ORIGINAL ARTICLE

Pesticide Exposure and Neurobehavioral Effects Among Mosquito Control Workers

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ABSTRACT

Introduction: The use of pesticides in pest management has increased rapidly and occupational exposures had adversely affect human health. This study investigated the types of pesticides used and their neurobehavioral effects towards mosquito control workers. **Methods:** A cross-sectional study was conducted among 46 Kelantanese mosquito control workers in two vector control units by using purposive sampling. Risk assessment on pesticides was based on the Chemical Health Risk Assessment (CHRA). A questionnaire was used to assess neurobehavioral symptoms and neurobehavioral performance was conducted using the Neurobehavioral Core Test Battery (NCTB). The individuals' cumulative pesticide exposure was calculated by average fogging session within a month (session/month) and multiplying with the average duration for each fogging session (hours/session). **Results:** The risk level was moderate for all pesticides, except for Actellic 50 EC. Neurobehavioral symptoms reported were fatigue after work (80.4%), drowsiness (39.1%), fatigue after wake-up early in the morning (32.6%), and dizziness (32.6%). None of the reported neurobehavioral symptoms was associated with cumulative pesticide exposure ($p > 0.05$). Cumulative pesticide exposure was associated with Digit Symbol (*Adj* OR = -0.19, 95% CI: -0.37,-0.01), Digit Span (Backward) (*Adj* OR = -0.28, 95% CI: -0.31,-0.05), Trail Making (A) (*Adj* OR = -0.32, 95% CI: -0.37,-0.01), Minnesota Manual Dexterity (Dominant) (*Adj* OR = -0.20, 95% CI: -0.38,-0.03), and Minnesota Manual Dexterity (Non-dominant) (*Adj* OR = -0.18, 95% CI: -0.36,-0.01). **Conclusion:** Cumulative pesticides exposures are associated with the perceptual-motor speed, short-term auditory memory, attention, and coordination. Effective risk communication is proposed as one strategy to reduce pesticide exposure in occupational setting.

Keywords: Pest Control, Hazard, Toxicity, Risk Assessment, Neurological System

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INTRODUCTION

Pesticides, more specifically insecticides are used extensively in agriculture and pest management for the sake of food security and public health, respectively. In 2019, the worldwide consumption of pesticides was approximately 2 million tonnes and is expected to increase by 75% in 2020. Mosquitoes are capable of transmitting diseases including dengue, yellow fever, zika virus, chikungunya (*Aedes aegypti*), malaria (*Anopheles*), and West Nile virus (*Culex*). Various physical, chemical, biological, and integrated control measures have been applied to suppress Aedes mosquitoes (2). The chemical control against mosquitoes by using dichlorodiphenyltrichloroethane (DDT) began in 1942 during the World War 2 (3). Mosquito control workers are considered as risk groups with high susceptibility towards pesticides according to their work characteristics. They are directly exposed to insecticides primarily during space spraying, mixing, maintenance, and cleaning the equipment as well as via transportation.

In 2019, the dengue cases in Malaysia increased by 61% with a 24% increase of deaths as compared to the previous year (4). Therefore, more fogging activities are required to control the outbreaks by health professionals. Pesticide exposures are extremely hazardous to humans and other living organisms due to their poisonous nature (5). Occupational exposure to pesticides either acute or chronic, both at very low or high doses has been associated with deterioration of workers' health. Pesticides are toxic, therefore affecting human neurological system particularly the central nervous system (CNS) or peripheral nervous

system (PNS). Pesticides exposure is linked with various diseases including cancer, hormone disruption, asthma, allergies, and hypersensitivity (6). Some evidence stated that the negative impacts of pesticide exposure leading to birth defects, reduction birth weight, fetal death, etc. (7-9). The negative effects of pesticides on human health and the environment were well documented in the literature (10).

Despite the serious implications of pesticides on human health, very few studies have been published on pesticide monitoring or pesticide adverse effects in pest control activities for community health purposes in Malaysia. They typically focused on the effect of pesticide exposure towards neurobehavioral, sensory, and cardiovascular among farmers (paddy and cocoa) (11-12), foggers (13), and mosquito control workers (14) respectively. However, very little information is available about the pesticide, hazards, potential risk, and the neurobehavioral effects of mosquito control workers due to pesticide exposure in vector control. To close the gap, this paper presents a study on pesticide risk assessment and the neurobehavioral effects of mosquito control workers. Hopefully, this would provide basic information on pesticide exposures, chemical safety management, and safety practices among this sub-group of health care workers in fogging activities (15).

MATERIALS AND METHODS

A cross-sectional study was conducted at the two Vector-Borne Disease Control Unit of District Health Offices in Kelantan (Kota Bharu and Bachok). The sampling frame was staff in Vector-Borne Disease Control Unit in both DHOs. A list of 82 staff in the Vector-Borne Disease Control Unit was obtained from the Kelantan Health State Department. Purposive sampling was used to select respondents as only certain staff with inclusion and exclusion criteria that could provide desired information related to pesticide use were invited to take part in this study. The inclusion criteria were staff aged 21 to 60 years old, has been working for more than 6 months, and able to understand and communicate either in Malay or English Language. Those with neurological problems and history of injuries on the head, eye, and hand which can cause difficulty in performing Neurobehavioral Core Test Battery (NCTB) were excluded from the study. Data Collection was performed from January to July 2019. Respondents were approached at the DHO and written consents were obtained from those who fulfil the selection criteria and were willing to participate in the study. This study used several types of data collection namely questionnaire (demographic and neurobehavioral symptoms), risk assessment, and Neurobehavioral Core Test Batteries (NCTB) for neurobehavioral performance.

The calculated sample size required for this study was 54 participants. A single proportion formula, $n = [z/\Delta]^2 p(1-p)$ was used to calculate the selected sample size, with p of 0.33 and Δ 0.05 referred from Afifah (16). A 10% dropout was considered in the sample size calculation to anticipate respondents who would not respond to the distributed questionnaires

STUDY INSTRUMENTS

Identification of Hazards and Evaluation for the Potential Risk

Details of all pesticides used by the mosquito control workers were listed in Table 1. The potential risk of each pesticide was evaluated by referring to the Manual of Recommended Practice: Assessment of the Health Risk Arising from the Use of Chemical Hazardous to Health in the Workplace published by the Department of Occupational Safety and Health (DOSH) Malaysia (17). Safety Data Sheet (SDS) of each pesticide was obtained from their respective manufacturers for hazard identification. Hazard rating was determined by referring to the acute toxicity data for inhalation (LC_{50}) of each pesticide. Other evaluations such as frequency, duration, and magnitude of exposure were performed qualitatively according to work characteristics of mosquito control workers

Degree of hazard

The degree of a hazard was used to rate the pesticides on a scale of 1 to 5 (from non-hazardous to the most hazardous) (17), in line with the Classification, Labelling and Safety Data Sheet of Hazardous Chemicals Regulation 2013 under the Occupational Safety and Health Act 1994 (18). Chemical Safety Data Sheet (CSDS) provided information for the evaluation of hazard rating (HR).

Evaluation of Exposure

The exposure was evaluated using a qualitative method by estimating the degree of chemical released based on frequency rating (FR) and magnitude rating (MR). The frequency of exposure was rated on a scale of 1 to 5 (from lower potential exposure to the higher potential exposure) while pesticide-related work activities were observed to determine the FR (17). Both the presence or release of pesticides and the degree of absorption (inhalation and dermal) were rated as low, moderate, or high. The magnitude rating (MR) was determined once the degree of chemical released or presence and degree of chemical inhaled was obtained. Finally, the exposure rating (ER) was assigned based on FDR and MR (17).

Evaluation of Risk

The level of risk was determined based on the risk rating (RR) using the equation RR = HR x ER or was computed through the risk matrix. The level of risk was determined based on the result of RR which were; Low risk (RR =1

to RR =4), Moderate risk (RR=5 to RR=12), and high risk (RR=15 to RR 25). The assessment was concluded based on the result of the level of risk and the adequacy of existing control measures (17).

Questionnaire

The questionnaire used in this study was adapted from several studies (16,19) and was modified according to the setting of this study. The interview-based questionnaire was provided in Malay. The questionnaire consisted of five parts namely Part A: Demographic Information, Part B: Occupational and Working Information, Part C: Personal Protective Equipment (PPE) Usage, Part D: Health Status, and Part E: Neurobehavioral Symptoms. A pre-test of questionnaires was conducted before data collection among representatives of mosquito control workers, to observe whether the questionnaire can be understood and to avoid any unfamiliar terms. The questionnaire was also tested for its reliability.

Individual Pesticide Exposure

The individual cumulative pesticide exposure was based on the average fogging session within one month and the average duration of each fogging session. It was calculated as below:

$$\textit{Cumulative pesticide exposure} = \textit{Average fogging session within one month} \left(\frac{session}{month}\right) X \textit{ Average duration for each fogging session} \left(\frac{hours}{session}\right)$$

Neurobehavioral Core Test Battery

The neurobehavioral core test battery (NCTB) assessment was used to determine the health effects measured in this study. The NCTB included seven tests which were Digit Symbol, Digit Span, Pursuit Aiming, Trail Making, Benton Visual Retention, Simple Reaction Time, and Minnesota Manual Dexterity. The full set of tests took about 45-50 minutes. Each subtest was administered to all subjects by one specific researcher. The operational guideline from the World Health Organization (17) was used as a reference document to ensure a standard manner of assessment. All testing procedures were understood and practiced by the researchers to avoid any bias. Furthermore, testing was conducted in a room where it was free from distracting noise, had adequate lighting, and comfortable room temperature. All instructions given to respondents were loud, concise, and clear. In terms of scoring, the standard score below 50 indicated that a respondent had poor neurobehavioral performance whereas a standard score above 50 indicated a good neurobehavioral performance level (19).

Statistical Analysis

All analyses was performed using IBM Statistical Package for Social Sciences (SPSS), version 24. Both the descriptive and inferential statistics were used to analyse data that were obtained in this study. The normality test was used to test the normality distribution of each data. The significance level was set at $p<0.05$. Multiple Logistic Regression (MLogR) was used to analyse the relationship between selected variables that influenced the neurobehavioral symptoms while Multiple Linear Regression (MLR) tests were used to identify the significant predictors of the selected neurobehavioral performance.

Ethical Issue and Clearance

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM USM) (JEPeM code: USM/JEPeM/18110643). This study was registered in the National Medical Research Registration (NMRR) under the Ministry of Health Malaysia. Ethical approval was also obtained from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia with NMRR ID: NMRR-19-160-45668 (IIR).

RESULTS

Background of the Respondents

The response rate was 85.2% with a total of forty-six mosquito control workers. They were Malay males with the mean age of 40.33 ± 7.78 years old and the mean duration of employment was 12.93 ± 7.10 years. The majority of them (47.8%) were in the age ranged between 31-40 years old and 43.5% were below 10 years of employment. The majority of them were SPM holders (67.4%), while 8.7% of them were classified as 'others' and certified by the Public Health Institute, Ministry of Health Malaysia. The majority of them (52.2%) were active smokers, 32.6% were non-smokers and 15.2% were ex-smokers. The mean number of cigarettes smoked was 10.33 ± 5.01 sticks per day with a range between 3 to 20 cigarettes. The mean duration of smoking was 16.63 ± 8.54 years with 54.2% have been smoking between 10 to 20 years.

Degree of Hazard Rating (HR) Based on Pesticide Based and Hazard Category

A total of five different pesticides were identified for mosquito fogging activities by the Vector Borne Disease Control Unit to kill (knock-down) any adult dengue mosquitoes that might be carrying the dengue virus. All the pesticides used for fogging activities were grouped as insecticides. Actellic EC, Abate 500E, and Abate 1.1G were organophosphates with pesticide classes II, III, and IV respectively based on acute toxicity. Endmos-Q was pyrethroid with pesticide classes III while Vector Bac WG did not apply to any chemical class with pesticide class IV.

Table I characterises the active ingredients of pesticides with health effects. Cypermethrin, Temephos, and Bacillus thuringiensis subsp. Israelensis had HR equals to 2 respectively, while Pirimiphos-methyl had HR equals to 1. Cypermethrin was characterized under an acute health effect with an inhalation category of LC_{50}> 2.5 mg/L, LD_{50}=2000 mg/kg for dermal toxicity,

and LD_{50}= 1800 mg/kg for oral toxicity. Both Temephos had inhalation category of LC_{50} (rat) : > 4.79 mg/L (4 hr) and oral toxicity of LD_{50}=3500 mg/kg (rat), LD_{50}=4204 mg/kg (male) and LD_{50} >10000 mg/kg (female) respectively. Meanwhile, it could be observed that Bacillus thuringiensis subsp. Israelensis also fell under category acute pesticide category with LC_{50} (rat)>2.84 mg/mL (inhalation), LD_{50}> (rat) 5400 mg/kg for oral, and LD_{50}(rat)> 5000 mg/ kg. Similarly, Pirimiphos-methyl also was characterised by acute health effects. Chemicals with moderate toxicity had an oral lethal dose range of 500 to 5000 mg/kg with a toxicity rating of 3. Pirimiphos-methyl, Cypermethrin, and Temephos were moderately toxic to human health while Bacillus thuringiensis subsp. Israelensis was slightly toxic. This classification was used to study the exposure rating of pesticides.

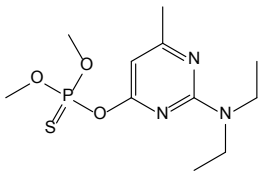
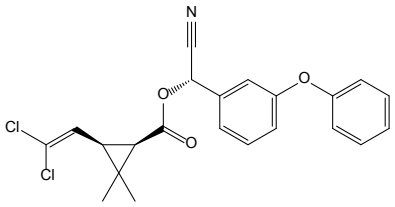
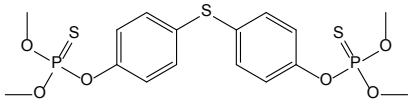
Exposures Rating

The risk of a pesticide depended on two factors, exposure, and toxicity. The exposure rating(ER) was measured based on the frequency-duration rating (FDR) and magnitude rating (MR) (Table III). All mosquito control workers were under FDR of 3. Most of the pesticides MRs were recorded to be placed between 2 and 3. According to DOSH (17), the degree of absorbed pesticides was considered "high" with more than 50% exposure to the pesticides. From the results of HR and MR, exposure rating (ER) was calculated to be 3.

Risk Rating

In this study, the risk rating of pesticides was in the range of 3 to 6. Control measures were adequate with proper PPE provided. Most of the workers (69.6%) wore PPE all the time during the handling of pesticides, such as apron (32.6%), goggles (43.5%), gloves (93.5%), covered shoes (80.4%), and face mask (69.6%). Four out of five pesticides (Endmos-Q, Abate 500E, Abate 1.1G, and VectoBac (WG) had RR = 6 with the risk level categorized as moderate. From here onwards, 'Moderate' means the evaluation of risk was significant with adequate control measures should be increased. Only Actellic 50EC had RR=1 with low risk level. Table II summarizes the risk assessment for each pesticide used, its Hazard Rating (HR), Magnitude Rating (MR), Frequency-Duration Rating (FDR), Exposure Rating (ER), Risk Rating (RR), and Risk Level.

Table I : Health effects of pesticides used in mosquito fogging activities

Trade Name	Active Ingredient	Chemical Structure	Pesticide Origin	Health Effects				
				Inhalation	Oral Toxicity	Dermal Toxicity	Skin Irritation	Eye Irritation
Actellic EC	Pirimiphos-methyl		Organophosphate	4-hours (Rat) LC50 > 5.04 mg/L	Acute: (Rat) LD50 = 1414 mg/kg	Acute: (Rat) LD50 > 2000 mg/kg	Slightly irritant (Rabbit)	Mild irritant (Rabbit)
Endmos-Q	Cypermethrin		Pyrethroid	4-hours (Rat) LC50 > 2.5 mg/L	Acute : (Rat) LD50=1800mg/kg	Acute : (Rabbit) LD50=2000 mg/kg	Slightly irritant (Rabbit)	Mild irritant (Rabbit)
Abate 500E	Temephos		Organophosphate	4-hours (Rat) LC50 > 4.79 mg/L	Acute: (Rat) LD50 = 3506 mg/kg	Acute: (Rat) LD50 = 1855 mg/kg	Mild irritant (Rabbit)	Non-irritant (Rabbit)
Abate 1.1G	Temephos		Organophosphate	4-hours (Rat) LC 50> 4.79 mg/L	Acute: (Rat) LD50=4204 mg/kg(male) and LD50>10 000mg/kg (female)	Acute: (Rat) LD50 = 2000 mg/kg (male) and LD50 > 2378 mg/kg (female)	Non- irritant (Rabbit)	Non-irritant (Rabbit)
Vecto-Bac WG	Bacillus thuringiensis subsp. Israelensis strain AM 65-52	None	Bacteria	4-hours (Rat) LC50 > 2.84 mg/L	Acute: (Rat) LD50 > 5000 mg/kg	Acute: (Rabbit) LD50 > 5000 mg/kg	Slightly irritant (Rabbit)	Non-irritant (Rabbit)

Pesticide Exposure and Personal Protective Equipment Usage

The mean average of fogging activities within one month was 23.26 ± 2.74. Most of them (67.4%) had conducted an average number of fogging activities between 20 to 25 sessions. The mean average of duration for each fogging session completed was 1.93 ± 0.68 hours. Most of them (54.3%) completed the fogging session for approximately 2 hours. They claimed that have been exposed to the pesticide through inhalation (95.7%), skin contact (39.1%), and ingestion (2.2%). Most of them (69.6%) claimed wore personal protective equipment (PPE) all the time during fogging activities. Others used PPE when necessary or being supervised (26.1%) and 4.3% were seldom.

Table II : Risk assessment on each pesticide used by mosquito control workers

Trade Name	Pesticide Origin	HR	MR	FDR	ER	RR	Risk Level
Actellic 50 EC	Organo-phosphate	1	3	3	3	3	Low
Endmos-Q	Pyrethroid	2	3	3	3	6	Moderate
Abate 500E	Organo-phosphate	2	3	3	3	6	Moderate
Abate 1.1G	Organo-phosphate	2	2	3	3	6	Moderate
VectoBac WG	Bacteria	2	2	3	3	6	Moderate

HR=Hazard Rating, MR=Magnitude Rating, FDR=Frequency Duration Rating, ER=Exposure Rating, RR=Risk Rating

Neurobehavioral Symptoms

The most-reported neurobehavioral symptom was fatigue after work (80.4%). There were four other neurobehavioral symptoms had been reported by more than 25% which were drowsiness during daytime (39.1%), fatigue after wake-up early morning (32.6%), often dizziness at least once a week (32.6%), and impaired vision (28.3%).

Association Between Pesticide Exposure and Neurobehavioral Symptoms

None of the reported neurobehavioral symptoms was found to be associated with cumulative pesticide exposure. However, there was a significant association between duration of employment and often dizziness at least once a week (p=0.025, *Adj* OR=1.32: 95% CI=1.04, 1.69). Based on the Nagelkerke R^2 values, the neurobehavioral symptoms of fatigue each time after work, drowsiness during daytime, fatigue after wake-up early morning, often dizziness at least once a week, and impaired vision were explained by the cumulative pesticide exposure, which constituted 15.3%, 17.3%, 25.6%, 28.4%, and 18.9% of the variations, respectively (Table III).

Neurobehavioral Core Test Battery (NCTB) Score

The highest mean score of NCTB was Digit Backward (50.43 ± 9.95). Meanwhile, the lowest mean score of NCTB was Benton Visual Retention (48.11 ± 9.83). Others mean score of NCTB elements were; Digit Symbol (49.59 ± 9.94), Digit Forward (48.84 ± 10.04), Pursuit Aiming (50.33 ± 10.07), Trail Making A (50.02 ± 9.93), Trail B (50.02 ± 10.04), Simple Reaction Time (50.13 ± 10.16), Minnesota Manual Dexterity Dominant (49.6 ± 9.95) and Minnesota Manual Dexterity Non-Dominant (50.07 ± 9.98).

Association Between Pesticide Exposure and Neurobehavioral Score

Table IV to VII show the association between pesticide exposure and neurobehavioral score. There was a significant association between cumulative pesticide exposure with Digit Symbol (*Adj* β=-0.19: 95% CI=-0.37, -0.01), Digit Span (Backward) (*Adj* β =-0.28: 95%CI=-0.51, -0.05), Trail Making (Trail A) (*Adj* β =-0.32: 95% CI=-0.52, -0.12), Minnesota Manual Dexterity (Dominant) (*Adj* β =-0.20: 95% CI=-0.38, -0.03) and Minnesota Manual Dexterity (Non-dominant) (*Adj* β =-0.18: 95% CI=-0.36, -0.01). An increase of 1 hour/month cumulative pesticide exposure was found significantly to decrease the score of Digit Symbol, Digit Span (Backward), Trail Making (Trail A), Minnesota Manual Dexterity (Dominant) and Minnesota Manual Dexterity (Non-dominant) by 0.19, 0.28,0.32,0.20,and 0.18 respectively.

Age was found to be associated with Digit Symbol (*Adj* β =-0.64: 95% CI=-1.17, -0.10), Digit Span (Forward) (*Adj* β =-0.65: 95% CI=-1.26, -0.04) and Trail Making (Trail B) (*Adj* β =-0.87: 95% CI=-1.42, -0.32). An increase of 1 year of age would significantly decrease the score in Digit Symbol, Digit Span (Forward), and Trail Making (Trail B) by 0.64, 0.65, and 0.87, respectively. Therefore, the predicted model for NCTB scores among 46 mosquito control workers was shown as below:

Digit Symbol = 84.66 – [0.64*Age] – [0.19*Cumulative Pesticide Exposure]
Digit Span (Forward) = 81.40 – [0.65*Age]
Digit Span (Backward) = 70.03 – [0.28*Cumulative Pesticide Exposure]
Trail Making (Trail A) = 79.80 – [0.32*Cumulative Pesticide Exposure]
Trail Making (Trail B) = 87.27 – [0.87*Age]
Minnesota Manual Dexterity = 72.00 – [0.20*Cumulative Pesticide Exposure]
(Dominant)
Minnesota Manual Dexterity = 74.74 – [0.18*Cumulative Pesticide Exposure]
(Non-dominant)

Table III : Factors associated with neurobehavioral symptoms among respondents (N=46)

Neurobehavioral Symptoms	SLogR[a]		MLogR[b]		
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	Wald stat (df)	p-value
Fatigue each time after work					
Age (year)	0.99 (0.90, 1.09)	0.882	0.92 (0.77,1.11)	0.72 (1)	0.396
Duration of employment (year)	1.04 (0.93, 1.17)	0.482	1.11 (0.89, 1.39)	0.92 (1)	0.338
PPE Usage (Yes)	0.23 (0.03, 2.05)	0.189	0.27 (0.03, 2.73)	1.24 (1)	0.266
Health Problem (Yes)	0.34 (0.04, 3.05)	0.334	0.31 (0.03, 3.17)	0.97 (1)	0.325
Smoking (Yes)	1.18 (0.27, 5.12)	0.821	0.99 (0.20, 4.97)	0.00 (1)	0.985
Cumulative Pesticide Exposure (hour/month)	1.01 (0.97, 1.05)	0.728	1.00 (0.94, 1.06)	0.00 (1)	0.973
Nagelkerke R^2 = 0.153					
Drowsiness during daytime					
Age (year)	1.06 (0.98, 1.15)	0.142	1.06 (0.91, 1.24)	0.55 (1)	0.458
Duration of employment (year)	1.06 (0.97, 1.16)	0.174	0.99 (0.84, 1.16)	0.02 (1)	0.894
PPE Usage (Yes)	0.80 (0.22, 2.87)	0.732	0.55 (0.12, 2.58)	0.59 (1)	0.444
Health Problem (Yes)	0.26 (0.06, 1.08)	0.065	0.29 (0.06, 1.32)	2.57 (1)	0.109
Smoking (Yes)	0.55 (0.17, 1.84)	0.333	0.49 (0.12, 2.01)	0.98 (1)	0.324
Cumulative Pesticide Exposure (hour/month)	1.02 (0.98, 1.05)	0.333	1.00 (0.95, 1.05)	0.00 (1)	0.973
Nagelkerke R^2 = 0.173					
Fatigue after wake-up early morning					
Age (year)	1.11 (1.02, 1.21)	0.020*	1.12 (0.95, 1.33)	1.77 (1)	0.183
Duration of employment (year)	1.12 (1.02, 1.23)	0.019*	1.05 (0.89, 1.25)	0.33 (1)	0.567
PPE Usage (Yes)	0.52 (0.14, 1.93)	0.330	0.43 (0.08, 2.23)	1.02 (1)	0.313
Health Problem (Yes)	0.48 (0.12, 1.94)	0.302	0.58 (0.11, 2.89)	0.45 (1)	0.501
Smoking (Yes)	1.39 (0.40, 4.78)	0.604	1.82 (0.40, 8.33)	0.60 (1)	0.439
Cumulative Pesticide Exposure (hour/month)	1.03 (0.99, 1.07)	0.164	0.97 (0.92, 1.03)	0.87 (1)	0.351
Nagelkerke R^2 = 0.256					
Often dizziness at least once a week					
Age (year)	1.05 (0.97, 1.14)	0.225	0.87 (0.70, 1.07)	1.81 (1)	0.178
Duration of employment (year)	1.13 (1.03, 1.24)	0.013*	1.32 (1.04, 1.69)	5.02 (1)	0.025*
PPE Usage (Yes)	0.52 (0.14, 1.93)	0.330	0.91(0.18, 4.73)	0.01 (1)	0.913
Health Problem (Yes)	0.80 (0.19, 3.32)	0.761	1.26 (0.21, 7.64)	0.07 (1)	0.799
Smoking (Yes)	0.93 (0.27, 3.21)	0.913	0.95 (0.22, 4.22)	0.00 (1)	0.950
Cumulative Pesticide Exposure (hour/month)	1.02 (0.99, 1.06)	0.251	0.99 (0.93, 1.05)	0.10 (1)	0.990
Nagelkerke R^2 = 0.153					
Impaired vision					
Age (year)	1.06 (0.97, 1.15)	0.184	1.14 (0.96, 1.35)	2.25 (1)	0.134
Duration of employment (year)	1.01 (0.92, 1.10)	0.858	0.87 (0.72, 1.06)	1.92 (1)	0.166
PPE Usage (Yes)	1.67 (0.38, 7.32)	0.499	1.12 (0.21, 6.07)	0.02 (1)	0.895
Health Problem (Yes)	2.06 (0.38, 11.18)	0.401	2.78 (0.45, 17.41)	1.20 (1)	0.274
Smoking (Yes)	0.59 (0.16, 2.18)	0.427	0.50 (0.11, 2.25)	0.81 (1)	0.367
Cumulative Pesticide Exposure (hour/month)	1.02 (0.98, 1.06)	0.381	1.03 (0.97, 1.09)	0.69 (1)	0.405
Nagelkerke R^2 = 0.189					

[a]Simple Logistic Regression, [b]Multiple Logistic Regression

The model reasonably fits well. Model assumptions were met. There were no interaction and multicollinearity problems.

Significant at *p < 0.05

Table IV : Factors associated with Digit Symbol score among respondents (N=46)

Factors	SLR[a]		MLR[b]		
	B (95% CI)	p-value	Adjusted B (95% CI)	t-statistics	p-value
Constant			84.66 (68.86, 100.47)	10.834	0.001**
Age (year)	-0.88 (-1.16, -0.60)	0.001**	-0.64 (-1.17, -0.10)	-2.412	0.021*
Duration of Employment (year)	-0.81 (-1.16, -0.46)	0.001**	0.06 (-0.51, 0.62)	0.204	0.839
PPE Usage (Yes)	0.39 (-6.10, 6.88)	0.905	-0.37 (-5.57, 4.83)	-0.144	0.886
Health Problem (Yes)	-4.83 (-11.68, 2.02)	0.162	-0.30 (-5.63, 5.03)	-0.114	0.909
Smoking Habits (Yes)	-2.10 (-8.05, 3.85)	0.481	-2.78 (-7.44, 1.89)	-1.204	0.236
Cumulative Pesticide Exposure (hour/month)	-0.35 (-0.48, -0.21)	0.001**	-0.19 (-0.37, -0.01)	-2.088	0.043*
R^2 = 0.535					

[a]Simple Linear Regression, [b]Multiple Linear Regression

The model reasonably fits well. Model assumptions were met. There were no interaction and multicollinearity problems.

Significant at *p < 0.05, **p < 0.001

Digit Symbol = 84.66 – [0.64*Age] – [0.19*Cumulative Pesticide Exposure]

An increase of age and cumulative pesticide exposure by one will significantly decrease the score of Digit Symbol by 0.83.

Table V : Factors associated with Digit Span score among respondents (N=46)

Factors	SLR[a]		MLR[b]		
	B (95% CI)	p-value	Adjusted B (95% CI)	t-statistics	p-value
Digit forward					
Constant			81.40 (63.39, 99.39)	9.147	0.001**
Age (year)	-0.76 (-1.08, -0.44)	0.001**	-0.65 (-1.26, -0.04)	-2.159	0.037*
Duration of Employment (year)	-0.63 (-1.01, -0.24)	0.002*	0.19 (-0.46, 0.83)	0.587	0.560
PPE Usage (Yes)	2.08 (-4.44, 8.61)	0.524	1.12 (-4.80, 7.05)	0.384	0.703
Health Problem (Yes)	-1.46 (-8.52, 5.60)	0.679	2.62 (-3.46, 8.69)	0.872	0.389
Smoking Habits (Yes)	-2.32 (-8.32, 3.68)	0.441	-2.83 (-8.14, 2.48)	-1.077	0.288
Cumulative Pesticide Exposure (hour/month)	-0.29 (-0.44, -0.13)	0.001**	-0.18 (-0.39, 0.02)	-1.789	0.081
$R^2 = 0.409$					
Digit backward					
Constant			70.03 (49.89, 90.17)	7.034	0.001**
Age (year)	-0.45 (-0.81, -0.09)	0.017*	-0.21 (-0.89, 0.48)	-0.611	0.545
Duration of Employment (year)	-0.38 (-0.79, 0.03)	0.066	0.22 (-0.51, 0.94)	0.604	0.550
PPE Usage (Yes)	0.61 (-5.89, 7.10)	0.851	0.45 (-6.18, 7.08)	0.138	0.891
Health Problem (Yes)	-1.53 (-8.52, 5.47)	0.662	1.59 (-5.20, 8.39)	0.474	0.638
Smoking Habits (Yes)	-1.96 (-7.91, 4.00)	0.512	-3.65 (-9.59, 2.30)	-1.241	0.222
Cumulative Pesticide Exposure (hour/month)	-0.25 (-0.41, -0.10)	0.002*	-0.28 (-0.51, -0.05)	-2.451	0.019*
$R^2 = 0.246$					

[a]Simple Linear Regression, [b]Multiple Linear Regression

The model reasonably fits well. Model assumptions were met. There were no interaction and multicollinearity problems.

Significant at *p < 0.05, ** p < 0.001

Digit Span (Forward) = 81.40 – [0.65*Age]

An increase of age by one will significantly decrease the score of Digit Span (Forward) by 0.65.

Digit Span (Backward) = 70.03 – [0.28*Cumulative Pesticide Exposure]

An increase of cumulative pesticide exposure by one will significantly decrease the score of Digit Span (Backward) by 0.28.

Table VI : Factors associated with Trail Making score among respondents (N=46)

Factors	SLR[a]		MLR[b]		
	B (95% CI)	p-value	Adjusted B (95% CI)	t-statistics	p-value
Trail A					
Constant			79.80 (62.35, 97.25)	9.251	0.001**
Age (year)	-0.61 (-0.95, -0.27)	0.001*	-0.51 (-1.10, 0.08)	-1.763	0.086
Duration of Employment (year)	-0.49 (-0.89, -0.09)	0.017*	0.46 (-0.16, 1.09)	1.497	0.142
PPE Usage (Yes)	-2.80 (-9.24, 3.63)	0.384	-2.87 (-8.62, 2.87)	-1.012	0.318
Health Problem (Yes)	-3.14 (-10.07, 3.80)	0.367	0.41 (-5.48, 6.29)	0.140	0.889
Smoking Habits (Yes)	2.48 (-3.45, 8.41)	0.404	0.02 (-5.12, 5.17)	0.009	0.992
Cumulative Pesticide Exposure (hour/month)	-0.35 (-0.49, -0.22)	0.001**	-0.32 (-0.52, -0.12)	-3.179	0.003*
$R^2 = 0.432$					
Trail B					
Constant			87.27 (70.97, 103.56)	10.831	0.001**
Age (year)	-0.82 (-1.12, -0.52)	0.001**	-0.87 (-1.42, -0.32)	-3.201	0.003*
Duration of Employment (year)	-0.66 (-1.04, -0.28)	0.001*	0.38 (-0.20, 0.97)	1.317	0.196
PPE Usage (Yes)	-1.47 (-8.01, 5.080	0.653	-1.97 (-7.33, 3.40)	-0.741	0.463
Health Problem (Yes)	-3.97 (-10.94, 3.00)	0.257	-0.15 (-5.65, 5.34)	-0.057	0.955
Smoking Habits (Yes)	3.61 (-2.33, 9.56)	0.227	2.67 (-2.13, 7.48)	1.125	0.268
Cumulative Pesticide Exposure (hour/month)	-0.35 (-0.49, -0.21)	0.001**	-0.17 (-0.36, 0.02)	-1.853	0.071
$R^2 = 0.516$					

[a]Simple Linear Regression, [b]Multiple Linear Regression

The model reasonably fits well. Model assumptions were met. There were no interaction and multicollinearity problems.

Significant at *p < 0.05, **p < 0.001

Trail Making (Trail A) = 79.80 – [0.32*Cumulative Pesticide Exposure]

An increase of cumulative pesticide exposure by one will significantly decrease the score of Trail Making (Trail A) by 0.32.

Trail Making (Trail B) = 87.27 – [0.87*Age]

An increase of age by one will significantly decrease the score of Trail Making (Trail B) by 0.87.

Table VII : Factors associated with Minnesota Manual Dexterity score among respondents (N=46)

Factors	SLR[a]		MLR[b]		
	B (95% CI)	p-value	Adjusted B (95% CI)	t-statistics	p-value
Dominant					
Constant			72.00 (56.56, 87.44)	9.431	0.001**
Age (year)	-0.80 (-1.10, 0.49)	0.001**	-0.20 (-0.72, 0.33)	-0.756	0.454
Duration of Employment (year)	-0.92 (-1.24, -0.60)	0.001**	-0.44 (-0.99, 0.11)	-1.606	0.116
PPE Usage (Yes)	-3.07 (-9.52, 3.38)	0.342	-1.02 (-6.10, 4.06)	-0.406	0.687
Health Problem (Yes)	-4.63 (-11.51, 2.26)	0.183	0.02 9-5.19, 5.22)	0.006	0.995
Smoking Habits (Yes)	3.00 (-2.93, 8.93)	0.314	2.08 (-2.48, 6.63)	0.923	0.362
Cumulative Pesticide Exposure (hour/month)	-0.39 (-0.51, -0.26)	0.001**	-0.20 (-0.38, -0.03)	-2.304	0.027*
R^2 = 0.559					
Non-dominant					
Constant			74.74 (59.55, 89.93)	9.951	0.001*
Age (year)	-0.82 (-1.12, 0.52)	0.001**	-0.32 (-0.84, 0.19)	-1.274	0.210
Duration of Employment (year)	-0.89 (-1.22, -0.56)	0.001**	-0.28 (-0.82, 0.27)	-1.036	0.307
PPE Usage (Yes)	-2.61 (-9.06, 3.840	0.420	-1.22 (-6.22, 3.78)	-0.493	0.625
Health Problem (Yes)	-7.59 (-14.21, -0.97)	0.026*	-3.30 (-8.43, 1.82)	-1.303	0.200
Smoking Habits (Yes)	3.05 (-2.86, 8.97)	0.304	-2.30 (-2.19, 6.78)	1.036	0.307
Cumulative Pesticide Exposure (hour/month)	-0.38 (-0.51, -0.25)	0.001**	-0.18 (-0.36, -0.01)	-2.088	0.043*
R^2 = 0.571					

[a]Simple Linear Regression, [b]Multiple Linear Regression

The model reasonably fits well. Model assumptions were met. There were no interaction and multicollinearity problems.

Significant at *p < 0.05, **p < 0.001

Minnesota Manual Dexterity (Dominant) = 72.00 – [0.20*Cumulative Pesticide Exposure]

Minnesota Manual Dexterity (Non-dominant) = 74.74 – [0.18*Cumulative Pesticide Exposure]

An increase of cumulative pesticide exposure by one will significantly decrease the score of Minnesota Manual Dexterity (Dominant) and (Non-dominant) by 0.20 and 0.18, respectively.

DISCUSSION

Five pesticides, namely Acetellic EC, Endmos-Q, Abate 500E. Abate 1.1G, and VectoBac WG from the insecticide group were used in mosquito fogging activities. There was no difference between the types of pesticides used by mosquito control workers in both DHO (Kota Bharu and Bachok) due to these similar pesticides were recommended and supplied by the Kelantan State Health Department. The pesticides were used as liquid formulation based on their usage during fogging activity. The pesticide was mixed with water to form an emulsion before being applied to the fogging machines. Pesticides in liquid formulation had a higher potential of poisoning because they were prone to splash and spillage (20).

Actellis 50 (an organophosphate) contains Pirimiphos-methyl as an active ingredient. Organophosphates are commonly used for pest control in residential and crops due to low cost, availability, non-lasting in the environment, and less vulnerable to pest resistance (21). At lower doses, it had low acute toxicity as proven by animal studies. At higher doses, organophosphates were more potent than acetylcholine and very toxic to the human nervous system. (22). Endmos-Q was a synthetic pyrethroid used in public health to control mosquito populations because it behaved as a fast-acting neurotoxin in insects. The risk level of Endmos-Q was considered as moderate. Its active ingredient had high acute toxicity data in animal studies. Hence, the neurotoxicity of cypermethrin had some potential risks to humans and might cause some adverse health effects. However, the effects of cypermethrin would depend on its concentration, duration, and frequency of exposure (23).

The risk level of Abate 500E and Abate 1.1G were moderate health. Both were organophosphate larvicides that were widely used to control the mosquito populations at the breeding sites. Both pesticide formulations used by mosquito control workers contain Temephos as its active ingredient which had low acute toxicity data in animal studies. Temephos was the same as other organophosphates cholinesterase inhibitors which resulted in the death of mosquito larvae before reaching the adult stage by affecting their central nervous system. Prolonged exposure to this chemical among humans could cause damage to the functions of different body organs and systems (24). VectoBac WG is a non-organophosphate, bacteria-based, water-soluble biological larvicide used to kill mosquito larvae (25). However, its risk level among mosquito control workers was considered as moderate based on the risk assessment conducted regarding its hazard rating and exposure rating.

Pesticide formulations contained only one active ingredient were Pirimiphos-methyl, Cypermethrin, Temephos, and Bacillus thuringiensis. The chemical class for each active ingredient was classed under Class II, III, and IV with the chemical class of organophosphate and pyrethroids. Of these, Cypermethrin was classified as "moderately hazardous", Primiphos-methyl as "slightly hazardous", Temephos as " moderately hazardous", while Temephos and Bacillus thuringiensis as "unlikely to present acute hazard in normal use' by the WHO (26). According to the classification by the US EPA (27) one product was classified as "warning", two were classified as "caution" and two were classified as non-required. Meanwhile, based on the Classification, Labelling and Safety Data Sheet of Hazardous Chemicals Regulations 2013 (CLASS Regulations) (18), Pirimiphos-methyl, Cypermethrin, and Temophoswere classified under acute toxicity hazard category 4 while Bacillus thuringiensis subsp. Israelensis was not classified (Globally Harmonized System Category 5). Besides, Actellic 50 EC was classified as poisonous, Abate 500E, and Abate 1.1G as harmful, while Vecto Bac WG as the least toxic under the Pesticide Act 1974 (28).

The majority of them (80.4%) reported experiencing fatigue each time after work. This condition might be due to their irregular working hours that exceeded 8-hours daily. Work-related factors such as long working hours, insufficient break time between shifts, shift rotations, inadequate rest, or a combination of these factors were the causes of fatigue after work (29). These work-related factors might also contribute to other neurobehavioral symptoms such as fatigue after wake-up early morning and drowsiness during the daytime. Workers started their work at 8.30 a.m. as they needed to prepare a visit to the dengue location area for on-site investigation of mosquito breeding sites. The number of dengue location areas depended on the number of dengue cases that have been notified to the Centre of Preparedness and Response Crisis (CPRC) of the district health offices. Then, in the evening, at 4.30 p.m., they needed to prepare for fogging activities which usually to be completed in the late afternoon from 6.30 p.m. to 7.30 p.m. Meanwhile, the prevalence of neurobehavioral symptoms such as fatigue, sleepiness, headache, feeling anxious, and dizziness was higher among pesticide applicators in the vector control unit (16) and farming (30) as compared to the control group. These symptoms might be caused by their chronic-low exposure to pesticide and other contributing factors that might influence their health.

In this study, none of the neurobehavioral symptoms reported was found to be associated with cumulative pesticide exposure as reported by Alia (31) and Muzammil (32) among farmers, respectively. In contrast, Afifah (16), Ismail et al. (30), and Negatu et al. (33) found a significant association between pesticide exposure and reported neurobehavioral symptoms among pesticide applicators. However, the prevalence of neurobehavioral symptoms could not be solely predicted by their direct pesticide exposure due to other contributing factors such as smoking and health status.

The duration of employment was another factor among occupational groups. A significant association was found between duration of employment and often dizziness at least once a week among mosquito control workers. However, no significant association was found between the duration of employment with neurobehavioral performances. The neurobehavioral symptom reported by workers was the delayed effects due to the neurotoxicity of pesticides that affected their central nervous system. Most of the mosquito control workers have been working for less than 10 years with an average of 13 years. Neurotoxin agents such as pesticides required about 5 to 10 years of exposure to induce the central nervous system (34).

Besides, a significant association between cumulative pesticide exposure and neurobehavioral scores was found in most of the NCTB tests such as Digit Symbol, Digit Span (Backward), Trail Making (Trail A), Minnesota Manual Dexterity (Dominant), and Minnesota Manual Dexterity (Non-dominant). Findings from this study showed that pesticide exposure was recognized as the main cause of deficiency in their neurobehavioral performance among workers. They were directly exposed to pesticides during fogging activity. The neurotoxicity of pesticides had the potential to affect neurobehavioral functioning by inducing their central nervous system.

This finding was in-line with some of the previous studies conducted by Afifah (16) Farahat et al. (35), and Sleim et al. (36) concluded the exposed group exhibited poorer performance towards pesticide exposure in most of the neurobehavioral tests as compared to control group. Similarly, Zubir (37) found that most of the neurobehavioral performance test scores showed a significant difference with total lifetime estimated pesticide intake. It was indicated that both pesticide intake groups, high and had lower mean scores than the non-pesticide intake groups. The differences between the mean score of the NCTB test might be also influenced by the reported neurobehavioral symptoms such as fatigue, difficulty concentrating, poor memory, lack of hand coordination, and trembling hands. These neurobehavioral symptoms reported might interfere with performance on all elements in NCTB.

Age was also found to be associated with neurobehavioral scores in Digit Symbol, Digit Span (Forward), and Trail Making (Trail B). According to the National Pesticide Information Center (38), older adults might be more likely to have adverse health effects due to the liver and kidneys became less able to remove pesticides from their bodies. The longer pesticides stayed in a body,

the more likely they were to build up to toxic effects. Hence, the neurotoxicity of the pesticide would affect the neurobehavioral functioning that might influence their performance in neurobehavioral tests.

Personal Protective Equipment (PPE) protected against pesticide exposures and reduced the potential risks of preparing, mixing, and applying the pesticides. However, no significant association was found between PPE usage either with neurobehavioral symptoms or NCTB scores. This might be due to the compliance of PPE usage among mosquito control workers. Most of them claimed that they used the PPE all the time during working (69.6%). The types of PPE that were used frequently during the preparation of pesticides were gloves, covered shoes, face masks, goggles, and aprons. During the fogging activities, the PPE used were respirator, covered shoes, earmuffs, coverall, gloves, and goggles.

Besides, current health problems suffered by the exposed subjects might also reduce their neurobehavioral performance (39). However, no significant association was found between health problems with neurobehavioral symptoms and neurobehavioral scores. A minority of them (23.9%) had some health problems such as hypertension, diabetes, and sinus. The symptoms associated with these health problems might be related to the neurobehavioral symptoms. Moreover, the reported neurobehavioral symptoms might be also related to each other.

Smoking was one of the contributing factors towards the prevalence of neurobehavioral symptoms and neurobehavioral performances. Nicotine in the cigarettes was a potent neurotoxin and it was also included in many insecticides (40). Smoking is associated with a lack of executive functions (41), cognitive flexibility (41,42), working memory (43,44), general intellectual abilities (45), auditory verbal-earning, and/or memory processing speed (46) would later affect the overall neurobehavioral performance. Half of them (52.2%) were smokers with more than 70% who had smoked for more than 10 cigarettes daily and been smoking cigarettes for 10 to 20 years. Smoking habits might influence their performance in neurobehavioral tests due to chemicals in the cigarettes However, no significant association was found between smoking habits and neurobehavioral scores.

Study Limitation

Larger sample size was needed to achieve more thorough and significant results. Moreover, the study design was a cross-sectional study in which causal inference could not be made. The total number of subjects that participated in this study could not fully represent the whole population of mosquito control workers in Kelantan. The generalisation of the results might be limited as the recruitment and sampling process only took place in two district health offices, Kota Bharu and Bachok, due to time constraints.

Pesticides used by mosquito control workers in Kelantan were not consistent. The types of pesticides used as recommended and supplied by the Ministry of Health have been always changing to suit with the current dengue situation. There might be different exposure levels from different types of pesticide used among the mosquito control workers. Besides, recall bias might be also introduced by the mosquito control workers regarding their past exposure, PPE usage, and work practices.

The Healthy Workers Effect (HWE) was a type of selection bias and another explanation for some non-significant results in this study. Some workers were not included in this study because they might be transferred to other non-pesticide related jobs or resigned from their current jobs due to illness caused by their susceptibility to pesticides. Improper workspace provided during data collection at the study location could prevent the researchers to retrieve accurate NCTB scores from the mosquito control workers.

CONCLUSION

The risk assessment found that the Endmos-Q, Abate 500E, Abate 1.1G, and VectoBac WG used in fogging activity were moderate. These contained the active ingredients Primiphos-methyl, Cypermethrin, Temephos, and Bacillus thuringiensis. The cumulative pesticide exposures (hour/month) was the main risk factor related to neurotoxic effects. The decreased score in the neurobehavioral assessment had provided an insight into the early effects of cumulative pesticide exposures by detecting impairment of mosquito control workers' perceptual-motor speed, short-term auditory memory, attention, and coordination. The neurobehavioral performances had provided the baseline health data to the relevant administration of these workers and could be used by the relevant authority to encourage the commitment of employers to protect workers through medical surveillance, assist in the amendment of existing guidelines for use, and providing adequate and suitable PPE. Future work is needed to understand more about the relationship between pesticide exposure and health as well as the best solution to reduce workers' exposure to pesticides.

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