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Occupational Exposure to Pesticides and the Occurrence of Mental Disorders: A Systematic Review of the Literature

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ABSTRACT

Pesticides use has allowed an increase in food productivity. However, harmful effects on human health have been reported, such as mental illness, especially in the rural population. In this context, the present work systematically reviewed the literature on the occurrence of depressive and anxiogenic disorders in farmers occupationally exposed to pesticides. The guidelines recommended by PRISMA were adopted, using the PICO strategy. The platforms used for the search were PUBMED, SCOPUS, and Google Scholar, with works published since 2002 to 2020. The inclusion criteria adopted considered cross-sectional and longitudinal studies, published only in English, whose investigation evaluated human exposure to pesticides and the occurrence of mental illness. After applying the inclusion filters, nine studies were selected. The combined studies reported that 5.681 farmers were occupationally exposed to pesticides. The main illnesses reported were depression and/or anxiety, accompanied by symptoms such as headaches, respiratory diseases, and mental fatigue. Despite the incidence of other factors such as cigarette use, lack of personal protective equipment, and socioeconomic components, occupational exposure to pesticides is directly associated with depression. It was also noted that the intensity, frequency, and duration of exposure if combined with the number of acute intoxications, potentiates the development of depressive conditions.

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Introduction

According to the Food and Agriculture Organization of the United Nations (FAO), Brazil ranked third as a consumer of pesticides globally, behind only China and the United States. However, when considering consumption per hectare, Brazil falls to 25th place, using about 0.28 kilograms of pesticides per ton of agricultural products. Observing a scale of the number of pesticides applied per cultivated area over the years, we observe an increase from 1 to 4.3 kg/hectare from 1991 to 2015, respectively [1]. In addition, it was found that this rise in the consumption in Brazil was higher than in the world, with values even higher than in the United States and some European countries [2].

The handling of this pesticides, when performed in partial or total absence of Personal Protective Equipment (PPE), leads to occupational exposure by rural workers, which is directly linked to the emergence of serious diseases that reflects public health problems [3]. In this specific population, the exposure in generally chronic and prolonged, with a high risk of contamination through the skin or respiratory system [4].

Thus, the World Health Organization (WHO) began to publish data regarding the possible negative impacts of pesticides on the health of occupationally exposed populations, including depression, anxiety, suicidal tendencies, Parkinson's disease, Alzheimer's, and cancer, among others PHUNG et al. [5].

It is known that the Central Nervous System (CNS) is a susceptible target for pesticide exposure. In this tissue, the organophosphates and carbamates may act through the inhibition of acetylcholinesterase on the synaptic cleft, inhibiting its degradation and keeping its action for a prolonged time. Thus, acetylcholinesterase (AChE) inhibition has been used as a marker of exposure to these substances. Its inhibition causes depression in neurological functions, resulting in the perception of physical pain, respiratory diseases, mental fatigue, and even episodes of serious illnesses such as anxiety and depression [6,7].

Furthermore, organophosphates can also affect calcium channels or block Gamma-Aminobutyric Acid (GABA). The neurotoxic effects of chronic exposure to pesticides can result in symptoms ranging from mild headaches to more severe clinical signs such as seizures and coma [1,8].

There is a growing increase in the number of cases of depression and anxiety worldwide; on the other hand, this significantly affects the relationship of these individuals with their work. According to WHO, depression is associated with poor performance at work, the second leading cause of absence from work, and the high economic impact of this disease is linked to lack of treatment [9].

Therefore, this literature review aimed to compile results published in the literature that correlates anxiety and depression in individuals occupationally exposed to pesticides.

Material and Methods

This study is a systematic review based on the PRISMA guidelines (Key Items for Reporting Systematic Reviews and Meta-analyses, MOHER et al.), which used the PICO strategy (Patients/participants, Interventions/exposure, Comparisons, Outcomes) involving the four components: Population to be studied (patient), level or type of exposure (intervention), comparison between exposure and non-exposure to pesticides (comparisons), the occurrence of depression and anxiety (primary outcome). Thus, we sought to study: People occupationally exposed to pesticides (P); Occupational exposure to pesticides (I); People not occupationally exposed to pesticides (C); occurrence of anxiety and depression (O).

Articles published between 2002 and 2022 were selected, given the low number of articles included in the other inclusion criteria. Furthermore, only studies in which the development of signs and symptoms of depression and anxiety were associated with occupational exposure to pesticides were included. The bibliographic survey was carried out in the PUBMED, SCOPUS, and Google Scholar databases using the descriptors pesticide, agrochemicals, human health, depression, and anxiety.

The inclusion criteria adopted considered cross-sectional and longitudinal studies, whose investigation between exposure to pesticides followed by contamination and the appearance of depressive and anxiogenic symptoms and clinical signs were present as results. The exclusion criteria applied were environmental studies, case reports, experimental work, short communications, investigations carried out with children, and manuscripts published in languages other than English. Thus, the flowchart of the sorted results is shown in Figure 1.

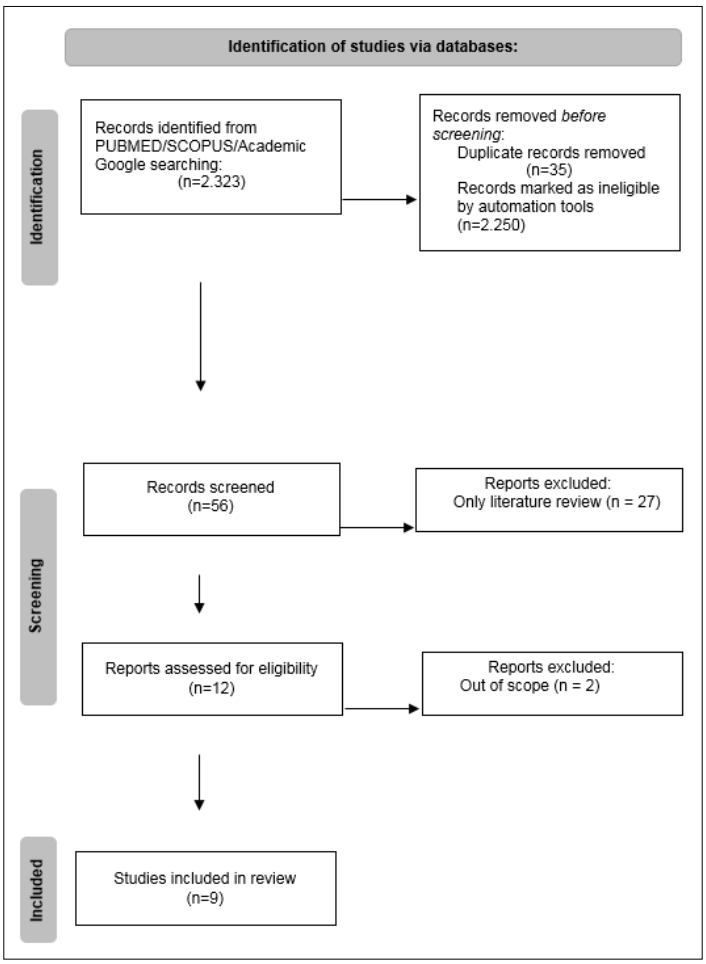

Figure 1: Criteria Used to Search the Databases based on the PRISMA and PICO Strategies

Furthermore, after reading the studies in full, studies that did not collect data through structured questionnaires and previously validated psychiatric scales were excluded. However, research carried out solely and exclusively through the collection of biological material, aimed at measuring toxicological biomarkers, book chapters and letters to the editor, allowed the exclusion of some more publications.

After applying the inclusion and exclusion criteria, eleven articles were selected, and are listed in Table 1.

Table 1: Studies Selected for the Literature Review according to the Selection Methods. The Works are Arranged in Chronological and Ascending Order on the Date of their Publication

Authors	Location	Title	Outcomes
Stallones & Beseler [12]	United States of America	Pesticide Poisoning and Depressive Symptoms among Farm Residents.	Exposure to pesticides in high concentrations was associated with depressive symptoms.
Beseler & Stallones [12]	United States of America	A Cohort Study of Pesticide Poisoning and Depression in Colorado Farms Residents.	Feeling uncomfortable and thinking that everything was an effort was associated with a history of pesticide poisoning, confirming the hypothesis that prolonged irritability may be due to pesticide poisoning.
Breard et al. [10]	United States of America	Pesticide exposure and self-reported incident depression among wives in the Agricultural Health Study.	Pesticide exposure is associated with an increased risk of depression and establishes that moderate levels of pesticide exposure experienced by farmers' wives are unlikely to increase the risk.
Weisskopf [11]	France	Pesticide exposure and depression among agricultural workers in France.	A risk rate for depression associated with the use of herbicides was observed in the occupationally exposed public.
Campos et al. [13]	Brazil	Exposure to pesticides and mental disorders in a rural population of Southern Brazil.	The results suggest that exposure to pesticides may be related to mental disorders.
Harrison & Ross [14]	United Kingdom	Anxiety and depression following cumulative low-level exposure to organophosphate pesticides.	Higher rates of anxiety and depression were observed in self-report questionnaires. As for confirmation of diagnosis, only anxiety was confirmed.
Koh et al. [15]	South Korea	Exposure to pesticide as a risk factor for depression: a population-based longitudinal study in Korea.	Exposure to pesticides in high concentration was associated with depressive symptoms among Korean adults.
Serrano-Medina et al. [18]	Mexico	Neuropsychiatric Disorders in Farmers Associated with Organophosphorus Pesticide Exposure in a Rural Village of Northwest México.	The results suggest a slight enzymatic inhibition, suggesting a diagnosis of major depression with suicidal attitudes, generalized anxiety, depression combined with anxiety.
Kori et al. [19]	India	Identification of markers of depression and neurotoxicity in pesticide exposed agriculture workers.	A significant increase in depressive symptoms was observed in workers exposed to pesticides compared to those not exposed.

Population

This work includes research involving populations whose occupational exposure to pesticides occurred directly or indirectly, whose exposed individuals developed depressive and anxiogenic symptoms.

The total population analyzed in this study was constituted by the sum of the number of individuals mentioned in the selected studies, and it encompasses 7.168 farmers, among which 5.681 were occupationally exposed to pesticides and 1.835 were not exposed.

Measurement of Exposure to Pesticides and Depression and Anxiety Symptoms

Occupational exposure to pesticides reported in the evaluated population occurred through direct handling of pesticides. The studies used questionnaires or validated scales to identify signs and symptoms of self-reported depression.

Results and Discussion

Searches carried out in the databases resulted in 2.323 articles. However, after applying the proposed inclusion and exclusion criteria, a total of 9 works were found, which are equivalent to 0.38% of the initial number. Reading the title allowed the exclusion of 2.261 manuscripts. Another 35 were also excluded because they were duplicated and, finally, the last 27 excluded presented only a literature review. Thus, Figure 2 shows the selection stages of the manuscripts.

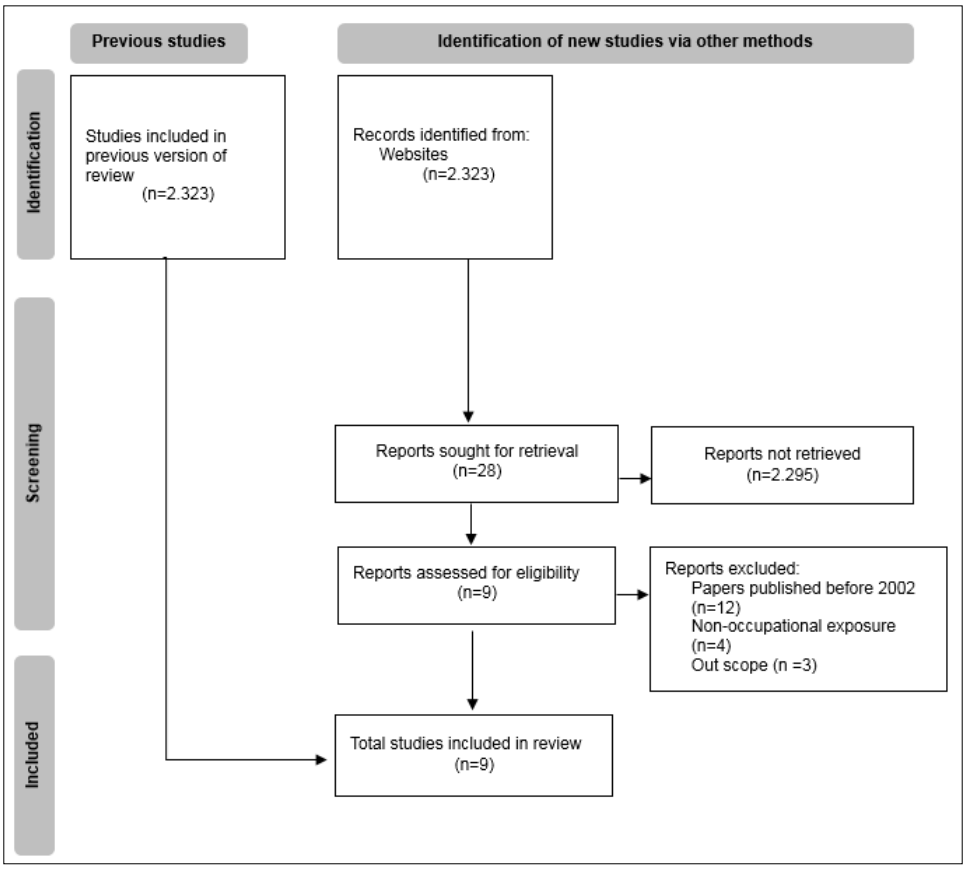

Figure 2: Article Selection Steps

In all cases, the type of exposure was assessed using questionnaires, and all publications had scores or self-reported signs and symptoms of anxiety and depression in the assessed individuals.

Among the selected articles, two assessed depressive signs and symptoms outside of scales standardized by the area of psychology and psychiatry. However, respondents in these two studies should answer whether they had already received a diagnosis of anxiety or depression from Mental Health professionals [10,11]. In this sense, the instruments Self Report Questionnaire (SRQ-20), Center for Epidemiologic Studies Depression Scale (CES-D), CDI-2 and MASC-2, Mini International Neuropsychiatric Interview Diagnostic Test (MINI), Beck-II Depression Inventory (BDI-II) and Hospital Anxiety and Depression Scale (HADS) were used in the 11 selected studies.

Beseler and Stallones evaluated residents of agricultural farms in the Colorado region, USA, between 1992 and 1997 and observed that prolonged exposure to pesticides was associated with intoxication and depressive symptoms. Although this prevalence rate of depressive symptoms is lower than those observed in the general population and other areas of agricultural cultivation at the time, chest pain, breathing difficulty, and eye and skin irritation had an increased odds ratio in the population exposed to pesticides. In addition, signs of irritability were associated with more significant contact with pesticides such as organophosphate in the exposed population [12]. Thus, we believe that the difficulty in establishing a direct relationship between mental disorders and the referred clinical signs results from the time interval between exposure and disease development, which would not be sufficient since synthetic organic agrochemicals appeared after 1980 and there is a need for an exposure interval of approximately 15 years for the development of the disease [13-15].

Breard et al. when prospectively evaluating wives of farmers in the state of North Carolina, USA, also noticed an association between the occurrence of pesticide poisoning and the subsequent development of depression [10,11]. Also, ILowa and North Carolina states had a lower prevalence of depression in the wives of farmers in their region when compared to national values. However, due to the importance of this disease in the female population involved in the agricultural sector, a follow-up study was carried out, in which 16.893 women between 1993 and 1997 did not have the disease according to the medical assessment at the time. Thus, from 2005 to 2010, the researchers contacted the telephone lines and applied a self-reported depression questionnaire, reaching the number of 1054 cases of depression in the studied population. A recent study with the rural population of South Korea had 2151 participants, among which 1230 were female. Still, the diagnostic tool for the disease was the Scale of the Epidemiological Center for Studies on Depression (CES-D) [16].

Although there were efforts to find some association between the class of pesticides and specific types used by both women and their husbands, it was not possible to determine whether any class or use of any particular product was associated with the onset of depression in the population of female farmers [11]. Thus, the authors concluded that exposure to high levels of agrochemicals increases the risk of depression in this population. Similar results are described by Koh et al. [16]. since the level of intensity of pesticides and the number of cases of acute poisoning in the rural population analyzed was strongly associated with depression. Therefore, we understand that occupational exposure to pesticides triggers the emergence of mental disorders, which

are favored by the intensity of exposure and the occurrence of intoxication. However, it should be noted that these two works only had women in their study population, which should not be synonymous of female farmers with a greater tendency to mental disorders development.

Another work carried out by Beseler and Stallones, published in 2008, evaluated approximately 617 farmers during the years 1993 and 1996, and concluded that prolonged exposure to pesticides contributes to the feeling of irritability of the individuals [12].

Weisskopf evaluated 567 farmers between during the years 1998 and 2000 in France and found that 14.6% of respondents reported hospitalization or the use of medication at home for the treatment of depression [13]. In addition, this work showed differences between genders (male and female) and the type of exposure (occupational or not) that individuals reported. Thus, women with depression had less exposure and intoxication by pesticides than depressed men. On the other hand, men who worked exposed to pesticides for a long time presented more depressive symptoms. The results of Campos et al. in a study in Rio Grande do Sul, Brazil, that evaluated 869 individuals directly or indirectly involved in tobacco growing, showed the occurrence of anxiety, mood, and somatization disorders possibly associated with tobacco cultivation [13]. The previous diagnosis of self-reported depression in this study was 21%.

Harrison and Ross, whose study was developed in the United Kingdom using self-report scales (BDI-II, BAI, and HADS), found higher anxiety levels in the population exposed to pesticides. Furthermore, Koh et al. in a study carried out in South Korea and using the CES-D scale, show a positive association between the use of pesticides for more than 20 years and the occurrence of depressive symptoms [16]. In addition, it found the highest incidence of intoxication in depressed individuals.

It is important to highlight that, in general, the cited studies resort to the most diverse scales of mental disorders evaluation, referring mainly to the occurrence of depressive and/or anxiogenic disorders in individuals exposed or not to the different types of pesticides. However, these measurement tools, performed through self-report, may not be as reliable in diagnosing depression and anxiety [17,18].

The works by Serrano-Medina et al. and Kori et al. present hematological, biochemical, and enzymatic activity markers of AChE in workers who had direct contact with pesticides [19,20]. The inhibition of this enzyme stands out in the control and development of mental disorders. In this case, due to AChE inhibition in the synaptic clefts and neuromuscular junctions, there is an increase in the concentration of acetylcholine, which, in turn, binds to muscarinic and nicotinic receptors. Therefore, there is an excess in the performance of the parasympathetic system, especially in exposure and intoxication by carbamates and organophosphates, since they are good examples of AChE inhibitors and are widely used in agricultural activity [17].

In the study of Serrano-Medina et al. carried out in California with rural workers exposed and not exposed to pesticides, it was evaluated the enzymatic activity of AChE, where inhibition of its activity was observed in 25% of farmers who met the requirements for significant depression with suicidal tendencies [19]. As for the percentages whose AChE activity was strongly inhibited, it was observed that 23.9% had generalized anxiety, 23.5% were considered to have combined depression and anxiety, and 22% were diagnosed with major depression and the absence of other psychiatric disorders.

Kori et al. demonstratet that chronic pesticide exposure in rural farmers in India caused a reduction in AChE activity, in addition to a decrease in the level of dopamine (DP) and its metabolite 3,4-dihydroxyindoleacetic acid (DOPAC), serotonin (5-HT) and norepinephrine (NE), besides an increase in MAO-A and MAO-B levels [20]. In this sense, such neurochemical changes are associated with mental disorders.

Measurement of erythrocyte AChE activity is a biomarker of both acute and prolonged exposure to pesticides, with a decrease in hemoglobin concentration being one of the common laboratory findings in the exposed population. In addition, it is thought that the duration and frequency of exposure are related to the AChE inhibitory mechanism, as a 25% reduction in this enzymatic activity represented an increase in neurological symptoms, followed by an increase in suicidal ideation, and the clinical manifestations of depressive disorders [19].

Furthermore, studies have shown that a decrease in the level of 5-HT (a precursor of serotonin) and its metabolites is associated with serotonergic impairment, which may lead to irritability, insomnia, the speech of appetite, memory loss, and also to depressive and anxiolytic conditions. In this sense, pesticide exposure decreases the expression of 5-HT receptors since occupationally exposed individuals have an increased risk of becoming ill with the diseases, as mentioned earlier [20].

Furthermore, DA participates in the regulation of emotional, cognitive, and other functions. Therefore, the high levels of MAO-A and MAO-B resulted in the breakdown of DA, NE, and 5-HT, leading to a reduction in their metabolites DOPAC and 5-HIAA. Such alterations were also verified by the study by Kori et al., given that the population exposed to agrochemicals had decreased levels of both such neurotransmitters and their metabolites [20].

Conclusion

The present study observed that high exposure to pesticides, particularly concerning the intensity and frequency of intoxications observed in both occupational and familial environments in rural populations, increased the risk of developing mental disorders compared to the non-exposed rural population. Likewise, greater signs and symptoms of depressive disorders were observed in cases of non-use or complete absence of Personal Protective Equipment (PPE). Depression, anxiety, and irritability are the most commonly associated psychological alterations in individuals exposed to pesticides, and the number of acute intoxications may favor the onset of these diseases. Therefore, it is necessary to consider viable alternatives in agricultural productivity whose effects are less harmful to health.

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