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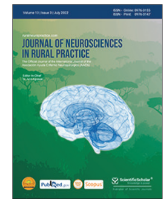

Systematic Review Article

Influence of pesticide exposure on farmers' cognition: A systematic review

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ABSTRACT

Objectives: Pesticide application has become necessary to increase crop productivity and reduce losses. However, the use of these products can produce toxic effects. Farmers are individuals occupationally exposed to pesticides, thus subject to associated diseases as well as cognitive impairment. However, this relation is not well established in the literature, requiring further investigation. To assess the potential association between farmers' pesticide exposure and cognitive impairment, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, considering participants, interventions, comparators, outcomes, and study strategies.

Materials and Methods: This study included articles published between 2000 and 2021 on the Scopus, Web of Science, ScienceDirect, and PubMed databases, retrieved by the terms "*pesticides and cognition*" and "*pesticides and memory*."

Results: In total, ten studies fit the established criteria and were included in the sample. All had farmers occupationally exposed to pesticides in their sample and only one study dispensed with a control group. Of the neurobehavioral tests, four studies used mini-mental state examination, six neurobehavioral core test batteries (tests recognized in the area), and the remaining, other tests. We observed that 90% of articles found an association between cognitive impairment and pesticide exposure. Overall, five studies measured the activity of cholinesterases in their sample, of which three found significant differences between groups, confirming intoxication in those exposed.

Conclusion: Despite the limited number of trials, we found scientific evidence to support the existence of adverse effects of pesticides on farmers' cognition. We recommend that future studies research similar projects, expanding knowledge on the subject.

Keywords: Cognition, Memory, Agriculture, Toxicity, Preferred reporting items for systematic reviews and meta-analyses

INTRODUCTION

As agriculture developed, pesticide application has become one of the necessary processes for increasing crop productivity.[1] About 3 billion kilos of pesticides are used every year worldwide to increase productivity and reduce losses caused by pests and diseases.[2,3] However, the deliberate use of these chemicals in the environment not only pollutes it – including the air, land, and water – but also accumulates pesticides and their metabolites in humans and animals, causing toxic effects.[1,4]

In this scenario, a large part of the population may be subjected to pesticides, especially in those occupationally exposed to it. Occupational exposure occurs in workers involved in the manufacture, handling, application, and disposal of these products. Thus, farmers are more likely to be exposed to pesticides.[5]

Farmers' exposure occurs mainly during the preparation and application of pesticides and cleaning of the spraying equipment. The most common routes of contamination are the respiratory and dermal tracts, but it can also occur orally.[4,6] Much of the exposure occurs due to a lack of risk perception, low educational attainment, farmers' lack of training, and defective or absent personal protective equipment (PPE).[6-8]

Based on exposure time and symptom development speed, pesticide toxicity can be classified as acute or chronic intoxication. Acute toxicity occurs from a single exposure incident. Chronic toxicity occurs from multiple exposure incidents. Low pesticide doses, absorbed in a single exposure,

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are often insufficient to produce diseases but frequent absorption can cause serious chronic diseases or even death.[9]

Acute exposure can lead to symptoms such as difficulty breathing, nausea, vomiting, diarrhea, and rashes.[7] Among the diseases associated with chronic exposure, cancer,[10,11] reduced fertility, birth defects,[12,13] and neurodegenerative diseases[14,15] stand out.

Pesticides are classified into three groups by their origin and chemical group: Natural, inorganic, and synthetic pesticides. The last group includes organochlorides, organophosphates, pyrethroids, and carbamates, among others.[16]

Organophosphorus compounds (OP) can inhibit the cholinergic enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), crucial for neurotransmission.[17] Intoxication by this type of anticholinesterase accumulates the neurotransmitter acetylcholine in the synaptic cleft by inhibiting cholinesterase, inducing excessive stimulation of nicotinic and muscarinic receptors in the central and peripheral nervous system and paralyzing cholinergic synaptic transmission.[18]

The classic signs of acute OP poisoning are diarrhea, polyuria, miosis, muscle weakness, bradycardia, emesis, tearing, salivation, and sweating.[19] More recently, several studies point to farmers' neuropsychological impairment associated with exposure to OP pesticides, such as memory and attention problems.[20-23]

When this relation is observed, it is necessary to know and estimate these individuals' cognitive status. For this, appropriate tests are used to evaluate overall intellectual performance or individual cognitive functions: attention or processing speed, space-time orientation, visuospatial ability, praxis (voluntary planning of movement), coordination and motor speed, memory, language, communication, reasoning, and executive and other functions related to the frontal lobes of the cerebral cortex.[21,24]

To date, the literature still lacks a full explanation of the relationship between pesticides and cognitive impairment. Despite the large number of studies involving the theme, their designs and discoveries are heterogeneous.[24] Thus, this literature review aimed to evaluate if farmers' exposure to pesticides is associated with cognitive impairment.

MATERIALS AND METHODS

This review was based on the preferred reporting items for systematic reviews and meta-analyses guidelines[25] and used the participants, interventions, comparators, outcomes, and study design strategy,[26] enabling us to define:

Participants

Studies whose participants were human beings of all genders aged 18 years or older were included in this research.

Interventions

To be included, studies needed participants who were occupationally exposed to pesticides, that is, farmers during their work in the field, and to have either reported mode of exposure to pesticides by a questionnaire or confirmed it by quantifying such substances in any type of biological sample from participants.

Comparators

In this review, studies needed to contain any of these comparators: no exposure, environmental exposure, occupational exposure, or different degrees of exposure to pesticides.

Main outcomes

Study results showed the relationship between pesticide exposure and cognitive impairment. To evaluate cognition, one or more tests could be performed to evaluate cognitive functions and/or tests for each of the following cognitive areas: memory, attention, language, perception, and executive functions.

Secondary outcomes

Some studies have evaluated a possible profile of exposure or even pesticide poisoning, performed through biochemical analysis of cholinesterase enzymes (AChE and/or BChE), which play a fundamental role in the cognitive system.

Study design

This review only included cross-sectional observational studies. Articles with other study designs were excluded from the study.

This study included articles published between 2000 and 2021. The databases used to search for scientific articles were Scopus, Web of Science, ScienceDirect, and PubMed. The terms used were "pesticides and cognition" and "pesticides and memory." Studies were initially selected by title, then by abstract. Next, they were read in their entirety and those eligible were selected.

RESULTS

A total of 2071 articles were first retrieved by the keywords in all chosen databases, of which 695 were duplicates and excluded. Of the remaining 1376 selected articles, 748 were excluded after we read their titles, leaving us with 628 articles. Next, after reading their abstracts, 601 articles were excluded since they failed to fit our defined criteria. Of the 27 eligible studies, 17 were excluded after a full reading of the text. The main reasons for exclusion were including individuals under 18 years of age, lacking farmers in their sample and cognitive tests, and having other study designs. Thus, we elected ten studies to compose this systematic review. Figure 1 shows a flow diagram of the search process.

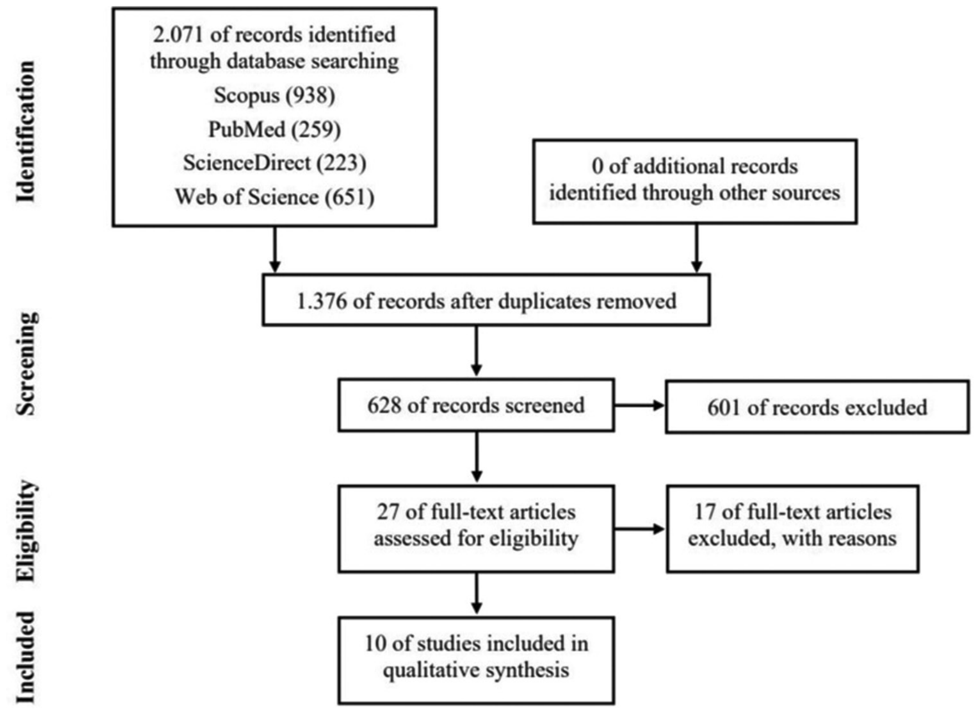

Figure 1: Flow diagram of the selection of systematic review articles.

Study population

This review only included cross-sectional observational studies. Sample sizes ranged from 66[27] to 339 (288 farmers and 51 control participants)[28] individuals. Regarding gender, six studies surveyed only men and four studies surveyed all genders, as shown in Table 1.

Only one study failed to use a control group using blood AChE values for its analyses,[27] in which case different degrees of exposure were the comparator. The other studies used a control group with individuals unexposed to pesticide for analyses (5), mostly consisting of urban workers who had never performed agricultural work. While two used organic farmers for their control groups, comparing unexposed individuals with those occupationally exposed.[20,29] Furthermore, two studies used a third group in their sample, individuals living in agricultural areas under indirect exposure to pesticides.[29,30] These studies used three comparator parameters, unexposed individuals, and those environmentally and occupationally exposed.

Main outcomes

Most studies showed a complete evaluation of the assessed cognitive and psychomotor functions, considering the different cognitive areas, such as memory, executive functions, attention, language, orientation, general mental state, and neurobehavioral. The WHO recommends the mini-mental state examination (MMSE) and the Neurobehavioral Core Test Battery (NCTB), which are considered gold standard tests.[24] MMSE is a validated instrument to classify individuals' cognitive state and quantitatively estimate cognitive impairment severity.[31] NCTB consists of seven neurobehavioral tests: Digit Symbol, Digit Span, Benton visual memory test/recognition form, Santa Ana dexterity test, Simple Reaction Time, Pursuit Aiming II, and Profile of Mood States.[29] Among the ten studies analyzed, two did not use the MMSE or the NCTB in their analyzes.

In total, nine studies found a relationship between pesticide exposure and cognitive impairment (90%). The results found are shown in the subsections below.

Cognitive impairment

Among the studies that analyzed cognitive functions, four used the MMSE test. It consists of an interview aiming to evaluate interviewees' temporal and spatial orientation, attention and calculation, memories, and language.[31] Furthermore, two studies did not use the MMSE for evaluating cognitive functions, instead using the test named memory impairment screen (MIS)[27] and the event-related potentials.[32]

Five studies are available on performance in executive functions, verbal fluency and comprehension, visual and auditory memory, stages of attention, and information processing. In all these studies, farmers presented a lower performance than control groups.[21,27,30,32,33]

The studies that used three sample groups found a significant difference between these groups, no difference between the direct and indirect exposure groups but between the direct exposure group and the control group.[30,31]

Table 1. Description of the methods, participants, and findings of the selected articles.

Authors/Year/Country	Pesticides	Cognitive and Psychomotor Functions	Trials	Sample Description	Type of Exposure	Findings
Farahat *et al.*/2003/Egypt	OP	Verbal abstraction, visuomotor speed, problem solving, attention memory	Part of NCTB (*Digit Symbol; Digit Span;* BVRT); *Similarities; Block Design, Paced Auditory Serial Addition; Story Recall tests; Trailmaking part A and B; Letter cancellation*	52 farmers and 50 male control participants	Questionnaire - occupational exposure+serum AChe	Farmers performed worse in specific tests (*Similarities, Digit Symbol, TrailMaking part A&B, Letter Cancelation, Digit Span, Benton Visual Retention*). Significantly lower level of serum AChE in exposed participants
Kamel *et al.*/2003/EUA	Not described	Cognitive function, sensory function, psychomotor function, balance function	Part of NCTB (*Digit Symbol; Digit Span; Santa Ana*) and *Vibrotactile threshold; Visual contrast sensitivity; Tapping; Grip strength; Postural sway*	288 farmers and 51 controls	Questionnaire - occupational exposure	Farmers performed worse in specific tests (*Digit Span, Tapping, Santa Ana, and Postural sway*)
Roldán-Tapia *et al.*/2005/Spain	OP and carbamates	Attention, reasoning, memory, perception, visuomotor skills, expressive language, and motor ability	Part of NCTB (Digit Symbol; Digit Span; BVRT) and Stroop; "A" Cancellation Letter; Trail Making; Picture; Completion; Similarities; Rey–auditory; ROCF; Complex Figure; Logical Memory; Poppelreuter; Block Design; Boston Naming; Luria	40 farmers and 26 male control participants	Questionnaire - occupational exposure+plasma BChe	Farmers exposed to pesticides for more than 10 years show lower neuropsychological performance (perceptual-constructive and visual praxis). BChE plasma level failed to differ significantly between the groups
Hong *et al.*/2006/South Korea	OP and carbamates	Guidance, record, memory, language, attention, calculus, and mental processing	MMSE; Wechsler Adult Intelligence Scale; Bender Gestalt; Projection-drawing	50 farmers and 30 male control participants	Questionnaire - occupational exposure+plasma and red cell BChe	None of the psychological evaluations differed between the groups. AChE plasma level failed to differ significantly between the groups
Dassanayake *et al.*/2009/Sri Lanka	OP	Neurophysiological processes and neuroanatomical correlates of underlying cognitive functions	ERPs	35 farmers and 38 male control participants	Questionnaire - occupational exposure	Farmers performed worse on a specific test (more counting errors, suggesting impaired stimulus classification accuracy)
Munõz-Quezada *et al.*/2016/Chile	OP	Verbal comprehension, perceptual reasoning, processing speed, intelligence quotient, deep reflexes, and discriminative sensitivity	MMSE; nctb (BVRT); Wechsler Intelligence Scale for Adults; Copy; ROCF	93 farmers and 84 controls	Questionnaire - occupational exposure	Farmers performed worse on specific tests (verbal comprehension, processing speed, IQ, reflexes, and discriminative sensitivity)

(Contd...)

Table 1. (*Continued*)

Authors/Year/Country	Pesticides	Cognitive and Psychomotor Functions	Trials	Sample Description	Type of Exposure	Findings
Corral *et al*./2017/Chile	OP	General mental status, memory, attention, visuoconstructive praxis, and executive functions	MMSE; nctb (Digit Span); ROCF; Stroop; d2 test of attention; FAB; Verbal fluency semantin	32 farmers (direct exposure), 32 residents in agricultural areas (indirect exposure), and 38 control participants	Questionnaire - occupational exposure+ environmental exposure	Farmers performed worse in specific tests (MMSE, digit span, d2 test of attention, frontal assessment batter, and verbal fluency semantin) and the indirect exposure group scored lower than control
Halim *et al*./2018/Indonesia	OP	Memory and attention	MIS (group A); ANT (group B)	66 male farmers (divided into two groups)	Questionnaire - occupational exposure+blood AChe	Significant correlation between AChE activity and memory function. Negative correlation between AChE activity and level of attention, alertness, and guidance. 51% showed a change in AChE blood levels (low intoxication)
Akhoundzardeini *et al*./2021/Iran	Not described	Memory, attention, executive, and visual and verbal functions	MMSE and FAB	60 farmers (direct exposure), 31 residents in agricultural areas (indirect exposure), and 30 male control participants	Questionnaire - occupational exposure+blood AChe	Farmers performed worse in specific tests (MMSE and FAB). There was no significant difference between AChE activity in the three groups
Fuhrimann *et al*./2021/Uganda	Different chemical groups	Language, memory, attention, and executive and motor functions	Part of NCTB (Digit Symbol; Digit Span; BVRT) and Semantic verbal fluency; Verbal fluency phonetic; Color trail part 2; Trail making A; Digit vigilance; Purdue pegboard; Finger tapping	208 farmers and 80 male control participants (organic farmers)	Questionnaire - occupational exposure	Farmers performed worse in specific tests (BVRT, Finger Tapping, Trail making A, Digit symbol, and Semantic verbal fluency). Association between exposure to glyphosate and visual memory impairment

AChE: Acetylcholinesterase, ANT: Attention network test, BChE: Butyrylcholinesterase, BVRT: Benton visual retention test, ERPs: Event-related potentials, FAB: Frontal assessment battery, MIS: Memory impairment screen, MMSE: Mini mental state examination, NCTB: Neurobehavioral core test battery, OP: Organophosphorus compounds, ROCF: Rey-osterrieth complex figure Test.

In turn, the study that used MIS and a group of occupationally exposed to OP for at least 2 years found evidence that indicated a correlation between chronic OP exposure and memory and attention impairment.[27]

However, one study found no significant differences in cognitive assessments between evaluated groups.[34] Intelligence quotient (IQ), orientation, memory, calculus, similarities, visual sensitivity, and psychomotor speed were similar between groups, but both groups' IQ was significantly lower than that of the general population's, supporting the results in Muñoz-Quezada *et al*. The sample group consists of a farmers' group (n = 50) who regularly applied a variety of pesticides, including OP and carbamates for at least 10 years, and who did not apply pesticides for 2 weeks before the study. Moreover, as a control group, they used organic farmers who had not used pesticides for at least 10 years. However, they used pesticides before this period. Furthermore, they suggested that since the control group had been exposed before the beginning of organic agriculture that they may be subject to an impact on cognitive deficit.[34]

Neurobehavioral

To evaluate neurobehavioral six studies used the NCTB tests, but no one of the selected studies used this full test battery, but specific tests, mainly digit symbol, digit span, benton visual retention test, and Santa Ana Dexterity Test.[20,21,28,30,35,36]

These studies found evidence that pesticides exposure can be related to impaired visuomotor velocity, visual and auditory attentions, verbal abstraction, and visual memory.[34,35] Furthermore, they found that working time in agriculture, and a cumulative OP and carbamate exposure were inversely correlated with neurobehavioral performance.[35,36]

Finally, Fuhrimann *et al*. used pesticide applicators and organic farmers in their sample, which should use organic pest control practices for at least one of their crops. They measured exposure degree from factors which increased (such as applying pesticides manually) or reduced it (such as using PPE). In their sample, 62% of farmers were applicators and reported the use of 14 active ingredients in their pesticides in the last 12 months before research, with glyphosate as the most common. From 11 neurobehavioral tests, researchers found that general pesticide exposure was associated with visual memory, language, perceptual-motor function, and complex attention problems. When individually examining the active ingredients, glyphosate exposure was positively associated with impaired visual memory.

Cholinesterases (secondary outcome)

Of the eligible studies, five evaluated a possible profile of exposure or even pesticide poisoning through biochemical analysis and an exposure questionnaire. The authors measured participants' AChE activity in different ways. Farahat *et al*. (2003) measured serum AChE; Hong *et al*. (2006), red cell and plasma AChE; Halim *et al*. (2018) and Akhoundzardeini *et al*. (2021), blood enzyme levels; and Roldán-Tapia *et al*. (2005), plasma BChE activity.

Three studies that evaluated the AChE activity found a significantly lower level of this enzyme in farmers than in control groups.[27,31,35] One of these, which used three sample groups, found that the decrease is lower in the directly exposed group than the indirect exposure and control group. That result may indicate pesticide exposure, confirming the intoxication profile.[31]

However, just one study related that a decrease of AChE can be associated with impaired memory function (prevalence ratio of 1.78), total attention, alertness, and orientation. Furthermore, this study suggests 51% of farmers with a mild intoxication due to pesticides exposure.[27]

Meanwhile, the last study which evaluated AChE activity found no significant differences in the AChE levels between groups. As seen, this study used organic farmers in their control group and failed to find differences in cognitive function in their sample.[34]

Furthermore, the study, which measured plasma BChE at the time of evaluation as the primary marker of recent exposure, found no significant differences between groups. Thus, the authors claim that the cognitive deficits found do not seem to be an acute effect of BChE decrease, but rather of chronic exposure to pesticides.[36]

DISCUSSION

After analyzing the studies, the findings supported the association of neurobehavioral deficits with work in agriculture. We can observe that farmers had a lower performance in selective attention, information processing, stimulus accuracy,[29] verbal comprehension, processing speed, discriminative sensitivity,[21] general memory, alertness and orientation[27] visual memory, language, and perceptual-motor function and complex attention when compared with control groups.[20]

The longer the agricultural work period and, consequently, the greater the exposure to pesticides, the more negatively it affects the cognitive performance of the exposed participants compared to the controls.[35] Research on individuals indirectly exposed to pesticides found an important profile of intoxication since they are close to agricultural areas. Thus, the authors suggest that chronic low-level exposure, whether direct or indirect, also influences cognitive functioning.[30,31]

Another gap in studying pesticide exposure effects is the susceptibility of the general population to experiencing intoxication. In this review, most studies examined farmers and control groups mostly formed by the general population. However, some studies involved people indirectly exposed to pesticides and observed a degree of cognitive impairment in this group as well. Thus, adding to the knowledge of contamination of water, soil, air, and food by pesticides,[4] we suggest that the general population is also susceptible to exposure and adverse effects.

The mechanisms by which pesticides produce cognitive impairments are still being described, but it mainly pointed to the cholinergic syndrome. Studies in humans and animals have indicated the central cholinergic system as an important regulator of cognitive functions such as learning and memory.[37] Thus, OP and carbamates harm cholinergic synapses since they are anticholinesterase compounds. Cognitive deficiencies associated with AChE inhibition can be explained by the overstimulation and persistent activation of muscarinic and nicotinic receptors due to acetylcholine accumulation in the synaptic cleft.[18]

In relation to cholinesterase, most studies showed decreased activity in individuals exposed to pesticides. While, not all of them were associated with these individuals' cognitive function, and it was impossible to establish consensus on this variable. However, in agreement with another literature review,[24] we found that the available studies hardly show similar study designs, making more assertive outcomes on this topic difficult.

Furthermore, it has been a challenge to reliably quantify pesticide exposure levels[24] since there is often no validated instrument to research the forms and degree of exposure to which farmers are subject, showing heterogeneous data. Thus, it is important to know if there is a profile of intoxication by cholinesterase but only half of the studies in this review included biochemical analyses of these enzymes; of which, more than half found some degree of intoxication in individuals exposed to pesticides.

Regarding individual active ingredients, one study observed an association of glyphosate exposure with visual memory impairment.[20] Moreover, we observed that a specific class of pesticides can rarely be localized in the studies, and it is impossible to study it in isolation. This is due to the fact that pesticide exposure is evaluated through questionnaires and personal interviews, in which subjects are sometimes incapable of exactly name the used compounds, using mixtures of substances or the pesticides used differ in the sample, making it impossible to establish relations.

CONCLUSION

Despite the limited number of trials available within this study design, we found scientific evidence to support the existence of adverse effects of pesticides on farmers' cognitive function. Although exposure to pesticides may not be the only factor involved in cognitive impairment, it may be sufficient to trigger it, often in combination with other factors, not yet fully explored in the literature.

We suggest that future studies engage in similar projects, addressing the aspects mentioned above and assessing the specific categories of pesticides most harmful to cognition and the toxicological mechanisms by which they act. Finally, we consider the monitoring of the mode of pesticide application to be important, favoring lower occupational exposure of farmers to pesticides and, consequently, lower cognitive impairment.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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