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Pesticide Exposure, Neurobehavioral Symptoms, and Neurobehavioral Performance in Pesticide Applicator in West Java, Indonesia

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Abstract

It was known that pesticide applicators are at risk of experiencing neurotoxicity and neurobehavioral alterations related to occupational pesticide exposure. This study aims to evaluate the association between pesticide exposure and the neurobehavioral performance of pesticide applicators in West Java, Indonesia where chemical pesticides were heavily used. We conducted a cross-sectional study in a vegetable farming center in West Java Province, Indonesia. A total of 88 pesticide applicators were included in the study on November 2022. A structured interviewer-administered questionnaire was used to obtain the participants' characteristics. We performed the German Q18 questionnaire to screen the neurobehavioral symptoms and the WHO Neurobehavioral Core Test Battery (NCTB) for each participant to identify the neurobehavioral performance among pesticide applicators. Data were summarized descriptively and statistical analysis using chi-square and independent sample t-test was performed. We found that the most common neurobehavioral symptoms were symptoms related to memory, concentration, and fatigue. Poor neurobehavioral performance was found in 29.5% of participants and it was found to be associated with those grouped at age ≥ 44 years and categorized as having a high CEL. The pieces of evidence presented here suggest that neurobehavioral performance was associated with pesticide exposure.

Introduction

The agricultural sector in Indonesia is one of the main economic drivers, however, most of the workers are in the small-scale agricultural sector. It is believed that more than any other occupational group, agricultural workers especially those in the small-scale sector are heavily exposed to chemical pesticides (Liem *et al.*, 2021). Chemical pesticides are widely used in agriculture, in particular, to control pests including weeds, insects, and plant diseases. Previous studies have shown that pesticide handling among smallholder farmers is generally poor as indicated by more frequent application, higher concentration, use of pesticide mixture, and infrequent use of appropriate personal protective equipment (PPE) (Maden *et al.*, 2014.; Liem *et al.*, 2021; Yuantari *et al.*, 2015). They are less aware that pesticides should be used as part of an integrated approach to pest, weed, and disease control. Accordingly, failure to use pesticides properly can harm people and the environment. The deleterious effects of pesticide exposure arise as a result of the interaction of several factors including pesticide toxicity, dose, length of exposure, route of entry, the work practices or control measures i.e., application method, PPE used, personal hygiene, and spill management, as well as the metabolism in the human body that can be influenced by genetic susceptibility (Liem *et al.*, 2022; Damalas and Koutroubas, 2018).

For that reason, it was known that

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farmers and workers in the agricultural sector, especially pesticide applicators, are at risk of experiencing health problems including respiratory disorders, hematological alterations, and endocrine disruptions (De-Assis *et al.*, 2021; Liem *et al.*, 2023). Not only that, neurotoxicity and neurobehavioral alterations related to occupational pesticide exposure were also reported in several studies (Tiwari *et al.*, 2022; Fuhrimann *et al.*, 2021). A recent study of farmers in Central Java, Indonesia, showed that most participants were indicated to have been exposed to the acetylcholinesterase inhibitor pesticides, and 59.2% had symptoms of neuropathy (Setyopranoto *et al.*, 2020). In another study, chronic low-level exposure to organophosphates has been reported to alter cognitive and psychomotor domains including impaired memory, attention, and alertness, as well as impaired psychological domains such as anxiety, depressed mood, and irritability (Ismail *et al.*, 2012). Therefore, our study aims to evaluate the association between neurobehavioral performance and pesticide exposure of pesticide applicators in West Java, Indonesia where chemical pesticides were heavily used.

Method

Our research was a cross-sectional study, conducted in Cibodas Village, West Bandung Regency, West Java Province, Indonesia. The main commodities in this area are romaine lettuce, broccoli, and chilies. The eligible study population was all farmers in the Cibodas area, totaling approximately 500 people. The minimum sample size of our study was 84 participants determined by the Slovin formula using a 10% margin of error. Using a consecutive sampling method, a total of 100 vegetable farmers participated in the recruitment process of our study. Among them, 10 farmers did not apply pesticides, while 2 other farmers did not complete the neurobehavioral test, leaving 88 farmers who actively applied pesticides included in the study. The recruitment process was held in November 2022. Since the farming activities are relatively similar throughout the year, the timing of recruitment does not affect the assessment of the actual exposure situation.

The information on the individual and occupational characteristics of the study participants was identified using a structured interviewer-administered questionnaire. The occupational characteristics primarily consisted of several parameters related to agricultural activities which were then used to calculate the intensity level and cumulative exposure level (CEL). We calculated the intensity level and the CEL of pesticide exposure using a quantitative approach from Dosemeci that has been shown effective in Agricultural Health Study (Dosemeci *et al.*, 2002). The intensity level of exposure to pesticides was estimated using parameters of pesticide handling practices which include application-related activities (e.g., mixing, repairing, and/or washing used equipment, mode of application), personal protective equipment utilization, personal hygiene practices, and spill management as explained in the previous study (Dosemeci *et al.*, 2002; Liem *et al.*, 2021). Furthermore, the CEL was calculated based on the intensity level, the number of days of applying pesticides in a year, and the lifetime of pesticide exposure. Based on the median CEL value, the participants were then categorized into high and low CEL groups (Liem *et al.*, 2022).

The 18 questions on the German Q18 questionnaire were used to screen the neurobehavioral symptoms among pesticide applicators. Cut-off points of 5 for men and 6 for women were applied to determine the presence of neurobehavioral symptoms (Ihrig *et al.*, 2001). The WHO Neurobehavioral Core Test Battery (NCTB) is intended to identify or screen for the neurological effects of chemical exposure. In this study, we performed the Digit Symbol, Digit Span, Pursuit Aiming, and Trail Making tests for each participant, according to NCTB operational procedures. All testing procedures were well understood and properly implemented by the research team to avoid testing bias. This test was conducted at a comfortable room temperature with sufficient lighting and relatively free from distracting noise to minimize disturbance to participants during the test. The overall neurobehavioral performance was classified into two (2) categories according to the score test. Score tests above 40 were categorized as good (normal), otherwise categorized as poor (abnormal) if one of the score tests was 40 or less (Anger, 2014; Anger *et al*., 1993).

The analysis was performed using SPSS 20 for Windows. We summarised the study population characteristics as frequency distribution for categorical variables while using mean (SD) or median (minimum-maximum) to describe the continuous variables. An independent sample t-test was used to evaluate the difference in NCTB score according to the presence of neurobehavioral symptoms and CEL groups. The chi-square test was used to analyze the association between neurobehavioral performance and both the individual and occupational characteristics of the study participants. All p-values are two-sided, and p<0.05 was considered significant. The Medical and Health Research Ethics Committee of the Faculty of Medicine and Health Sciences Universitas Kristen Krida Wacana (UKRIDA) approved the study protocol on September 28, 2022 (No. SLKE: 1361/SLKE-IM/UKKW/FKIK/KE/IX/2022). We obtain written informed consent from all participants.

Results And Discussion

Our research participants have been farmers for many years and pesticide application methods have been implemented for generations. The characteristics of the pesticide applicators who participated in our study are shown in Table 1. The mean age of our study participants was 44.2 years, most were male and had low levels of education. They had been spraying pesticides for approximately 15 years, with a median frequency of 65 spraying days per year. Almost all farming and pesticide handling activities were done manually. The application equipment and pesticide handling practices in our study are described in Table 2. We found that all of our participants wore long trousers during pesticide application. However, the proportion of goggles and chemical gloves users in our study population was considered small. Therefore, pesticide applicators may experience exposure to pesticides which can occur through skin contact, inhalation, or ingestion. Apart from mixing and spraying pesticides, several agricultural activities, including cleaning used equipment, re-entering sprayed areas, and harvesting crops that may be contaminated with pesticides are the primary sources of occupational pesticide exposure (Gangemi et al., 2016). Not only that, combining multiple pesticides in a single spraying activity was found to be a common practice in our study. Most of our study participants use a minimum of 2 (two) combinations of pesticides in a single spraying activity. Mancozeb, difenoconazole, and emamectin were the most frequently used pesticides as detailed in Table 3.

Table 1. Characteristics of the Study Participants

Characteristics (n =88)	Description
Age ⁋	44.2 (10.1) years
Male – n (%)	85 (96.6)
Low level of education – n (%)	66 (75.0)
Obese (Body mass index ≥ 25 kg/m^2) – n (%)	33 (37.5)
Smoking – n (%)	71 (80.7)
Lifetime pesticide exposure #	15 (1 – 40) years
Number of days spraying per year #	65 (13 – 208) days
Intensity level (IL) #	6.5 (0.4 – 62.8)
Cumulative exposure level ($x10^3$) #	7.7 (0.1 – 98.0)
Daily work duration #	5.5 (2 – 12) hours
Duration of spraying pesticide #	0.43 (0.02 – 2.3) hours/day

⁋Mean (SD), # Median (minimum – maximum)

Using the Germany Q18 questionnaire, we identified the neurobehavioral symptoms experienced by our participants. The most common neurobehavioral symptoms were symptoms related to memory, concentration, and fatigue as shown in Table 4. Poor performance on digit symbol, digit span, pursuit aiming, and trail-making tests were 17%, 12.5%, 15.9%, and 4.5%, respectively. Overall, poor neurobehavioral performance was found in 26 (29.5%) participants. We discovered that neurobehavioral symptoms and cumulative exposure level (CEL) were associated with lower scores on the digit symbol and pursuit aiming tests, as well as longer processing time in the trail-making test as shown in Table 5.

Table 2. Distribution of Application Equipment and Pesticide Handling Practices Used by the Study Participants

Parameter	Frequency - n (%)	
	Never / rare	Frequent
Application equipment		
Hat	7 (8.0)	81 (92.0)
Face mask	49 (55.7)	39 (44.3)
Goggles	86 (97.7)	2 (2.3)
Long sleeves	2 (2.3)	86 (97.7)
Long pants	0 (0)	88 (100)
Chemical gloves	72 (81.8)	16 (18.2)
Boots	1 (1.1)	87 (98.9)
Pesticide handling practices		
Read the instruction label before using pesticides	38 (43.2)	50 (56.8)
Combining multiple pesticides in a single spraying activity	5 (5.7)	83 (94.3)
Direct contact with pesticide concentrates	56 (63.6)	32 (36.4)
Being splashed or spilled on pesticides during spraying	48 (54.5)	40 (45.5)
Spraying against the wind	70 (79.5)	18 (20.5)
Re-entering sprayed area	52 (59.1)	36 (40.9)
Wiping sweat with contaminated clothing	63 (71.6)	25 (28.4)
Smoking while spraying pesticides	85 (96.6)	3 (3.4)
Wash hands with water and soap after using pesticides	20 (22.7)	68 (77.3)
Changing clothes after spraying pesticides	12 (13.6)	76 (86.4)

Source: primary data (2022)

Table 3. Types of Pesticides Used by Study Participants

No	Active ingredient	Chemical class	Utilization	Frequency - n (%)
1	Mancozeb	Dithiocarbamate	Fungicide	53 (58.9 %)
2	Difenoconazole	Triazole	Fungicide	44 (48.9 %)
3	Emamectin	Avermectin	Insecticide	26 (28.9 %)
4	Chlorantraniriprole	Diamide	Insecticide	20 (22.2%)
5	Profenofos	Organophosphate	Insecticide	15 (16.7 %)
6	Azoxystrobin	Methoxyacrylate	Fungicide	12 (13.3 %)
7	Abamectin	Avermectin	Insecticide	11 (12.2 %)
8	Cypermethrin	Pyrethroid	Insecticide	10 (11.1 %)
9	Carbendazim	Benzimidazole	Fungicide	9 (10.0%)
10	Chlorotalonil	Chloronitrile	Fungicide	8 (8.9 %)
11	Propineb	Carbamate	Fungicide	7 (7.8 %)
12	Spinetoram	Spinosine	Insecticide	6 (6.7 %)
13	Imidacloprid	Neonicotinoid	Insecticide	4 (4.4 %)
14	Dimethomorph	Morpholine	Fungicide	3 (3.3 %)
15	Beta cyfluthrin	Pyrethroid	Insecticide	2 (2.2 %)
16	Diazinon	Organophosphate	Insecticide	2 (2.2 %)
17	Fipronil	Phenylpyrazole	Insecticide	2 (2.2 %)
18	Hexaconazole	Triazole	Fungicide	2 (2.2 %)
19	Chlorpyrifos	Organophosphate	Insecticide	2 (2.2 %)
20	Maneb	Carbamate	Fungicide	2 (2.2 %)
21	Methomyl	Organophosphate	Insecticide	2 (2.2 %)
22	Thiamethoxam	Neonicotinoid	Insecticide	2 (2.2 %)

No	Active ingredient	Chemical class	Utilization	Frequency - n (%)
23	Amylsubrom	Sulfonamide	Fungicide	1 (1.1 %)
24	Famoxadone	Oxazolidinedione	Fungicide	1 (1.1 %)
25	Fluxametamide	Isoxazoline	Insecticide	1 (1.1 %)
26	Lambda cyhalothrin	Pyrethroid	Insecticide	1 (1.1 %)
27	Oxathiapiprolin	Isoxazoline	Fungicide	1 (1.1 %)
28	Mefenoxam	Fenilamida	Fungicide	1 (1.1 %)

Source: primary data (2022)

Table 4. Neurobehavioral Symptoms Distribution According to the German Q18 Questionnaire

	Questions	Yes -n (%)	No - n (%)
1	Do you have a short memory?	28 (31.8)	60 (68.2)
2	Have your relatives told you that you have a short memory?	35 (39.8)	53 (60.2)
3	Do you often have to make notes about what you must remember?	25 (28.4)	63 (71.6)
4	Do you generally find it hard to get the meaning from reading newspapers and books?	31 (35.2)	57 (64.8)
5	Do you often have problems with concentrating?	33 (37.5)	55 (62.5)
6	Do you often feel irritated without any particular reason?	14 (15.9)	74 (84.1)
7	Do you often feel depressed without any particular reason?	10 (11.4)	78 (88.6)
8	Are you abnormally tired?	34 (38.6)	54 (61.4)
9	Do you have palpitations of the heart even when you don't exert yourself?	18 (20.5)	70 (79.5)
10	Do you sometimes feel an oppression in your chest?	9 (10.2)	79 (89.8)
11	Do you often perspire without any particular reason?	6 (6.8)	82 (93.2)
12	Do you have a headache at least once a week?	28 (31.8)	60 (68.2)
13	Are you less interested in sex than what you think is normal?	26 (29.5)	62 (70.5)
14	Do you often feel sick?	31 (35.2)	57 (64.8)
15	Do you have numb feelings in your hands or feet?	27 (30.7)	61 (69.3)
16	Is there a weak feeling in your arms or legs?	20 (22.7)	68 (77.3)
17	Do your hands tremble?	8 (9.1)	80 (90.9)
18	Does alcohol not agree with you?	78 (88.6)	10 (11.4)

Source: primary data (2022)

The association of neurobehavioral symptoms and the neurobehavioral core test battery score strengthens the notion that there has been a neurobehavioral alteration. Furthermore, as presented in Table 6, poor neurobehavioral performance was associated with those grouped at age ≥ 44 years and categorized as having a high CEL.

Our findings on the association of the cumulative exposure level (CEL) with neurobehavioral performance are in agreement with a recent study in Indonesia that showed a significant association between pesticide spraying frequency, spraying duration, lifetime pesticide exposure, and the utilization of PPE with neurobehavioral performance (Pawestri and Sulistyaningsih, 2021). High CEL scores occur due to high exposure intensity, application frequency, and lifetime years of pesticide exposure. We observed that more than 4 out of 5 pesticide applicators did not use chemical gloves. Since direct skin contact is one of the most significant routes of entry for pesticide exposure, direct contact with pesticides places them at a higher risk of pesticide exposure and health effects. For that reason, those in the high CEL group characterized by less adequate PPE utilization and poorer work practices had poor neurobehavioral performance. This finding aligns with the results of a recent review which stated that insecticide applicators without PPE tended to perform worse on neurobehavioral tests (Antonangeli *et al*., 2023), and also supporting a previous study that stated most farmers using PPE were categorized in the healthy group (Joko *et al*., 2020).

Table 5. The Neurobehavioral Core Test Battery Score of Study Participants Grouped by Neurobehavioral Symptoms and Cumulative Exposure Level

Parameter		n	Mean score	Mean difference	p	95% CI
Digit Symbol Test	NB Symptoms					
	Yes	41	46.40	-6.75	0.001	-10.77 ; -2.73
	No	47	53.14			
	CEL					
	High	45	46.78	-6.59	0.002	-10.61 ; -2.56
	Low	43	53.37			
Digit Span Test	NB Symptoms					
	Yes	41	47.31	-5.04	0.015	-9.08 ; -1.00
	No	47	52.35			
	CEL					
	High	45	48.39	-3.29	0.124	-7.49 ; 0.92
	Low	43	51.68			
Pursuit Aiming Test	NB Symptoms					
	Yes	41	46.03	-7.43	< 0.001	-11.40 ; -3.47
	No	47	53.46			
	CEL					
	High	45	46.17	-7.84	< 0.001	-11.76 ; -3.92
	Low	43	54.01			
Trail-Making Test	NB Symptoms					
	Yes	41	53.22	6.03	0.007	1.96 ; 10.10
	No	47	47.19			
	CEL					
	High	45	53.01	6.18	0.003	2.16 ; 10.19
	Low	43	46.84			

NB Symptoms: Neurobehavioral symptoms
CEL: Cumulative exposure level

Table 6. The Association Between Neurobehavioral Performance and Study Participants' Characteristics

Variable	Neurobehavioral performance		p^{cs}
	Poor	Good	
Age			
≥ 44 years	22 (84.6)	22 (35.5)	< 0.001
< 44 years	4 (15.4)	40 (64.5)	
Sex			
Female	0 (0)	3 (4.8)	0.345 (f)
Male	26 (100)	59 (95.2)	
Level of education			
Low (≤ 9 years)	23 (88.5)	43 (69.4)	0.059
High (> 9 years)	3 (11.5)	19 (30.6)	
Smoking			
Smoking	20 (76.9)	51 (82.3)	0.563
Not smoking	6 (23.1)	11 (17.7)	
Body mass index			

Variable	Neurobehavioral performance		p^{cs}
	Poor	Good	
Obese (≥ 25 kg/m²)	9 (34.6)	24 (38.7)	0.717
Not obese (< 25 kg/m²)	17 (65.4)	38 (61.3)	
Knapsack sprayer			
Manual pressurized	23 (88.5)	58 (93.5)	0.339 (f)
Motorized	3 (11.5)	4 (6.5)	
Cumulative exposure level			
High	21 (80.8)	24 (38.7)	< 0.001
Low	5 (19.2)	38 (61.3)	

cs: *chi-square*
f: *Fisher exact test*

Furthermore, as the categorization of CEL into high and low-exposure groups serves as a surrogate for chronic exposure among our study participants, our results suggest that the pesticide applicators in our study were chronically exposed to agents with neurotoxic properties. The results were consistent with a previous review that concluded that long-term low-level pesticide exposure was associated with impaired neurobehavioral functions including memory/attention, visuospatial abilities, and psychomotor speed (Ross *et al*., 2013).

The nervous system is susceptible to the effects of pesticides, and for that, there is growing evidence that chronic neurodegenerative conditions are associated with long-term pesticide exposure, including carbamates, pyrethroids, and organophosphates (Baltazar *et al*., 2014). Occupational exposure to pesticides may also result in changes in the level of several neurotransmitters, cause oxidative stress, and finally lead to neurological and behavioral disorders (Kori *et al*., 2018; Monnet-Tschudi *et al*., 2007). The use of these types of pesticides was common among our study participants, and in addition, we observed that most of our study participants use a combination of pesticides in a single application. Under these conditions, complex dose-response interactions are likely to occur as a result of the multiple modes of action involved and the fact that the individual chemicals can interfere with each other (Leemans *et al*., 2019), raising concerns about much more severe effects.

Aging is also linked to nervous system changes, which lead to alterations in various neurological examination findings (Schott, 2017). As expected, most of the applicators with poor neurobehavioral performance in this study were in the older group. This condition is compounded with pesticide exposure that may cause nerve cell alteration and deteriorating neurobehavioral functions. Regarding the nutritional status, there is an opinion that lipid storage may play a significant role in the elimination of OP pesticides. Since higher pesticide concentrations are present in adipose or fat tissues, pesticides that temporarily bind to adipose tissue will gradually be released and undergo biotransformation so that the effects can last longer (Eaton *et al*., 2008), and leads to speculation that individuals with obesity are more susceptible to experiencing the long-term effects of exposure to pesticides. About 38% of our participants were categorized as obese according to their body mass index. However, in our study body mass index was not associated with neurobehavioral performance. Thus, we assume that this result may be due to differences like the types of pesticides and complex mixtures used by our study participants.

More than 80% of our participants are active smokers, however, there is no association found between smoking habits and neurobehavioral performance in our study. A previous study stated that tobacco smoking was considered to alter the physiological transformation and metabolism of xenobiotics, including OP pesticides, although the precise mechanism remains unclear (Lee *et al*., 2010). The nicotine substances in tobacco may also significantly affect brain function and further cause nerve disorders by affecting catecholamine secretion (Kang *et al*., 2015).

We realized that our study had some limitations. The exact amount of pesticides or the composition of the mixture used is not measured quantitatively. Another limitation is that biological monitoring of exposure was not performed in this study and information regarding agricultural activities was self-reported. This limitation can lead to the misclassification of exposure estimates. Despite the limitations, our findings provide additional evidence of the impact of pesticides on neurobehavioral performance. Therefore, it can be used as a basis for promoting health impact prevention and the implementation of pesticide exposure control.

Conclusion

The pieces of evidence presented here suggest that the neurobehavioral performance of pesticide applicators was associated with pesticide exposure. As pesticide use among farmers seems unavoidable, the results of our study support the notion of the importance of multisectoral collaboration to provide access to safer methods of pest control, an understanding of the potential health implications of pesticide exposure, and comprehensive instruction and support on appropriate pesticides handling practices.

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