography + mass spectrometry	T0: Control Group: 1.3 ± 1.5 µg/g creatinine Exposed group: 1.8 ± 5.3 µg/g creatinine (among the exposed) of T0 and T30 p < 0.001) T30: Exposed Group: 14.9 ± 13 µg/g creatinine
Corsini, 2005[23]	Italy	26 vineyard workers	Control Group: 13 Exposed Group: 13	HPLC	Exposed group (Pre-exposure): < 0.5 µg/g creatinine Exposed group (post-exposure): 2.5 (p = 0.008) Control Group: < 0.5 (p = 0.001)
Mandic-Rajcevic, 2019 24	Italy	48 vineyard workers were exposed		UPLC	Pre-exposure: 0.93 (open tractor) and 0.51 (closed and filtered tractor) Post-exposure: 3.02 (open tractor) and 2.06 (closed and filtered tractor)
Jones, 2010[26]	United Kingdom	361[1] people	Population in general	Gas chromatography + mass spectrometry	Value ranged between below to the limit of detection: 54% of the samples to a maximum of 15.8 µmol/mol creatinine (14.3 µg/g creatinine). Percentile 95 was 5.7 µmol/mol creatinine (5.2 µg/g creatinine).
Raherison, 2019[25]	França	96 indivíduals	Students from a rural area where there are vineyards	Gas chromatography + mass spectrometry	Pre exposure: 4.4 µg/g creatinine Post exposure: 12.4 µg/g creatinine

[1]ETU: ethylenethiourea.

Table II. Studies on animals.

Characteristics of the studies used in the review Studies on animals					
Author (year)	**Country**	**No.**	**Group**	**Method**	**Results**
Yahia, 2015[29]	Algeria	24 male Wistar rats	Exposure: 8 weeks Control Group Group 1: 500 mg/kg/day Group 2: 1000 mg/kg/day		Statistical Data Regarding The Control Group[2] Group 1: Increased Urea (p<0.01), creatinine (p<0.05), WBC (p<0.05), AST (p<0.05), ALT (p<0.001), AP (p<0.001) and TB. Reduction of RBC, Hb, HCT (p<0.001) Group 2: Increased Urea (p<0.01), creatinine (p<0.01), WBC (p<0.01), AST (p<0.05) ALT (p<0.001) AP (p<0.001) TB Reduction of Proteins and lipids (p<0.001), WBC, Hb, HCT (p<0.001)
Yahia, 2014[9]	Algeria	8 adult rats	Exposure: 4 weeks Control group Group 1: 800 mg/kg/day Group 2: 1200 mg/kg/day		Statistical Data Regarding The Control Group[3] Group 1: Increased liver weight (p<0.05), AP, ALT (p<0.05), AST (p<0.05), Reduction of GSH (p<0.05) Group 2: Increased liver weight (p<0.05), AP (p<0.05), ALT (p<0.05), AST (p<0.05), Reduction of GSH (p<0.05)
Atamaniuk, 2013[30]	Ukraine		Fish Control Group Group 0.9 mg/L^{-1} Group 1.5 mg/L^{-1} Group 3 mg/L^{-1}		Increased SOD[4] 70-79%; catalase 23-52% and GPx 49% Carbonylated proteins: 92- 125% increase (1.31 ± 0.24 nmol mg^{-1})
Ahmed, 2017[28]	Saudi Arabia	30 healthy adult male albino rats	Exposure: 4 weeks Control group Group 1: 250 mg/Kg/day Group 2: 500 mg/Kg/day		Increased AST[5], albumin, acetylcholinesterase, TC, HDL and LDL, mean corpuscular volume and mean corpuscular hemoglobin. Increased weight of the liver, kidney, brain and testicles. Reduction of blood nitrogen urea, creatinine and triglycerides. Reduction of count of erythrocytes, leukocytes and total weight of the animal.
Goldoni, 2014[31]	Brazil	20 adults male Wistar rats	Control Group: 0.9% NaCl (n = 10) Exposed Group: 40 mg/Kg (n = 10)	MO cells for micronuclei	% of MN[6] Control Group: 3.2 ± 0.7 Exposed Group: 7.2 ± 1.1 (p=0.004)
Pirozzi, 2016[27]	Italy	HepG2 cell line	Exposure: 24 hrs (0.1; 1; 10; 100; 500 ppm) Exposure 48 hrs (1; 10; 100)		Reduction of cell viability by 50% [1-100 ppm] MTT test: death of all cells [100 ppm] (48h) Increased nr. of fat droplets [0.1- 100 ppm] x treatment with isolated fatty acid

[2]White blood cells; ALT: alanine aminotransferase; AP: alkaline phosphatase; TB: total bilirubins. RBC: red blood cells; Hb: hemoglobin; HCT: hematocrit. [3]AP: alkaline phosphatase; GSH: hepatic glutathione. [4]SOD: superoxide dismutase; GPx: glutathione peroxidase. [5]AST: aspartate aminotransferase; CT: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein. [6]MN: micronuclei.

EBDCs) for the study. Thirty-nine individuals presented urinary concentrations of ETU lower than the limit of detection (40% individual) and 56 samples with concentrations of ETU in the range from 0.5 to 11.6 μg/g of creatinine (60% individuals)[21]. Finally, for the purpose of investigating the effects on health induced by exposure to the fungicide Mancozeb in workers in Italian vineyards, 93 Italian individuals were included in the study by Colosio et al[22]: 48 vineyard workers exposed intermittently to Mancozeb and 45 healthy controls. They were assessed by means of gas chromatography and mass spectrometry in 3 steps. In all, the differences between the exposed individuals and the controls were not consistently correlated to any clinical involvement and suggest that the seasonal application of Mancozeb does not represent a significant risk to the health of individuals exposed[22].

On the other hand, data available in the literature suggest that the EBDCs may have immunomodulating effects. Corsini et al[23] aimed to investigate the immunological profile of vineyard workers exposed to Mancozeb. The authors suggested that exposure to low levels of Mancozeb has mild immunomodulating effects and points to the quantification of ETU as an adequate method to reveal immunological modifications in workers exposed occupationally to potentially immunotoxic compounds.

Mandic-Rajcevic et al[24] aimed to estimate the dose of Mancozeb absorbed by the workers who applied pesticide in one workday, considering the real duration of the exposure. In a series of field studies in 29 workers who applied Mancozeb to vineyards for 38 workdays, three sets of data were collected: information about work activities for each workday, exposure of the skin and ETU excretion in the pre-exposure and 24-hour post exposure urine samples. Although more than 90% of the estimated total dose absorbed comes from the hands, the estimated bodily dose, considering the two approaches, was still better correlated with the levels of ETU in 24-hour urine after exposure than the dose on the skin itself. A precise estimate of the dose absorbed, performed considering the real duration of exposure, results in a higher correlation with an occupational exposure biomarker, like ETU in urine, or at least produces more precise results. This may make it easier to interpret the biological monitoring data in agricultural workers exposed to pesticides, despite the absence of biological exposure limits. The ETU must be assessed as a potentially relevant source of exposure, due to the degradation of the EBDCs in the product formulated or in the spray mixture[24].

The study by Fustinoni et al[17] deals with the profile of exposure to pesticides in some European countries, specifically focusing on EBDCs. In all, 55 Bulgarian workers in greenhouses, 51 Finnish workers on potato farms, 48 Italian vineyard workers, 42 Dutch flower farm workers and 52 Bulgarians who used Zineb (fungicide) participated in the study. Each group was compared to a group of individuals who had not been occupationally exposed. The exposure data were obtained through self-applied questionnaires and from ETU dosage in two samples of local urine collected, respectively, before the beginning of seasonal exposure and after 30 days, at the end of the period of exposure. The controls were submitted to a similar protocol. The use of individual protection devices was varied and took into account the aerial and dermal penetration routes. It was found that the exposure to EBDC, assessed by urinary ETU after 30 days, followed this order: greenhouse workers, farmers who used Zineb, vineyard workers, potato farmers, flower farmers with mean levels of 49.6; 23.0; 11.8; 7.5 and 0.9 μg/g of creatinine; the last group with ETU at the same level of control (~0.5 μg/g of creatinine). Among the agricultural workers, the application of pesticides, especially using manual equipment, appears to be the main determinant factor of the internal dose. Although the analysis of the self-applied questionnaires presented problems, mainly related to the lack and/or low quality of the data reported, biological monitoring confirms that it is a powerful tool to evaluate exposure to pesticides.

Raherison et al[25], in their study, aimed at analyzing the association between the exposure to pesticides in the air, asthma and rhinitis in children. In a rural area, 281 children (3 to 10 years) were invited to participate in this study for two periods: winter, with low levels of pesticides in the air, and summer, when the fields are often treated with pesticides. Exposure to pesticides was assessed measuring 56 pesticides in the environmental air. The main pesticides detected were fungicides (89.3%; mainly folpet and dithiocarbamates) and insecticides (10.7%). No association was found between the score of symptoms and the pesticides in the outside air during summer, when pesticides were applied to the vineyards. Nevertheless, an association was found between the urinary concentration of ETU (> 0.974 μg/g of creatinine) and the symptoms of asthma and rhinitis (OR = 3.56; CI 95% 1.04-12.12). Thus, children who live in rural areas where vineyards are cultivated, run a greater risk of exposure to dithiocarbamate in the air during the summer period. Despite the limited size of the sample, the results suggest possible connections between a few measures of pesticides and allergy symptoms, such as rhinitis.

Another sensitive analytic method studied by Jones et al[26], was adapted to perform a quantitative analysis of ETU in urine and its application to samples of the population at large. The quantification was obtained by liquid chromatography – mass spectrometry using chemical ionization of positive ions in atmospheric pressure. The method was applied to monitor the ETU levels in urine samples of the general population in the United Kingdom. The results obtained in 361 samples contained ETU levels that varied from below the limit of detection (54% of the samples) to a maximum of 15.8 μmol/mol of creatinine (14.3 μg/g of creatinine). Percentile 95 was 5.7 μmol/mol of creatinine (5.2 μg/g of creatinine). The limits of detection and the variability are comparable to other recently reported methods, but the preparation of the sample is less expensive.

Pirozzi et al[27], in their *in vitro* study of a cell culture of HepG2, reported that Mancozeb has deleterious effects on human health and on the environment. Indeed, its massive use raised the issue of possible risks to the health of farming communities; the molecule can also reach human cells through the food chain and alter the metabolism, endocrine activity and cell survival. In particular, Mancozeb induces many toxic effects on the metabolism of the liver cells. For this reason, its effect on *in vitro* liver lesions was investigated by the incubation of hepatocytes. It was found that the liver toxicity of the fungicide exacerbated the steatosis induced by fatty acids, manifested by an increase in the intracellular accumulation of lipid droplets. Furthermore, Mancozeb altered the cell metabolism and induced cell death through the positive regulation of lactate dehydrogenase and cytochrome c, respectively, in ways that depend on the dose. Therefore, Mancozeb can play an important role in the pathogenesis and progression of chronic diseases in humans and at high doses is dangerous to human health.

Ahmed et al[28] analyzed the effects of Mancozeb on the hematological parameters and biochemical indices related to kidney and liver functions. Mancozeb was administered orally by catheter at the doses of 250 mg/kg and 500 mg/kg of body weight/day in male albino rats for 30 days. Treatment with pesticides induced biochemical, hematological and clinical alterations. These alterations include a significant reduction of the total count of erythrocytes, total count of leukocytes and significant elevation in the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Furthermore, these findings showed that Mancozeb had an effect on the clinical and biochemical parameters of male albino rats through elevation of the plasma aspartate aminotransferase, alkaline phosphatase, acetylcholinesterase activity, albumin and total lipids. On the other hand, the urea concentrations in blood, creatinine and triglycerides diminished. Besides, the investigation observed an increase in the weight of the liver, kidney, brain and testicles, but the weight of the heart of the intoxicated rats diminished. The importance of this compound and the number of people potentially exposed must be considered globally. Other studies also indicated that there were hepatotoxic[9] and renal[29] effects of Mancozeb in rats, and therefore an environmental risk to the health of living organisms can be evidenced based on the use of this substance.

Considering the effects of exposure of fish to different dosages of Mancozeb (0.9; 1.5 and 3 mg), Atamaniuk et al[30] evaluated the levels of oxidative stress markers, and in the system of antioxidants of the brain, liver and kidney of goldfish (*Carassius auratus*). The results showed collectively that the exposure of this species to fungicide led to the development of mild oxidative stress and the activation of antioxidant defense systems in its tissue[30].

Goldoni et al[31] investigated the genotoxic potential of Mancozeb using the micronuclei test on the bone marrow and a total blood assay of Wistar rats treated with a solution of Mancozeb at a concentration of 40 mg/kg/day, administered intraperitoneally for 18 days consecutively and compared to a control group. The results indicate that Mancozeb induced significantly higher damage to the DNA, as detected by the blood test and increased the frequency of the micronuclei. The results showed that Mancozeb is genotoxic and may adversely affect the integrity of the DNA of organisms exposed.

Intranuovo et al[32] evaluated the predictive power of the comet assay in the context of occupational exposure to pesticides. The subjects recruited completed a structured questionnaire and a blood sample was collected to measure exposure to the pesticide. Approximately, 50 images were analyzed for each sample by fluorescence microscopy and the extent of the damage to the DNA was estimated. A significant relation was observed between the DNA damage and the exposure score. The sensibility of the comet test was low (41%), the specificity (89%) and the positive predictive value (0.77) were considered acceptable. The validation of the comet test to monitor oncological diseases may be useful for future studies and should be considered in planning large multicenter studies with a large sample, several exposure routes and the analytic consideration of confounding factors.

Conclusions

About the widespread use of Mancozeb, through the studies found, it can be evidenced that this fungicide is a potential cause of several health problems, mainly hepatic, renal and genotoxic, demonstrating an increase in ETU dosages, as well as liver enzymes in most studies, corroborating the idea that the deliberate use of the product can induce potential systemic complications, becoming a public health problem.

Thus, we suggest the use of PPEs (personal protection equipment) for the handling of the fungicide, since most studies have shown that the greatest form of contamination is dermal contact, as well as providing guidance on possible damage to farmers in order to minimize risks.

We therefore conclude that that many data on the subject of the effects of Mancozeb were inferred but not sufficiently studied since we found few available bases in the literature, and it is essential to perform further research on the subject.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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