Cardiovascular effects of occupational exposure to pesticides

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Abstract

Agricultural workers are frequently exposed to pesticides, which can affect the cardiovascular system. The aim of the research was to review the association between occupational exposure to pesticides, the development of cardiovascular disease, and biomarkers used in the surveillance of workers' health. For this purpose, a non-systematic review of the literature was performed in three databases: PubMed, Embase and Scopus, with search equations elaborated with the terms "agrochemicals", "myocardial infarction", "occupational exposure" and "farmers", and included articles published between 2007 and 2022. It was found that pesticides cause elevated blood pressure in exposed workers and in pregnant women it is related to gestational hypertension and preeclampsia. Regarding acute myocardial infarction (AMI), contact with the pesticides chlorpyrifos, coumaphos, carbofuran, pendimethalin, trifluralin and acylalanine increase the risk of AMI in women, and among male workers exposure to ethylene dibromide, maneb/mancozeb and zinc dimethyl-dithiocarbamate was associated with higher mortality. Epidemiological surveillance is mainly performed by measuring erythrocyte acetylcholinesterase (AChE) activity. It can be concluded that pesticide exposure can trigger acute and chronic cardiovascular diseases, such as elevated blood pressure, fatal and non-fatal AMI. The pesticides dimethyl zinc dithiocarbamate, chlorpyrifos, coumaphos, carbofuran, pa-

rathion and malathion are the substances that have the strongest association with the development of cardiovascular disease.

Keywords: pesticide, cardiovascular diseases, myocardial Infarction, occupational exposure, occupational medicine

Resumen

Los trabajadores agrícolas se exponen frecuentemente a los pesticidas, los cuales pueden afectar el sistema cardiovascular. El objetivo de la investigación fue revisar la asociación entre la exposición ocupacional a pesticidas, el desarrollo de enfermedades cardiovasculares y los biomarcadores utilizados en la vigilancia de la salud de los trabajadores. Para ello se realizó una revisión no sistemática de la literatura en tres bases de datos: Pubmed, Embase y Scopus, con ecuaciones de búsqueda elaboradas con los términos "agrochemicals", "myocardial infarction", "occupational exposure" y "farmers", y se incluyeron artículos publicados entre 2007 y 2022. Se encontró que los pesticidas causan elevación de las cifras de presión arterial en trabajadores expuestos y en mujeres embarazadas se relaciona con hipertensión gestacional y preeclampsia. Respecto al infarto agudo de miocardio (IAM), el contacto con los pesticidas clorpirifós, coumafós, carbofurano, pendimetalina, trifluralina y acilalanina aumentan el riesgo de IAM en mujeres, y entre los trabajadores masculinos la exposición a dibromuro de etileno, maneb/mancozeb y dimetil-ditiocarbamato de zinc se asoció con mayor mortalidad. La vigilancia epidemiológica se realiza principalmente con la medición de la actividad de la acetilcolinesterasa eritrocitaria (AChE). Se puede concluir que la exposición a pesticidas puede desencadenar enfermedades cardiovasculares agudas y crónicas, como elevación de las cifras de presión arterial, IAM fatal y no fatal. Los pesticidas dimetil ditiocarbamato de zinc, clorpirifós, coumafós, carbofurano, paratión y malatión son las sustancias que tienen mayor relación con el desarrollo de enfermedad cardiovascular.

Palabras clave: pesticida, enfermedades cardiovasculares, infarto de miocardio, exposición ocupacional, medicina ocupacional.

Introduction

Agriculture is a fundamental activity for human development; during the last decades it has been required to improve its productivity exponentially to meet the food demands of the world population (1, 2). Currently, one of the strategies used to guarantee the viability of crops has been the application of pesticides, which are used in large quantities. According to reports from the Food and Agriculture Organization of the United Nations (FAO)

during 2019 in Chile 9,831 tons of agrochemicals were used, in Ecuador 34,081 tons and Colombia used 69,862 tons of these substances to meet market demands for potato, corn and coffee crops, among others (3).

Pesticides are any substance or mixture of substances intended to prevent, destroy, repel or mitigate any pest (2). Within this group of substances are organochlorines (OC), organophosphates (OF), carbamates (CAR), pyrethroids, neonicotinoids and bipyridines (2). Pesticides have multiple health effects, act as endocrine disruptors, and have been linked to conditions such as infertility, spontaneous abortion, fetal death, premature delivery, intrauterine growth restriction, congenital anomalies, hypothyroidism, and diabetes (4). The relationship between exposure to pesticides and oncological pathologies, neurological and immune system disorders, and alterations in the cardiovascular system is also recognized (5).

Cardiovascular diseases are the leading cause of death worldwide and in 2019 heart disease accounted for almost nine million deaths (6). Research has demonstrated the multifactorial nature in the etiology of cardiovascular disease, but the influence of certain environmental pollutants and occupational risk factors in the development of these diseases has been documented (4,7). Some highly prevalent cardiovascular pathologies such as arterial hypertension (AHT), acute myocardial infarction (AMI), and heart failure (HF) have been associated with exposure to pesticides (8).

OCs are compounds of synthetic origin that present substitution of hydrogen atoms by chlorine (9); some examples of these substances are dichloro diphenyl trichloroethane (DDT), aldrin, and endrin (10). This group of substances affect transmembrane ionic flux, which sensitizes the myocardium and can generate arrhythmias (11). On the other hand, OCs bind easily to lipoproteins, increase oxidative stress and fibrinogen, which can cause direct endothelial injury (12,13), with cardiovascular effects such as ST-segment elevation and AMI, prolongation of the QT interval, peripheral arterial disease and stroke (4,14).

OF inhibit the enzyme acetylcholinesterase (ACh), which increases available acetylcholine and overstimulates tissue muscarinic and nicotinic receptors, affecting cardiac muscle function (15). CARs are compounds from carbamic acid and n-methylcarbamate, also affecting ACh by carboxylation (16), causing nicotinic and muscarinic symptoms (agitation, tachycardia, urinary retention, mydriasis, hallucinations, fasciculations, sialorrhea, hypotension and sphincter relaxation) (17), and can trigger increased postganglionic

parasympathetic activity which affects the sinus node and atrioventricular conduction, leading to bradyarrhythmia and ventricular arrhythmias (18). Neonicotinoids act selectively on nicotinic receptors (19), causing fatigue, paresthesia and muscle weakness. Imidacloprid causes tachycardia and dizziness, and acetamiprid causes emesis, muscle weakness, hypothermia, tachycardia, hypotension and convulsions (20). The pesticide paraquat is the major representative of the bipyridyl and can cause multiple organ dysfunction syndrome with ingestion of high doses, leading to death in less than 24 hours due to hepatic and cardiac involvement (21).

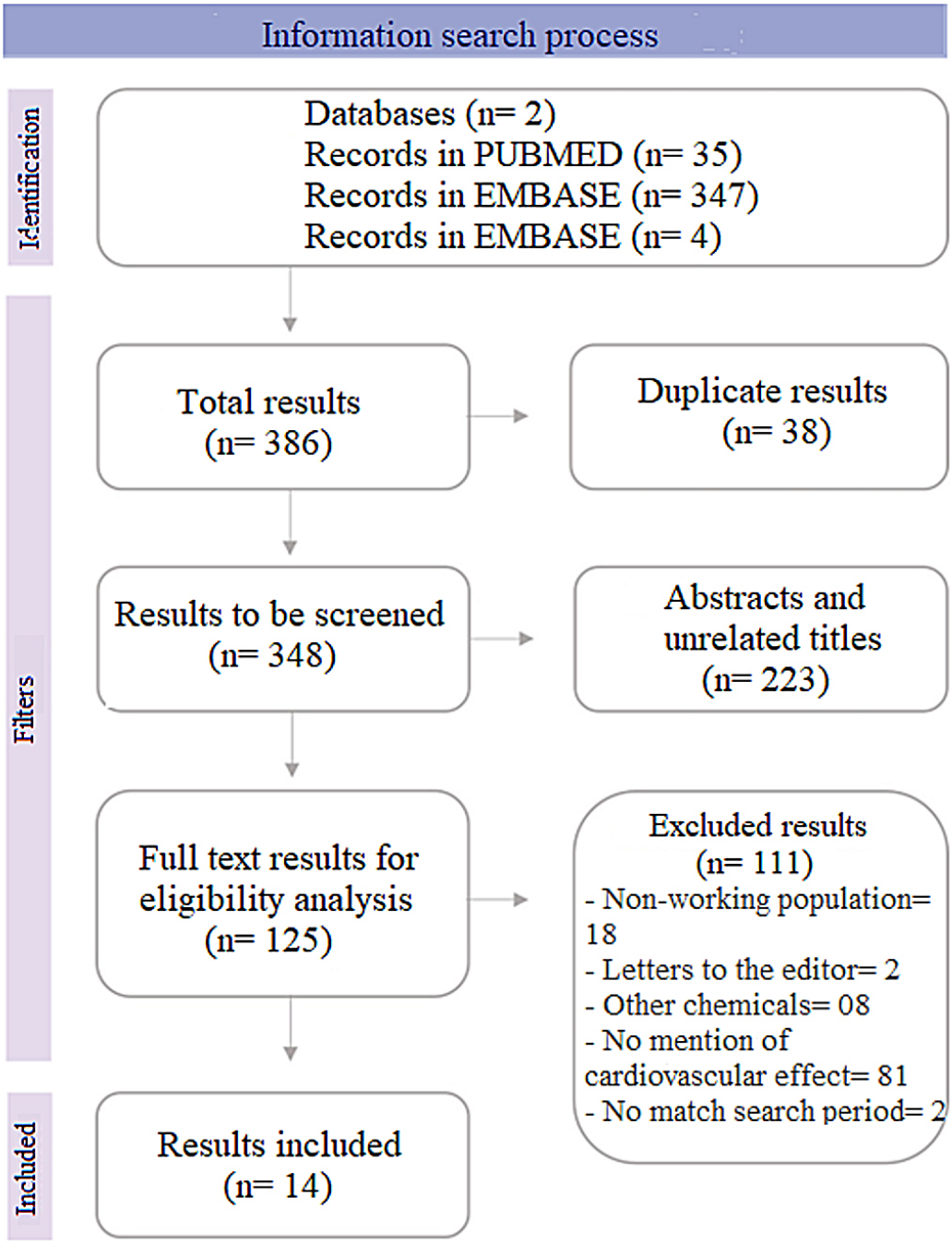
It is estimated that one third of the workforce worldwide corresponds to workers in the agricultural sector (22), but unsafe practices in this sector are frequent and exposure of workers can occur via the respiratory, digestive or cutaneous routes during the work process in the phases of handling, transport, mixing, application and cleaning of equipment (23). For this reason, it is necessary that workers exposed to agrochemicals are trained in their handling, have the appropriate personal protective equipment (PPE) and perform adequate risk management to reduce acute and chronic adverse effects on human health. Based on the above context, the main objective of this review is to know the cardiovascular effects of occupational exposure to pesticides and the biomarkers used in occupational medical surveillance of workers.

Methodology

A literature review was performed in three databases: PubMed, Embase and Scopus. The following types of studies were included: clinical trials, meta-analyses, cohort studies, cut-off studies, ecological studies and review articles published in the last 15 years (2007-2022). The exclusion criteria considered were: i) population not occupationally exposed; ii) articles related to chemicals other than pesticides, and iii) results not related to cardiovascular effects. The search equations were: agrochemicals OR organophosphates OR organochlorines AND “myocardial infarction” OR “coronary syndrome” OR “heart attack” AND “occupational exposure” OR “farmers”, agrochemicals AND “myocardial infarction” AND “occupational exposure”, agrochemicals OR organophosphates OR “hydrocarbons, chlorinated” OR pesticides AND ‘myocardial infarction’ OR ‘acute coronary syndrome’ OR ‘myocardial ischemia’ AND ‘occupational exposure’ OR ‘farmers’ and agrochemicals OR pesticides AND ‘myocardial infarction’ OR ‘myocardial ischemia’ OR ‘acute coronary syndrome’ AND ‘occupational exposure’.

The search produced 386 results, the Rayyan platform was used to eliminate duplicates, and the selection of articles was done by reading titles and abstracts. The articles were evaluated independently by the researchers to define their inclusion or not in the review, and when there were discrepancies in the selection, it was settled by a third researcher. Finally, 14 articles were included for the preparation of the article: cohort studies (5 articles), reviews (3), case reports (2), case-control studies (2) and cross-sectional studies (2) (Figure 1).

Figure 1. Information search process



Results

The deleterious effects of occupational exposure to pesticides on the cardiovascular system are diverse; the most important findings of the literature review are listed below. The study by Samsuddin et al. (24) found that workers exposed to pesticides had an increase in blood pressure (BP) of 7 mmHg for diastolic BP and 5 mmHg for systolic BP, and that contact with at least one pesticide during the workday increased the risk of AMI (Odds Ratio [OR] 1.6; 95% Confidence Interval [CI] 1.1-2.4). In this regard, the systematic review by Zago et al. (4), which included 24 scientific articles published in Europe, Asia, and America, concluded that the pesticides primaphos, fenitrothion, malathion, and deltamethrin are associated with elevated blood pressure in exposed workers. In addition, they found that pregnant women with occupational exposure to pesticides had an increased risk of gestational hypertension (OR 1.60; 95% CI 1.05-2.45) and preeclampsia (OR 2.07; 95% CI 1.34-3.21) in the first trimester of pregnancy.

The review conducted by Sekhotha et al. (25) found that there is greater symptomatology and fatal and non-fatal cardiovascular outcomes in agricultural workers, which is usually related to a longer time working in crops and to continuous exposure to pesticides. In this review, some of the pesticides related to the development of cardiovascular pathologies were dimethyl dithiocarbamate zinc, DDT, chlorpyrifos, coumaphos, and carbofuran.

Several studies have documented the relationship between AMI and pesticides. Dayton et al. (26) found 168 nonfatal AMI diagnoses in a population of more than 22,000 women who lived or worked in the field, and the research results showed increased risk of AMI with exposure to six specific pesticides: chlorpyrifos (OR 2.10; 95% CI 1.2-3.7), coumaphos (OR 3.2; 95% CI 1.5-7.0), carbofuran (OR 2.5; 95% CI 1.3-5.0), pendimethalin (OR 2.5; 95% CI 1.2-4.9), trifluralin (OR 1.8; 95% CI 1.0-3.1), and acylalanine (OR 2.4; 95% CI 1.1-5.3). Mills et al. (27), in an investigation of the Agricultural Health Study, consolidated data from more than 54 thousand men in agricultural work and found 476 deaths due to AMI and 839 non-fatal AMI in the average follow-up at 11.8 years and 5 years, respectively. The researchers note that exposure to ethylene dibromide (hazard ratio (HR) 1.54; 95% CI 1.05-2.27), maneb/mancozeb (HR 1.34; 95% CI 1.01-1.78), and zinc dimethyl dithiocarbamate (HR 2.40; 95% CI 1.49- 3.86) was associated with increased AMI mortality.

Kiyidoor et al. (28) reported the case of an agricultural worker who developed fatal AMI on the seventh day after consumption of parathion and other OF mixtures. In the literature review, the researchers found other cases of AMI and elevation of cardiac biomarkers in men and women following contact with CAR and OF. Likewise, Karasu-Minareci et al. (29) reported the case of a Turkish female farmer with no comorbidities and a history of exposure to OF and cigarette smoke who presented with non-fatal AMI. For their part, Svitlyk et al. (30) in a study of 113 workers with coronary artery disease and exposure to chemicals such as pesticides, found increased incidence of complications such as acute left ventricular aneurysm ($p = 0.0023$), thrombi in the left ventricular cavity ($r = 0.0277$), recurrence of AMI ($r = 0.0435$) and life-threatening ventricular arrhythmias ($p = 0.0116$).

It is important to mention that there are factors that increase the exposure of workers to agrochemicals. According to Olowogbon et al. (31) some factors that increase exposure to pesticides are the use of chemicals without labels (OR 2.31), incorrect timing of spraying (OR 1.21), frequency of spraying (OR 1.06) and prolonged application of chemicals during the day (OR 1.10), which correspond to frequent unsafe practices in agricultural work that increase the contact of chemicals with workers. Researchers point out that part of the problems associated with the use of pesticides in developing countries are due to the lack of training on chemical hazards, lack of experience in handling the substances, lack of PPE or inadequate selection according to the type of climate, the absence of pest-free periods and the use of pesticides with higher toxicity levels, among others (31). In this sense, it is important to train farmers on the safe application of chemicals, the proper use of PPE and compliance with basic safety and personal hygiene measures.

Health surveillance of workers exposed to pesticides is performed using biomarkers that allow monitoring of exposure. Several studies have shown that routine monitoring of acetylcholinesterase levels allows early assessment of pesticide exposure and reduction of cholinesterase to levels below 50% is indicative of possible poisoning (32). Epidemiological surveillance guidelines recommend the measurement of erythrocyte acetylcholinesterase (AChE) and plasma acetylcholinesterase (AChP) activity for at least six days in a month, parameters that are effective in monitoring chronic poisoning (33). Oliveira Pasiani et al. (34), in a study with Brazilian agricultural workers preparing or applying OF and CAR, reported that AChE inhibition

was significantly higher during exposure periods than during non-exposure periods. These variations between serum AChE levels in the exposure and non-exposure periods are the same as those reported by Hernandez et al. (35) in a Spanish study of 207 workers in Almeria. These authors also reported statistically significant elevation of transaminases (AST and ALP) and arginase in the exposed group and indicate that the elevation occurred prior to neurological symptoms, so it could be used as an early indicator of exposure. In addition, research suggests that pesticides can induce changes in erythrocyte size and volume (33,36), so that inexpensive and simple studies such as hemogram can be used in the evaluation of exposure.

Conclusions

Pesticide exposure in agricultural workers is an occupational reality that will not change due to the dependence of the sector to ensure crop productivity. Pesticides have serious effects on human health and the cardiovascular system is a target of these chemicals due to biochemical and electrical alteration of cardiac muscle and vascular endothelial cells.

Occupational exposure to pesticides can trigger cardiovascular symptoms, alterations in blood pressure and cardiovascular events such as fatal and non-fatal AMI in exposed men and women. According to the research reviewed, the pesticides dimethyl zinc dithiocarbamate, chlorpyrifos, coumaphos, carbofuran, parathion and malathion are the substances most associated with acute and chronic cardiovascular pathologies.

Workers who come into contact with pesticides are at greater risk of developing cardiovascular pathologies, so it is essential to carry out adequate monitoring of their health with laboratory tests such as AChE, blood count and liver enzymes, and to improve exposure control strategies for all agrochemical substances present in the workplace.

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