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Blood Cholinesterase Concentration And Neurobehavioral Performance Of Primary Schoolchildren At Tanjung Karang, Malaysia

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ABSTRACT

Background: Organophosphate pesticide is widely used to protect plants from pest are numerously used in agricultural activity. However, organophosphate also found to cause harm on human such as impaired neurobehavioral performance after prolonged chronic exposure. **Objective:** This study was aim was to determine the cholinesterase level and the relationship with neurobehavioral performance. **Results:** Result showed a significant difference in blood cholinesterase concentrations between the exposed and unexposed group ($\chi 2$ = 39.822, p=<0.001). The total score of NCTB test showed that the exposed group (351.08) score was significantly lower than the unexposed group (365.93). Reaction Time Test showed significant difference between the exposed and unexposed group. There was also significant relationship between blood cholinesterase concentration and Pursuit Aiming Test (p <0.001). Housing area (p = 0.017), total household income (p=0.011), father's occupation (p = 0.012) and mother's occupation (p = 0.001) were confounders which have influenced the blood cholinesterase concentrations. **Conclusion:** Blood cholinesterase have significantly influenced the Pursuit Aiming Test scores which reflected on the impairment of motor steadiness.

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INTRODUCTION

Organophosphates and carbamates are cholinesterase-inhibiting pesticides commonly used in agriculture. A study state that farm workers and their children, as well as rural populations living near agricultural fields, have higher exposures to organophosphate pesticides than other populations (Lu, 1999). Children are exposed to pesticides through a variety of pathways, including dietary and non-dietary ingestion, inhalation of indoor and outdoor air, dermal contact with contaminated surfaces, and the use of medications and personal care products (NRC,1993).This study was aimed at determining the whole blood cholinesterase concentrations and the relationship with neurobehavioral performance. The importance of this study was to identify the exposure of studied children to pesticide using blood cholinesterase as indicator and their neurobehavioral performance as indicator of health outcome.

Pesticides impair primarily the nervous system through the neurobehavioral performance. Neurobehavioral test methods have been used for detecting this impairment (Savage,1988). Organophosphate pesticide can be absorbed rapidly via all routes – respiratory, gastrointestinal, ocular, and dermal. Young children may be highly exposed to pesticide because of their tendency to explore their environment orally, combine with their proximity to potentially contaminated floors, surface and air.

MATERIAL AND METHODS

This was a cross sectional comparative study and was conducted at Sawah Sempadan, Tanjung Karang Selangor which is a small fishing with a small town located 7 km north. The study was conducted on exposed primary schoolchildren aged 10 – 11 years who lived near the paddy field planted at the Tanjung Karang. While the unexposed group consisted of schoolchildren who were from areas away from the paddy fields.

Random sampling method was used to sample the respondents. The sampling frame of this study was the name lists provided by the class teachers of the studied schools. However, only those school

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children that fulfilled the inclusion criteria were included in the study. From the list, 80 students from exposed and 60 students from the unexposed school voluntarily participated. The inclusion criterions included were; they were normal and healthy primary school children within the age range of 10-11 years and obtained written consent from their parents.

Questionnaire:

Self-administered questionnaire was distributed to the studied schoolchildren to gather their information related to socio-demographic characteristic, health status, and exposure-related risk factors.

LOVIBOND 412670 AF267 Cholinesterase Test Kit:

The individual blood cholinesterase level was collected and analyzed by using LOVIBOND 412670 AF267 Cholinesterase Test Kit. The test kit requires only 0.01 ml blood for each respondent, obtained from a finger prick technique. Two types of reagent used in this test were indicator solution and substrate solution. The indicator solution consists of bromothymol blue in 250ml of deionized water (CO2 free) while substrate solution consists of 0.25g acetycholine perchlorate in 50ml.of deionized water (C02 free). The entire test were completed in below 30 minutes, facilitating the rapid evaluation of poisoning status. The blood cholinesterase activity in the blood from the respondent was expressed as a percentage of the activity in normal blood based on the colorimetric method.

Neurobehavioral Core Test Battery (NCTB):

The NCTB test comprised the Simple Reaction Time, Digit Span, Santa Ana Dexterity, Digit Symbol, Benton Visual Retention, Trail Making Test and Pursuit Aiming Tests were conducted in series to monitor the neurobehavioral performance.

Table 1: Neurobehavioral Core Test Battery items

Test	Function
Benton Visual Retention	Visual perception/memory
Time Reaction Movement	Attention/ response speed
Santa Ana Manual Dexterity	Manual Dexterity
Trail Making Pursuit Aiming Digit Symbol Digit Span	Motor & visual coordination/steadiness Motor steadiness Perceptual Motor Speed Short-term Memory Capacity

Result:

Background Information of Respondents:

Variables such as gender, number of student's sibling, body mass index (BMI), their parents education levels, parents' occupations, total household income, transport used, house location, and distance of their houses from school were compared to observe if there were significant differences between the two groups. The Man-Whitney U Test was used since they were not normally distributed according to the Shapiro-Wilk test. Both BMI ($z = -1.655$, $p= 0.098$) and number of sibling ($z = -1.045$, $p = 0.296$) variables, did not show any significant difference between the two study group. The household income, mother's occupation, house location and distance of study group's house to school showed significant differences between study groups.

Total household income showed a significant difference between exposed and unexposed group ($\chi^2= 15.220$, $p = 0.009$). Mother's Occupation ($p = 0.005$), house location ($p =0.001$), and distance of house to school ($p = 0.028$) also showed significant difference between the two groups. There was no significant difference in the BMI, family size, parental education levels and mode of transportations between the exposed and unexposed group.

Table 1: Comparisons of background information between the two groups.

Variable	Exposed n=80	Unexposed n=60	χ^2	p
Gender				
Male	33(41.25)	27(45)	0.197	0.657
Female	47(58.75)	33(55)		
Father's education level				
Primary School	17(21.25)	11(18.33)	1.517	0.824
Secondary School	59(73.75)	45(75)		
STPM/Diploma/degree	4(5)	4(6.67)		
Mother's education level				
Primary School	13(16.25)	7(11.67)		
Secondary School	62(77.5)	44(73.34)	7.361	0.118
STPM/Diploma/degree	5(6.25)	9(14)		
Total Household income				

<1000	29(36.25)	6(10)	15.220	0.009*
1000-2000	37(46.25)	39(65)		
2001-3000	9(11.25)	6(10)		
>3000	5(6.25)	9(15)		
Father's occupation level				
Professionals	3(3.75)	5(8.33)		
General worker/Normal Staff	19(23.75)	25(41.67)	9.132	0.058
Business/Self-employee	51(63.75)	27(45)		
Jobless/Pension	7(8.75)	3(5)		
Mother's occupation level				
Professional	2(2.5)	12(20)		
General worker/Normal Staff	8(10)	8(13.33)	16.656	0.005*
Business/Self-employee	12(15)	4(6.57)		
Jobless/Pension	7(8.75)	1(1.67)		
Housewife	51(63.75)	35(58.33)		

*Significant at p<0.01

Blood cholinesterase Level:

Cholinesterase enzyme is one of the biological indicators for acute and chronic organophosphate pesticide exposure. To measure the level of cholinesterase enzyme in the body, blood collection through finger prick were taken from the respondents. Based on the results, there was a significant difference in the blood cholinesterase concentration between the exposed and unexposed group (p = < 0.001).

Table 2: Blood cholinesterase concentrations of the respondents

Variable	Median (IQR)		z	p
	Exposed n=80	Unexposed n=60		
Blood Cholinesterase Level (%)	50 (12.50)	75 (25)	-7.112	< 0.001*

N=140

**Significant at p<0.001*

Distribution of Blood Cholinesterase Concentration:

Based on the results, only 42.9% of the children were found in the normal range, while 47.1% were in the over exposed range. This study also found 10.0% of the children were in the serious over exposed range.

Table 3: Distributions of Blood Cholinesterase Concentration

Variable	Frequency (%)		
	Exposed n=80	Unexposed n=60	Both Group N=140
Normal	16 (20)	44 (73.3)	60 (42.9)
Over exposed	50 (62.50)	16 (26.7)	66 (47.1)
Seriously Over Exposure	14 (17.5)	-	14 (10.0%)
Very Serious Over Exposed	-	-	-

N=140

Statistical results, showed that there was a significant difference between exposed and unexposed group in their blood cholinesterase concentration (p <0.001).

Table 4: Comparisons of blood cholinesterase between the two groups.

Category	Exposed	Unexposed	χ^2	p
Normal	16(20)	44(73.33)	42.594	<0.001*
Over Exposed	50(62.5)	16(26.67)		
Seriously over exposure	14(17.5)	0		

N=140

**Significant at p<0.001*

Neurobehavioral Performance:

For the neurobehavioral performance, a set of seven NCTB tests were carried out on the schoolchildren. Based on the results obtained, only Time Reaction/Movement Test showed a significant difference between the exposed and the unexposed group (p = 0.025).

Table 5: Comparison of neurobehavioral performance between two groups

Variable	Median (IQR)/Mean(SD)		z^a/t^b	p
	Exposed	Control		
Benton Visual Retention Test[a]	52 (12)	50 (14)	-0.258	0.796[a]
Digit Span Test[a]	50 (10)	50 (10)	-1.123	0.261[a]
Santa Ana Manual Dexterity Test[a]	51 (14)	51 (12.50)	-0.454	0.650[a]
Time Reaction/ Movement Test[a]	52 (14)	70.5 (108.25)	-2.247	0.025*[a]
Pursuit Aiming Test[a]	48 (15)	47 (13.50)	-0.394	0.693[a]
Trail Making Test[a]	48 (9)	47 (9)	-0.032	0.975[a]
Digit symbol Test[b]	50.08 (1.0164)	50.43 (1.0164)	-0.206	0.837[b]
Total NCTB score	351.08	365.93	-0.516	0.606

N=140
IQR = Inter-quatile range
SD = Standard Deviation
*Significant p<0.05
[a]Man-Whitney U test
[b] Independent T-test

The relationship between the Blood Cholinesterase and the Neurobehavioral Performance:

There was no significant correlation between the blood cholinesterase with all neurobehavioral performance scores except with Pursuit Aiming Test.

Table 6: The relationship between Blood Cholinesterase and Neurobehavioral Performance

Variable	Cholinesterase Level (%)					
	Exposed n=80		Unexposed n=60		Both Group N=140	
	r	p	r	p	r	p
Benton Visual Retention Test	0.204	0.069	-0.082	0.535	0.085	0.318
Digit Span Test	0.136	0.228	-0.194	0.137	0.031	0.721
Santa Ana	-0.118	0.295	0.059	0.652	<0.001	0.997
Time Reaction/Movement Test	0.010	0.931	-0.029	0.826	0.019	0.821
Trail Making Test	0.012	0.918	-0.045	0.731	-0.007	0.933
Pursuit Aiming Test	0.071	0.532	0.113	0.390	0.353	<0.001***
Digit Symbol Test	-0.88	0.437	0.208	0.111	0.088	0.301

N=140
****Significant at p<0.001*

Selected Variables Which Influenced Blood Cholinesterase Concentrations of studied children:

Multiple Linear Regression test was carried out to identify if there is any independent variable which may significantly influenced the blood cholinesterase levels. In this test, the dependent variable was blood cholinesterase while independent variable were transportation, housing area, distance from house to school, parents occupation, parents' education, and total household income data. From the overall selected variables, housing area, parents' occupation and total household income showed significant relationship with the blood cholinesterase of the studied schoolchildren.

Table 7: Selected Variables Which Influenced Blood Cholinesterase

Dependent Variable	B		t	P	F	p
(Constant)	101.81		5.853	<0.001**	2.284	0.021*
Transportation	-5.558		-1.717	0.088		
House location	7.331		2.428	0.017*		
Distance from house to school	0.297		-0.060	0.952		
Father's Education	-2.520		-1.298	0.197		
Mother's Education	1.980		0.924	0.357		
Father's Occupation	-6.106		-2.533	0.012*		
Mother's Occupation	-4.578		-3.369	<0.001**		
Total Household Income	-0.005		-2.590	0.011*		
BMI	0.421		1.132	0.260		
Gender	5.242		1.823	0.071		

N=140
Regression Method = Enter
**Significant at p<0.05*
**Significant at <0.001

Model I:
Cholinesterase Level:

101.811 -5.558 (*transportation*) + 7.331(*House location*) + 0.297*(distance from house to* school)-2.520 (*father's education*) + 1.980(*mother's education*) – 6.106 (*father's occupation*) – 4.578 (*mother's occupation*)-0.005(*total household income*) + 0.421(*BMI*) + 5.242 (*gender*).

R^2=0.179 (17.9% fit the model)

From the equation, the factor of housing area showed significant direct relationship while parents' occupation while the total income showed significant inverse relationship with cholinesterase concentrations in the blood.

Selected Variables Which Influenced Each NCTB test:

Multiple Linear Regression was carried out to identify independent variable which significantly influenced the Pursuit Aiming score. In this test, the dependent variable was Pursuit Aiming score while independent variable is the level of blood cholinesterase.

Table 8: Selected variables which influenced Pursuit Aiming Test among studied children

Dependent Variable	B		t	p	F	p
(Constant)	21.183		1.930	0.056	2.945	0.007*
Blood Cholinesterase Level	0.222		4.407	<0.001*		
Father's Education	0.739		0.650	0.517		
Mother's Education	-0.018		-0.014	0.989		
Father's Occupation	2.050		1.405	0.162		
Mother's Occupation	0.480		0.559	0.577		
Total Household Income	0.001		1.009	0.315		
Number of siblings	0.186		0.324	0.747		

N=140
Regression Method = Enter
**Significant at p<0.01*
**Significant at <0.001

Model II:
Cholinesterase Level:

21.183 + 0.222(*blood cholinesterase level*) + 0.739 (*father's education*) -0.018 (*mother's occupation*) + 2.050 (*father's occupation*) + 0.480(*mother's occupation*) + 0.001 (*total household income*) + 0.186 (*number of siblings*).

R^2=0.368 (36.8% fit the model)

From the equation, the blood cholinesterase showed significant positive relationship with the neurobehavioral performance.

Discussion:
Blood Cholinesterase Concentrations:

In this study, there was a significant difference in the cholinesterase concentrations between exposed and control group. In order to evaluate the degree of exposure to these children, activity of cholinesterase enzymes in the blood can be utilized as a biomarker for the organophosphate effects. The abnormal children showed abnormally low concentrations of cholinesterase enzymes measured in the red blood cell (Leilanie.J, 2007). In this study, it is shown that organophosphate caused depression on blood cholinesterase in exposed children compared to the control group. Previous study, showed that 56.31% of children living in farming area are overexposed to compared with 79.55% with normal blood cholinesterase in control group (How,2014).

The Cholinesterase Test Kit is based on the colorimetric concept of colour changes depending on the pH which varies when blood cholinesterase liberates acetic acid. The normal blood cholinesterase activity must be in the range of 100 – 75%. Below than that the respondents are said to have overly

exposed, seriously over exposed or perhaps very seriously exposed.

Neurobehavioral Performance:

Neurobehavioral performance is one of the methods used to indicate any significant effect of human nervous system as a result of any neurotoxic chemical exposure. From a study in Northern Ecuador on 79 elementary school children, organophosphate metabolites levels were associated with other domains of neurobehavioral (Grandjean et al., 2006). Others studies also demonstrated the effect of pesticide on neonates whom had abnormal reflexes on the assessment scale (Engel et al.,2007, and Young. 2005). Young children had a poorer performance on measures of response speed and latency, difficulties when performing tasks that involved short-term memory and attention (Ruckart, 2004).

In this study, the schoolchildren were required to complete all of the seven NCTB test items. NCTB was recognized by NIOSH and WHO expert group who have selected seven of the most widely used tests in human behavioural neuro toxicology research that were judged to be sensitive neurotoxic chemical. Based on the results shown, there was no significant difference in the neurobehavioral performance scores for each test items except for Time Reaction Test between the exposed and control group. However, there was still a difference in the total score of NCTB performance between the two groups in which the exposed showed a lower score than the control group. Previous study, in California, where children were measured through the error of commission, and hit reaction time, proved that the exposure to pesticide affected the attention of the young children (Amy, 2010).

Relationship Blood Cholinesterase and Neurobehavioral Performance:

Based on the result there was no significant relationship between blood cholinesterase and neurobehavioral test performance except for Pursuit Aiming Test. Even though the blood cholinesterase did not significantly affect the total impairments of the neurobehavioral performance of the studied children but the motor hand steadiness, speed and coordination of the children were impaired. Numerous studies on agricultural workers, found that organophosphate reduced the normal function of human motor steadiness. A study on workers poisoned by organophosphate showed that the affected group scored lower than the control group on all of the neuropsychological subtests, with significantly worse performance on five of the six subtests of the NCTB (WHO) and on 3 of 6 additional tests that assessed verbal and visual attention, visual memory, visuomotor speed, sequencing and problem solving, and motor steadiness and dexterity (Rosenstock, 1991). Several other studies showed detrimental measure on the performance of motor speed and coordination, sustained attention, and information processing speed (Reidy et al., 1992, Steenland et al.,1994 and Rothlein et al., 2006).

Selected Variables which Influenced the Blood Cholinesterase:

In this study, few variables were selected to determine if they affect the blood cholinesterase concentration. Based on the findings, three variables, namely the parents' occupation, housing area and total household income, significantly influenced the activity of the blood cholinesterase.

If parents or other family members worked with pesticides, there were tendencies that chemicals might be brought into the home on work boots, work clothing, tools, or on the body. Several studies have demonstrated that farmers' children have significant higher exposures to workplace chemicals than control children (NIOSH, 1995 and Whelan et al., 1997). For instance, a study from Nicaragua showed that the aerial drift of pesticides caused health symptoms and lowered cholinesterase concentration in the population living near to a sprayed cotton field (Keifer et al, 1996).

Total household income might also have significant influence in which families with better education and income might be able to provide better storage of pesticide so that their children are less exposed. Furthermore, the parent' occupation made them lived in the agricultural area. Study findings on these children who lived in or near to these paddy farming areas for an extended period of time, showed that the house location as one of the factor which contributed to the pesticides exposure.

Selected variables influenced Neurobehavioral Performance:

Multiple Linear Regression analysis showed that there were several confounding variables which significantly influenced the neurobehavioral performance of the studied children. From the seven tests conducted, only Pursuit Aiming Test showed significant relationship with the blood cholinesterase. Acetylcholinesterase terminates signal transmission in cholinergic neurons by catalysing the hydrolysis of the neurotransmitter acetylcholine, which allows these neurons to return to their resting state after activation. Inhibition of acetylcholinesterase, due to organophosphate exposure, lead to the accumulation of acetylcholine at the synapse, resulting in over stimulation of cholinergic neurons which impaired the motor functions (Kobayashi, 1986).

Conclusion:

In conclusion, blood cholinesterase of the exposed children showed significantly lower concentrations than the unexposed group. Confounding variables were found to have

significant influence on the blood cholinesterase, namely the parents' education, and the total household income of the family. The blood cholinesterase was also found to be significantly related to Pursuit Aiming Test. Occupational organophosphate pesticide, is a neurotoxin, thus the use of such pesticide should be controlled.

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