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Effect of Pesticide Exposure on Respiratory Symptoms in Agroindustrial Farmers: A Systematic Review

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Abstract: Pesticides are a mixture of substances used to control pests, plants, or animals. The inappropriate uses can cause serious problems for farmers. About 3 million cases of global pesticide acute poisoning, 25 million mild acute poisonings, and 300.000 deaths. The inhalation route is the main entry route for chemicals and pesticides. Exposure through inhalation associated with respiratory pathology, can cause respiratory symptoms due to the accumulation of pesticide substances in the respiratory tract. Inhaled pesticides will be stored in the human respiratory tract indicating damage and irritation of respiratory organs, which can cause serious respiratory symptoms. This review aimed to summarize the association between pesticides exposure and respiratory symptoms in agroindustrial farmers. This systematic review was reported based on criteria from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A literature search was conducted with electronic databases, such as PubMed, ScienceDirect, Cochrane Library, and Portal Garuda. P-value with the confidence interval (CI) of 95% was used to determine the association between pesticides exposure and respiratory symptoms. Ten studies were included in the qualitative synthesis. The current study showed pesticides exposure increases respiratory symptoms in farmers. Farmers who use pesticides have a greater frequency of respiratory symptoms than other farmers. Organochlorine and organophosphate have a significant risk of causing respiratory problems, such as cough, phlegm, wheezing, and shortness of breath. **Conclusion**: This systematic review provides valuable evidence suggesting the correlation between pesticides exposure and respiratory symptoms in agroindustrial farmers.

Keywords: Pesticide; Respiratory; Farmer

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1. Introduction

Pesticides are substances or mixture substances used to control and prevent pests, plants, or animals that can interfere with the process of agricultural production.[1–3] Pesticide misuse may have major consequences for farmers, consumers, and the environment.[4] Pesticide exposure to farmers usually occurs as a result of the behavior and action of farmers. Some factors increase the risk of pesticide exposure such as overuse of pesticides, long duration of exposure, wrong procedures, improper pesticide storage, inadequate spray equipment, and farmers often using the same containers for water and food storage.[5] Other risk factors are also influenced by the level of education farmers in agroindustrial areas. Farmers with a higher level of education have a better understanding of pesticide exposure, follow pesticide safety rules, and are more aware of the risk of exposure.[6,7]

Pesticide poisoning is frequent in many countries as a result of excessive pesticide exposure. Globally, there were about 3.000.000 cases of pesticide acute poisoning, 25 million mild acute poisonings, and 300.000 death.[8] Based on a global agricultural population of around 860 million, it means about 44% of farmers are exposed to pesticides every year which causes pesticide poisoning cases and affects farmer health. The largest estimated cases occur in South Asia, followed by Southeast Asia and East Africa.[9] For each organ system, each route of exposure has various consequences and complications.[10]

Pesticides can enter the human body in several ways, through inhalation, oral intake, skin contact (dermal), and the eye.[11–15] Most chemicals and pesticides enter the body via the inhalation route, which can include vapors, fumes, and particles. Exposure to particular pesticide by inhalation related to respiratory pathology, induced respiratory symptoms due to the accumulation of pesticide substances in the respiratory tract.[16–18] Inhaled pesticides will be stored in the human respiratory tract that causes damage and irritation of respiratory organs as a result of direct contact with respiratory tract tissues, which can cause serious respiratory symptoms.[19]

Pesticides can impact the nose, throat, and lungs of humans to serious damage, in the last 20 years there has been a considerable increase in respiratory problems, which has become a major health concern in the agroindustries, specifically among farmers.[16] Pesticide exposure causes respiratory symptoms in an estimated 10% of cases in agroindustrial areas.[20] Cough, wheezing, shortness of breath, and chest pain are common respiratory symptoms in agroindustrial farmers. Pesticide exposure affects respiratory symptoms as well as an impairment in human respiratory function.[19,21,22] Pesticide exposure can injure respiratory system tissue and induce respiratory symptoms in pesticide users, especially farmers.

2. Materials and Methods

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and statements. Articles used in this review were original research with cross-sectional, cohort, and case reports. Review, study protocol, letter to the editor were excluded. The inclusion and exclusion criteria used in this review were the following: articles published between 2012-2021, fully accessible, correlated to the aim of this paper, articles were written in English, and using samples of farmers in the agro-industrial area. Papers without full-text availability, and articles with unrelated topics were all excluded from the study. Original research showed the association of pesticides exposure to respiratory symptoms in agroindustrial farmers.

2.1 Data Sources and Search

A literature search was conducted using electronic databases such as PubMed, Science Direct, Cochrane Library, and Portal Garuda. Keywords were used in the search field using the Boolean operator included in Table 1. All the studies from these databases were stored in the authors' library in Rayyan QCRI. The process of study searching and selection is illustrated in Figure 1. After duplicates were removed, all collected articles were screened based on year, titles, and abstract by five independent reviewers (SZR, DA, SA, AS, and TW). Then, full-text articles were assessed for eligibility. The final results were 10 studies that were included in the qualitative synthesis.

2.2. Data Extraction and Analysis

Study characteristics included in this review were shown in Table 4. The data extracted from selected studies were author, year, location, design study, pesticide type, samples, and summary results.

2.3. Risk of Bias in Individual Studies (Qualitative Synthesis)

The selected study's quality was assessed using the "Joanna Briggs Institute's Critical Appraisal Tools". It depends on the study design of research, which refers to the research process, intervention, outcome data, and reported result. Five independent reviewers (SZR, DA, SA, AS, and TW) analyzed quality assessment with scores "yes", "no", "unclear", and "not applicable". The score was presented based on cut-off>50%, if the total score assessment is above the cut-off, it will be included in the extraction study.

3. Results

3.1. Study selection

Our search collected 1527 articles from 4 databases as described in Table 1 below. From hand searching, we found 29 articles that matched our topics. Seven hundred fourteen articles duplicates and years from those databases were removed. Then, the authors read the titles and abstracts of the remaining 632 articles for preliminary screening. The authors excluded the articles that did not fulfill our eligibility criteria. Full texts were retrieved for 77 articles, and 1 study was excluded because those articles did not clearly explain the association of pesticides and respiratory symptoms. Full-texts were retrieved again for 22 studies, and 55 studies were excluded because the studies did not explain clearly the design study and sample. Full-texts 10 articles were included in qualitative systematic reviews. Our study selection process was presented in the PRISMA diagram in Figure 1.

Table 1. Database searching results

Database	Keywords	
Pubmed	(Pesticides OR Herbicides OR Fungicides OR Insecticides OR Organophosphate OR Carbamates)) AND (Respiratory function OR Pulmonary function OR Lung Function OR Respiratory symptoms OR Respiratory disease OR Wheeze OR Dyspnea OR Cough OR Phlegm)) AND (Farmer OR Farmworker)	173
Science Direct	("Pesticides" OR "Herbicides" OR "Fungicides" OR "Insecticides") AND ("Respiratory symptoms" OR "Respiratory disease" OR "Respiratory function") AND ("Farmer" OR "Farmworker")	1181
Cochrane Library	(Pesticides OR Herbicides OR Fungicides OR Organophosphorus OR Pesticide Residues) AND (Respiratory Function OR Lung Function OR Respiratory Symptoms OR Respiratory Disease)	56
GARUDA	Pesticides	88

The results of the studies were 1527. All the studies were stored in the authors' library in Rayyan QCRI.

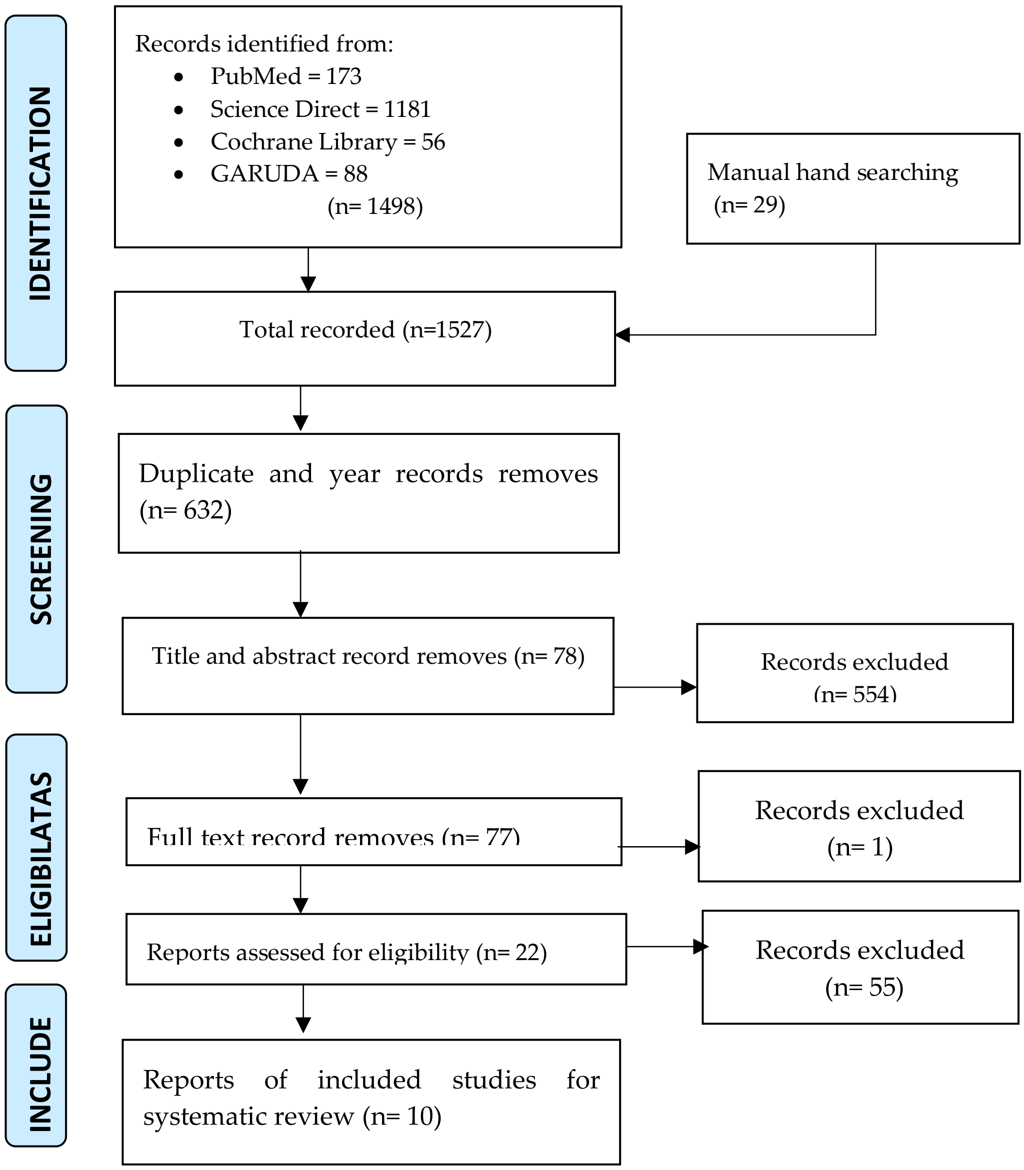

Figure 1. PRISMA Flow Diagram

3.2. *Characteristics of Individual Studies*

The individual studies were agroindustrial farmers who used pesticides and had respiratory symptoms. The age distribution in all studies ranged from 20 to 60 years as described in Table 4. Based on the sociodemographic characteristic of the 10 selected studies, the highest percentage of farmer subjects was male compared to females. The population is diverse and varied. Some studies also include behavioral and individual factors, such as smoking, alcohol status, personal protective equipment (PPE), age, gender, and duration of work.

3.3. *Characteristics of Included Studies*

The process of assessing the quality of articles with the JBI Critical Appraisal tools, is classified as good because it has a score above the cut-off (>50%) that has been determined by the researcher.[23] There were 8 articles with cross-sectional studies and 2 articles with cohorts. All selected articles are in English. The studies countries include Pakistan, Turkey, Ethiopia, India, Brazil, Ghana, Nigeria, Thailand, the United States, and Egypt. The year of publication of the article used is the last 10 years as described in Table 4.

3.4. ***Risk of Bias in Individual Studies (Qualitative Synthesis)***

This systematic review used the JBI Critical Appraisal Checklist to assess the study quality and methodology of research articles. Each checklist has some questions that are answered after reading the entire research article. Articles with cut-off more than 50% include inclusion criteria and continue to be reviewed in the data results table. There are 8 articles with a cross-sectional research design adapted to the 8 questions from the checklist. The results of the critical appraisal score for the cross-sectional research design showed in Table 2.

Table 2. Critical Appraisal Cross-Sectional Studies

Author	Checklist Critical Appraisal Cross-Sectional Studies								Score
	1	2	3	4	5	6	7	8	
Khoso et al., 2019	✓	✓	✓	✓	✓	✓	✓	✓	100%
Negatu et al., 2017b	-	✓	✓	✓	✓	✓	✓	✓	87.5%
Fareed et al., 2013	✓	✓	✓	✓	✓	✓	✓	✓	100%
Buralli et al., 2020	-	✓	✓	✓	✓	✓	✓	✓	87.5%
Quansah et al., 2016	✓	✓	✓	✓	✓	-	✓	✓	87.5%
OO Desalu et al., 2014	-	✓	✓	✓	✓	✓	✓	✓	87.5%
Sapbamrer and Nata, 2014a	✓	✓	✓	✓	✓	-	✓	✓	87.5%
Sak et al., 2018	✓	✓	✓	✓	✓	✓	✓	✓	100%

There are 3 articles with a perfect score of 100% and 5 articles with an 87.5%. The score of each research article has a cut-off of >50%, which means it can be continued for review. Regarding each question on the checklist, 3 articles did not receive a score on question number 1, because the contents of the article did not identify and explain the inclusion and exclusion of criteria studies. There were also 2 articles that did not receive a score on question number 6, because the study lacked strategies and methods for dealing with confounding factors. Question 5 is the confounding factor, many articles identify confounding factors but some articles did not write how to handle it.

The results of the second critical appraisal score are for the cohort research design. There are 11 questions on the critical appraisal checklist from JBI for assessed cohort design which were answered after reading the entire article. The results of the critical appraisal scores are presented in Table 3.

Table 3. Critical Appraisal Cohort Studies

Author	Checklist Critical Appraisal Cohort Studies											Score
	1	2	3	4	5	6	7	8	9	10	11	
Catherine et al., 2014	✓	✓	✓	✓	✓	✓	✓	✓	-	-	✓	82%
Hoppin et al., 2017	✓	✓	✓	✓	✓	✓	✓	✓	-	-	✓	82%

There are 2 research articles included in the cohort studies. Their critical appraisal scores above 50%, with 82%, indicating that the article meets the inclusion criteria and can be reviewed. In each article, the answers to questions number 9 and 10 are "no". Question number 9 is related to the explanation of subjects who were followed up until the completion of the study or not, whereas question 10 concerns the methods and strategies for dealing with research subjects who were lost to follow-up.

Table 4. Study Characteristics

Author, Year	Location	Type of Pesticides	Study Design	Age	Sample
Fareed et al., 2013	India	Not identified	Cross-sectional	**Applicator:** 38.12 ± 15.39 **Control:** 37.28 ± 14.13	243
Catherine et al., 2014	Egypt	Organophosphate	Cohort	**Applicator:** 15.6 (1.5) **Control:** 15.4 (2.2)	62
Sapbamrer and Nata, 2014	Thailand	Not identified	Cross-sectional	**Applicator:** 54.3 ± 9.5 **Control:** 53.4 ± 14.4	304
Desalu et al., 2014	Nigeria	Not identified	Cross-sectional	**Applicator:** 57.5 (9.0)	228
Quansah et al., 2016	Ghana	Pyrethroid, organochlorines	Cross-sectional	**Applicator:** 40.3 (9.6)	100
Hoppin et al., 2017	USA	Organophosphate, carbamates, organochlorine, pyretroid	Cohort	*	22134
Negatu et al., 2017	Ethiopia	Not identified	Cross-sectional	**Applicator** 27.39 ± 6.58 **Control:** 27.97 ± 6.01	**Survey 1**: 1085 **Survey 2**: 387
Sak et al., 2018	Turkey	Pyretroid	Cross-sectional	**Applicator:** 42.3	66
Khoso et al., 2019	Pakistan	Not identified	Cross-sectional	**Applicator:** 34.4 (12.4)	381
Buralli et al., 2020	Brazil	Not identified	Cross-sectional	**Applicator:** 44.1 ± 11.3 **Control:** 48.4 ± 14.1	78

**Not mentioned*

Table 5. Qualitative summary of literature study

Author, Year	Type of Pesticide	Respiratory Symptoms	Summary Results
Fareed et al., 2013	Not identified	Cough	20 applicators (12.05%) had cough with p < 0.01, which means statistically significant. Farmers who are exposed have a 10 fold risk of respiratory symptoms of cough. OR= 10.41, 95% CI= 1.58-47.09
		Wheezing	A total of 9 individuals (5.42%) had wheezing. Data found OR 2.15, 95% CI 0.43-20.87 and p <0.01. It means that pesticide exposure has a significant effect on wheezing
		Sore Throat	Another respiratory symptom was found. Found 3 applicators (1.81%) with p<0.01. Compared to the control, applicators are more at risk to had a sore throat
Catherine et al., 2014	Chlorpyrifos Organophosphate	Wheezing	9 applicators had wheezing from 38 samples and 2 non-applicator had wheezing. Farmers who are exposed have a 3.5 times risk of wheezing.
Sapbamrer and Nata, 2014b	Not identified	Cough	51 farmers had cough (28%), more than the control sample. Farmers who are exposed to pesticides have a greater potential to had coughing disorders. The data found are OR (95% CI) = 1.2 (0.7-2.1)
		Shortness of breathing	Around 33 farmers had shortness of breathing. The results compared to controls are quite far. Farmers who were exposed had three times the potential for shortness of breathing. Data found OR (95%CI) = 2.8 (1.3-6.0) and p-value < 0.01
		Chest pain	36 farmers out of 182 had chest pain. Farmers exposed to pesticides had 3 times higher risk of developing shortness of breath. OR (95%CI) = 2.5 (1.2-5.1) and p<0.05
		Dry throat	Symptoms of dry throat disorders due to exposure to pesticides were 43 farmers (23.6%) with OR (95%CI) = 0.9 (0.6-1.6) and p>0.05
Desalu et al., 2014	Not identified	Cough	It was found 47.7% of the 19 farmers who used pesticides had coughs. Research data OR (95% CI) = 2.96 (1.21-7.23) and p value = 0.02

Author, Year	**Type of Pesticide**	**Respiratory Symptoms**	**Summary Results**
		Wheezing	19 samples (5.3%) of applicators had wheezing respiratory disorders. Data showed OR (95%CI) = 1.91 (0.18-20.41) and p value = 0.06.
Quansah et al., 2016	Beta HCH, delta HCH, heptachlor, endosulfan sulfate organochlorine	Cough	The results of beta HCH with coughing showed p =0.0276 and endosulfan sulfate p = 0.0202. It was different from heptachlor and delta HCH, which showed p = 0.1229 and p = 0.2733
		Wheezing	The results of wheezing showed that beta HCH and endosulfan organochlorine influence wheezing, indicated by p=0.0071 and p=0.0123. Delta HCH and heptachlor showed p value> 0.05
		Phlegm	The findings showed that beta HCH, heptachlor, and endosulfan sulfate were statistically related to the p-value <0.05, while the type of organochlorine delta HCH did not show significance because the p-value = 0.5749
Quansah et al., 2016	Lambda sialotrin and pyrethroid cypermethrin	Cough	Pyrethroid showed no significant cough symptoms, the p-value= 0.692 and 0.7477.
		Wheezing	Pesticide exposure to wheezing did not show significance because the p-value of the two pyrethroid pesticides was more than 0.05
		Phlegm	Pesticide exposure to phlegm symptoms did not show a significant because p>0.05
Hoppin et al., 2017	Organophosphates, carbamates, pyrethroids, and organochlorines	Wheezing	5249 applicators had wheezing. Details of the symptoms of wheezing were 1310 allergic wheezing and 3939 non-allergic wheezings. Pesticide exposure to wheezing had a significant statistically. Carbaryl carbamate showed p-value = 0.001, dimethoate organophosphate with p-value = 0.008, and permethrin pyrethroid with p = 0.005. However, the different results obtained between organochlorine lindane and wheezing were not significant, indicated by p=0.087

Author, Year	Type of Pesticide	Respiratory Symptoms	Summary Results
Negatu et al., 2017b	Not identified	Cough	First survey= 36 exposed farmers had cough symptoms. Significant because p < 0.01. (OR= 3.15, 95% CI= 1.56-6.36). Second survey, there were 26 farmers had cough (12.6%). Data showed p < 0.01 OR = 5.76, 95% CI = 1.90-17.42
		Wheezing	First survey, total of 13 farmers (2.2%) had wheezing. Pesticide exposure did not have a significant statistically (p = 0.13) and OR = 3.16, 95% CI = 0.96-10.47. A total of 5 non-exposed farmers had wheezing symptoms with OR (95% CI) = 1.00 The second survey, 26 applicators had to wheeze (12.6%). Pesticide exposure was not associated with wheezing (p=0.17) with OR= 1.75, 95% CI= 0.81-3, 78
		Phlegm	The first survey, 9 applicators had phlegm symptoms (1.5%). Pesticide exposure was not associated with phlegm (p = 0.28), the p-value was not significant and showed OR = 2.02, 95% CI = 0.58-7.01. Second survey, 12 applicators had phlegm (5.8%). It was not associated with phlegm symptoms (p = 0.07, OR = 2.98, 95% CI = 0.76 -11.58)
		Shortness of breath	The first survey, 35 applicators had shortness of breath (5.8%). Pesticide exposure was associated with symptoms (p < 0.001) and OR = 6.67, 95% CI = 2.60-17.58. Second survey, 58 applicators had shortness of breath (28.2%). The results showed p < 0.01 with OR = 4.09, 95% CI = 2.12-7.90
Sak et al., 2018	Lambda cyhalothrin pyrethroid	Cough	There was 45 applicators who had a cough (68.2%). Pyrethroid exposure was associated with symptoms indicated by p<0.001

Author, Year	Type of Pesticide	Respiratory Symptoms	Summary Results
Khoso et al., 2019	Not identified	Cough	A total of 196 farmers had a cough, but it was not statistically significant because p=0.71.
		Wheezing	There were 251 applicators (65.9%) who had wheezing respiratory symptoms. The result data showed p=0,10
		Phlegm	A total of 196 farmers (51.4%) had phlegm. The result data showed p=0.71
Buralli et al., 2020	Not identified	Cough	The results were different from other articles, there were 11 controls (30.6%) who had a cough, so the control results were more than the applicators which were only 7 (16.7%). However, this number shows a statistically significant result (p<0.05).
		Wheezing	It was found that the control sample had wheezing Research findings: 10 individuals, compared to only 1 individual applicator (2.4%) with p<0.05
		Shortness of breath	14 individuals (38.9%) of the helper and 5 individuals (11.9%) of applicators had shortness of breath (p-value <0.05)

Abbreviations: OR= odds ratio, 95% CI= 95% confidence interval

4. Discussion

Ten articles have been systematically reviewed through a study selection process based on PICOS, inclusion criteria, and exclusion criteria. Articles are collected from international and national databases, Pubmed, Science Direct, Cochrane Library, and Portal Garuda. Buralli et al. (2020) found a significant correlation between organophosphates and respiratory symptoms. Coughing, wheezing, and shortness of breath are common symptoms in farmers. Shortness of breath has a prevalence ratio of 3.83, wheezing has a prevalence ratio of 16.07, and cough has a prevalence ratio of 2.64.

Low level of plasma cholinesterase among farmers indicate that they were overexposed with pesticides.[34–36] Normal cholinesterase levels in males varied from 4620 to 11500 U/L, whereas in women they ranged from 3930 to 10800 U/L. If there is a decrease in cholinesterase activity in the blood of less than 3500 U/L, it is considered poisoning or exposure.[37,38] Farmers are also at a higher risk of developing symptoms as a result of improper usage of personal protective equipment (PPE) when using pesticides, the length of time they use pesticides, and living in agricultural areas where pesticides enter the body more easily.[39–43] This study also found that farmers' alcohol intake is unrelated to the severity of respiratory symptoms, similar to the findings of Sapbamrer and Nata (2014) and Fareed et al. (2013). Sak et al. (2018) showed the correlation between pesticide exposure and various respiratory symptoms. All symptoms were statistically significant because their p values were less than 0.001. The number of farmers who had respiratory symptoms was quite significant, with almost 50% of them having cough, 65.2% having phlegm, 62.1% having chest pain and wheezing, and 66.7% having shortness of breath. The study of Sak et al. (2018) is intriguing because dust measurements were taken, namely PM10 (particulate matter), particles with a diameter of 10 m or less, and PM2.5 particles with a diameter of 2.5 m or less. [44] In farmers, high levels of PM10 enhanced respiratory symptoms such as cough, phlegm, and shortness of breath. Another study showed pesticides that are less than 10 microns easily reach the lungs, but those greater than 50 microns can irritate the mucous membranes of the nose, throat, and esophagus.[45]

Farmers who work for more than 5 hours and smoke have a higher risk of respiratory symptoms and also farmers over the age of 50 have a 1.5-fold increased respiratory symptom, which relates to a physiologic reduction in lung function in those over the age of 40. [46–48] The farmer who smoked had their lung function affected by stimulating mucus secretion and paralyzing cilia[49–52], leading to a considerably lower FEV1 in smokers exposed to pesticides than farmers who had never smoked.[18,53] Carbamates and organophosphates inhibit acetylcholinesterase, leading to an increase in acetylcholine at parasympathetic neuroeffector junctions, which might result in cholinergic overexpression in airway smooth muscle and excessive muscular contraction.[54–56] Meanwhile, the mechanism of organochlorines and pyrethroids on respiratory symptoms is increased production of ROS, which may induce cell damage due to redox signaling activity.[57–60] The redox system imbalance contributes to cell and tissue damage by stimulating the production and activation of pro-inflammatory genes such as IL-1A, IL-6, and IL-8, which promote inflammation in the respiratory tract. [44,61,62]

5. Conclusions

Based on the findings of the systematic review, pesticides exposure can induce various symptoms of respiratory problems in agroindustrial farmers. Farmers who use pesticides have a greater rate of respiratory symptoms than farmers who do not use pesticides. Coughing, phlegm, wheezing, and shortness of breath are the most common symptoms. The pesticide mechanism on respiratory symptoms occurs through the production of ROS and inhibition of acetylcholinesterase. In this study, it should be highlighted that the mechanism is also influenced by behavioral factors and individual characteristics of farmers, such as age, smoking behavior, and duration of work.

Recommendation: Pesticides' effect on other human systems, besides respiratory, might be the focus of future research.

Conflict Of Interest: No conflicts of interest have been declared.

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