Mosquito control workers in Malaysia: Is lifetime occupational pesticide exposure associated with poorer neurobehavioral performance?

Muhammad Zubir Yusof[a,b], John W Cherrie[c, d], Niza Samsuddin[e], Sean Semple[f]

[a]Kulliyyah (Faculty) of Medicine, International Islamic University Malaysia
[b]Division of Applied Health Sciences, University of Aberdeen, UK
[c]Institute of Biological Chemistry, Biophysics and Bioengineering, Heriot Watt University, UK
[d]Institute of Occupational Medicine, Edinburgh, UK.
[e]Kulliyyah (Faculty) of Allied Health Sciences, International Islamic University Malaysia
[f]Institute for Social Marketing and Health, University of Stirling, UK

Corresponding author:

Muhammad Zubir Yusof

Department of Community Medicine
Kulliyyah (Faculty) of Medicine,
International Islamic University Malaysia,
Bandar Indera Mahkota Campus,
Jalan Sultan Ahmad Shah, 25200 Kuantan,
Pahang Darul Makmur. MALAYSIA
Fax: +609-5716798
Phone: +609-5704601
E-mail: zubiryusof@iium.edu.my

Abstract

Background Use of pesticides has been linked to neurobehavioral deficits among exposed workers. In Malaysia, organophosphate and pyrethroid pesticides are commonly used to control mosquito-borne diseases. **Objective** This study aims to assess workers' lifetime occupational pesticide exposure and examine the relationship with neurobehavioral health. **Methods** A cross-sectional study was conducted on 158 pesticide-exposed and 176 non-exposed workers. To collect historical exposure and job tasks, a questionnaire and an occupational history interview were used. Pesticide exposure was measured in a subgroup of workers via inhalation and skin contact. The total pesticide intake of each worker was assessed using inhalation and dermal exposure models. CANTAB® computerised neurobehavioral performance assessments were used. **Results** The participants' mean age was 31 (8) years. Pirimiphos-methyl (median = 0.569 mg/m^3, IQR = 0.151, 0.574) and permethrin (median = 0.136 mg/m^3, IQR = 0.116, 0.157) had the highest measured personal inhalation concentrations during thermal spraying. The estimated total lifetime pesticide intake for exposed workers ranged from 0.006 g to 12,800 g (median = 379 g and IQR = 131, 794 g). Dermal exposure was the predominant route of pesticide intake for all workers. Compared to controls, workers with high lifetime pesticide intake had lower Match to Sample Visual (adjusted B = -1.4, 95% CI = -2.6, 0.1), Spatial Recognition Memory (adjusted B = -3.3, 95% CI = -5.8, 0.8), Spatial Span (SSP) (adjusted B = -0.6, 95% CI = -0.9, 0.3) scores. Workers with low pesticide intake performed worse than controls (adjusted B = -0.5, 95% CI = -0.8, -0.2) in the SSP test, but scored higher in the Motor Screening test (adjusted B = 0.9, 95% CI = 0.1, 1.6). Higher Paired Associates Learning test scores were observed among higher (adjusted B = 7.4, 95% CI = 2.3, 12.4) and lower (adjusted B = 8.1, 95% CI = 3, 13.2) pesticide intake groups. There was no significant difference between the Reaction Time and Pattern Recognition Memory tests with lifetime pesticide intake after adjusting for confounders. **Conclusion** Pesticide exposure has been linked to poorer neurobehavioral performance. As dermal exposure accounts for a major fraction of total intake, pesticide prevention should focus on limiting dermal exposure.

KEYWORDS: Pesticide, worker, neurobehavioral, lifetime, dermal, inhalation, exposure, organophosphate, pyrethroid

Introduction

Approximately 2.4 million metric tonnes of pesticides are used worldwide each year. The World Health Organization (WHO, 2011) reported that the commonest insecticides globally used for vector control were organochlorines (4,429 tonnes), followed by organophosphates (OP) (1,375 tonnes), pyrethroids (414 tonnes) and carbamates (30 tonnes). South East Asia uses the greatest amount of organochlorines and OPs. In Malaysia, OPs and pyrethroid pesticides are commonly used to control mosquito-borne diseases. Mosquito control is a part of vector-borne disease control program especially in reducing the transmission from mosquitos to humans of Dengue and Zika viruses.

Mosquito control workers are likely to be highly exposed to pesticides during spraying and this repeated, long-term pesticide exposure may affect their health. Previous studies showed pesticide exposure is associated with poorer neurobehavioral performance, particularly cognitive function, psychomotor function, sensory and motor function, and nerve function (Baldi et al., 2012; Berent et al., 2014; Blanc-Lapierre et al., 2013; Rohlman et al., 2014).

Most previous research examining the health effects of pesticides have focused on workers in the agricultural sector. There is limited information on the exposure or health of workers involved in tasks to control vector-borne diseases. As mosquito control is increasing, there is the potential for more workers to be frequently exposed to high levels of pesticide. In addition, no previous data characterising the inhalation and dermal exposure of these workers has been reported. This study aimed to examine the association between estimated lifetime occupational exposure to pesticides and neurobehavioral test performance of mosquito control workers in Malaysia in a cross-sectional epidemiological study.

Methodology

Recruitment

The recruitment and sampling process took place across Health District offices in Malaysia from January to September 2014. Workers aged 18 years and older in the mosquito control team and a comparison group of administrative workers in the same Health District offices were invited to participate. The target sample size was 400 workers to represent a minimum clinically significant effect in health outcome measurement in this study. Written informed consent was gained prior to participation.

Exposure assessment

Expert interviews were conducted with three long-service Vector Control Unit workers with a minimum of 10 years of employment. Information about work process changes over the period of their employment was collected to construct a questionnaire to gather information on exposure of all workers. A short, structured occupational history interview was also administered to all participants in order to gather additional detail to enable an estimation of personal exposure to pesticides over their lifetime. This consisted of personal history questions, a review of occupational history, and specific pesticide task questions for each job where pesticide exposure was identified. The participants were given an opportunity to provide as much detail as possible about pesticide use tasks as the questionnaire had open-ended questions. This strategy was designed to maximise the collection of data relating to exposure variables such as areas sprayed, quantities of pesticide used, methods of application and time periods. Data of pesticide exposure in non-occupational settings was also gathered.

Pesticide exposure data was gathered from a variety of sources, including personal communication with the management staff, a review of safety data sheet (SDS) of current pesticides used and relevant scientific literature to pesticide-related activity. This provided data on the type of pesticide used by the worker at the workplace along with some information on pesticide constituents. It also provided information about ventilation and pesticide application methods. An observational walkthrough or ride-along survey was the initial step for researchers to gain a knowledge of how mosquito control activities are carried out. The preliminary information gathered from this survey assisted the researcher in developing questions regarding potential factors that could influence exposure levels. There were no historical occupational hygiene monitoring reports available from these vector control units.

For a subset of workers measurements of personal inhalation and dermal exposure to pesticides were made during pesticide mixing, handling and application tasks. The size of the subset was determined based on similar exposure groups such as mixing, thermal spraying, and ULV spraying. A minimum of nine workers per similar exposure group were recruited for these measurements. A task-based sampling strategy was used to collect personal airborne pesticide exposure measurements. During the morning shift mosquito control workers were mostly involved in a non-pesticide related activity such as surveying mosquito breeding sites. Pesticide-related tasks in this study tended to be conducted in the ‘early morning shift’ (before sunrise), mainly using Ultra Low Volume (ULV) spraying and the afternoon shift (typically from 3.00 pm to 8.00 pm) for mixing, thermal spraying and ULV spraying. Each worker wore personal air sampling train to collect a sample in the workers’ breathing zone using Occupational Safety and Health Administration (OSHA) Versatile Sampler (OVS) polyurethane foam (PUF) tubes (SKC Inc, USA) with an Apex sample pump (Casella CEL, UK), operating at a flow rate of 1 to 5 L/min. Two tasks were sampled for each worker: the first included from commencement of pesticide preparation until the end of equipment clean-up for the mixing task and the second involved the application of pesticide during spraying activity. All the collected tube samples were kept refrigerated and shipped to the Institute of Occupational Medicine (IOM), UK for analysis. The results obtained were expressed as mg/m^3 (and ppm) of pesticide, averaged over the duration of the task sampled. The U.S. NIOSH manual Analytical Methods (Eller & Cassinelli, 1994) was used to design the air sampling and analysis strategy.

Dermal exposure was assessed using a skin wipe method performed in accordance with OSHA standards (US OSHA, 2008) using clinical wipes saturated with 70% isopropyl alcohol. The skin wipe samples were taken from the entire palm of both hands, both left and right forearms, neck and forehead, both pre- and post- task. An acetate template with an open aperture of 25 cm^2 was used to wipe samples from inner surfaces of forearms, neck and forehead. Three sequential wipes were collected for each sample area and stored in a single labelled sealed container for each worker. To avoid cross contamination the researcher used a clean template and a fresh pair of gloves for each worker and sample area. The samples were kept refrigerated and shipped to IOM where they were analysed for the relevant pesticide compounds using gas chromatography-mass spectrometry. The results were expressed in microgram (μg) for all three wipes combined.

The inhalation exposure modelling developed by Cherrie and Schneider (1999) was used to reconstruct workers' inhalation pesticide exposure. This model allows the estimation of an airborne exposure level for single work tasks by applying numerical factors linked to personal exposures. The factors include the intrinsic emission of the pollutant (ε_i); the method of handling or processing at the source (h); the efficiency of any local controls, such as local ventilation ($1-\eta_{lv}$); the time that the source is actively emitting (t_a); passive emission (ε_p), the use of personal protective equipment ($1-\eta_{ppe}$) and general ventilation (d_{gv}):

$$C = (\varepsilon_i \cdot h \cdot (1-\eta_{lv}) \cdot t_a + \varepsilon p) \cdot (1-\eta_{ppe}) \cdot d_{gv}$$

The workers' environment was divided into two zones of emission: the near-field and far-field. The near-field was defined as a volume of approximately 8 m^3 surrounding a person (i.e. a cube of side 2 m, centred on the workers head) (Cherrie, 1999). The far-field is considered as the room space outside the near-field where the contaminant concentration can be affected by dilution or general ventilation. Numeric factors were assigned to each of the parameters for each task for sources in the workers' near and far-field to aid the consistency of the exposure for exposure reconstruction (see Supplementary, Table S2).

In the first step of reconstructing the inhalation exposure, each of the four job titles (Environmental Health Inspector (EHI), Public Health Assistant (PHA), 'Fogger', and Driver) was divided into component tasks that included supervising, mixing of pesticides, spraying and cleaning up of the equipment (see Supplementary, Table S1). Then, the reconstructed exposure level was assessed across three different eras (1970 – 1989; 1990 – 2004; and 2005 – 2014). The division of these three eras was based on the information gathered from interviews with long-service employees and the management staff about changing work practices, types of pesticide used and the usage of PPE. Finally, the calculated exposure level for each component tasks and eras was combined for each job title to generate the estimated mass of pesticide received by inhalation, expressed in grams.

The exposure modelling method devised by Semple *et al.* (2001a) was used to reconstruct workers' dermal pesticides exposure. This model required similar information used as in the inhalation exposure modelling. From a review of the tasks carried out by the workers, it was concluded that there were two conditions that might cause the deposition of pesticide onto workers' skin: pesticide spraying; and the mixing of pesticides. During pesticide spraying, the overspray can deposit on the worker's skin when the pesticide is sprayed on solid objects such as walls; overspray can also occur from sudden changes in wind direction. Additionally, leaks can also occur if the worker did not tighten up the cap of the pesticide tank closely, especially when using a hand-held thermal sprayer. Mainly during mixing of dilute pesticides, the leak and splash may result in the deposition of pesticides onto the skin. Poor hygiene practice can also contribute to leaks of pesticides that can contaminate skin during spraying and mixing (see Supplementary for guidance materials, Table S3). A formula from Sartorelli *et al.* (1998) was used to predict pesticide flow across the skin (J). It used the pesticide's permeability coefficient (K_p) and the pesticide's concentration on the skin (C). A first-order kinetics model was used to calculate the amount of pesticide absorbed per unit of exposed surface over the drying time. The pesticide uptake rate over time was combined with the total area of clothes or skin exposed to the pesticide.

The estimated skin loading of diluted pesticides was calculated for each task; mixing, thermal spraying, and ULV spraying. In a typical mixing task, 96 L of dilute pesticides was prepared. Using assumptions from the Semple *et al.* (2001a) dermal model of spray painters' exposure it was estimated that 0.1% of 96 L of prepared pesticides (i.e. 9.6 mL) was likely to spill or splash onto an exposed skin area of 421 cm^2. This skin area was derived based on the estimate of 10% of the total surface area of hands and arms. The estimated loading of pesticide on the exposed skin area was then calculated by multiplying the concentration of the prepared pesticides by the volume of pesticide per cm^2 of exposed skin. Meanwhile, for both thermal and ULV spraying, the skin loading of pesticide was estimated by multiplying the concentration of pesticides on skin with thickness of pesticides formed by single droplet deposition on each cm^2 of bare skin. The average of skin loading of pesticides measured for each body part (hands, forearms, neck and forehead) were calculated to give total amount of skin loading for each task and pesticide. During the fieldwork, only diluted pesticides were used for mosquito control, thus the diluted pesticides were selected to compare between estimated and measured skin loading.

Current airborne and dermal exposure measurements collected during this study were also used to provide a degree of validation of the estimates produced (see Supplementary for model validation). The mean measured data (ppm.hours) and estimated inhalation exposure data (exposure unit.hours) for the era of 2005 to 2014 for each job title and tasks were compared, and the ratio for each comparison was derived.

The masses of pesticide received by both inhalation and dermal routes were combined using a simple calculation. The mass of pesticide absorbed by inhalation was calculated by considering the respiratory minute volume (m^3/min) (R_{vol}), exposure time (T), the concentration of pesticide in air (mg/m^3) (C_{air}) and any respiratory protective equipment (RPE) the worker may have been wearing. The concentration of pesticide in the air was derived from reconstructing the inhalation exposure as described previously. The RPE factor was a dimensionless unit which was based on similar guidance to that inhalation exposure modelling. The formula for calculating the mass of pesticide uptake by inhalation is shown below:

$$U_{inh} = (R_{vol} \cdot T \cdot C_{air}) / RPE$$

Finally, the pesticide intake per task for combined inhalation and dermal reconstructed exposure level was calculated for each job title and component tasks based on three different eras. Then, these calculated values were used to estimate the total lifetime pesticide intake for each worker by combining the information gathered from the ‘expert’ and occupational history interviews including average days on task undertaken per year and number of years doing that particular task based on the eras they worked (A worked illustrative example is provided in Supplementary materials).

Neurobehavioral assessment

A series of neurobehavioral tests was administered to all the study participants by using the CANTAB® (see Supplementary for test description, Table S15). The tests used were non-invasive, language-independent and utilized touch screen technology and a press pad button for reaction timing test. The tests were performed in a private room with a guide from the researcher to avoid any distraction. The tests cover cognitive domains including attention, visual memory, executive function and induction. In general, about 40 minutes was needed to complete all seven tests. The tests were performed after the study participants completed the questionnaire and occupational history interview.

Statistical analysis

Questionnaire data were extracted and entered directly into an SPSS® (IBM Corp., 2015) database. Simple descriptive statistics were generated to compare workers based on their exposure to the pesticide. The scores for neurobehavioral performance tests were automatically generated by the CANTAB®.

In estimating total lifetime pesticide intake among exposed workers, the parameter values to reconstruct pesticide exposure for both inhalation and dermal were entered manually into MS Excel 2013 worksheet. The exposure was then calculated to generate the total value of pesticide intake for each individual worker (expressed in grams).

A chi-square and an ANOVA test were employed to examine the relationship between the exposure groups and socio-demographic characteristics of the workers. A multiple linear regression analysis using the enter method was selected to identify the relationship between neurobehavioral performance tests and estimated total lifetime pesticide intake. The linear relationship between pesticide exposure and test scores was assumed after we checked that there was no multicollinearity problem by obtaining the tolerance for each independent variable. A tolerance value of more than 0.4 is considered acceptable to assume a linear relationship (Chan, 2004). High level of multicollinearity, which occurs when variables are too closely related, are indicated by tolerance values close to zero. We also checked the linearity and assumed equal variance based on the scatter plot between residual (x) and predicted values (y) (see Supplementary for scatter plots, Figure S16 a to g). The potential confounders including age, educational attainment after finishing school and smoking status were undertaken for adjustment.

Results

A total of 334 participants completed the study with an overall response rate of 83.5 %. The mosquito control workers were sub-divided into two groups based on their calculated pesticide exposure (High, n = 79 and Low, n = 79). This division was based on the median of the estimated total lifetime pesticide intake. High intake was defined as total estimated lifetime pesticide intake of 379 g or more. The third (control) group had no pesticide intake from exposure in the workplace. The three groups were used to further analyse the relationship between exposure and neurobehavioral performance.

Sociodemographic

Table 1 presents the socio-demographic characteristics of all workers. There were no statistically significant differences between the exposure groups except for smoking status, which was lower in the control group (no intake). The majority of the workers (n = 147, 93%) having less than ten years of pesticide exposure. The longest duration of exposure was 32 years (n = 2, 1.3%), whereas the shortest duration of exposure was one year (n = 38, 24.1%).

Personal air sampling and skin wiping

Table 2 summarises the measured air concentrations of active compounds of pesticide and sampling duration for each task. These data also showed that both OP (pirimiphos-methyl (median (IQR) = 0.569 (0.151, 0.574) mg/m^3)) and pyrethroid (permethrin (median (IQR) = 0.136 (0.116, 0.157) mg/m^3)) during thermal spraying produced a higher concentration in the workers breathing zone, compared to mixing and ULV spraying.

The results of skin wiping based on the body parts are presented in Table 3. The forehead constituted the highest detectable median pirimiphos-methyl (4.04 μg/cm^2) skin loading (based on three measurements). The highest measurement median value for fenitrothion was observed on forearms (right = 4.94 μg/cm^2; and left = 3.82 μg/cm^2) – based on only two samples. In contrast to the OP measurements, approximately 60% of samples analysed for pyrethroids (permethrin and d,d,T-cyphenothrin) had detectable values.

Exposure modelling

Based on a comparison of mean measured data (ppm.hours) and estimated inhalation exposure data, the overall median ratio was 132.5 (exposure unit.hours). One exposure unit.hours equal to 0.008 ppm.hours was considered as a conversion factor based on one divided by the median ratio (132.5). Generally, there was a 'fair' relationship between the log-transformed measured and estimated exposure concentration (rs = 0.44) even though the correlation was not significant (see Supplementary, Figure S1).

It shows that values of skin loadings for mixing and ULV spraying are close to the 1:1 line but values for thermal spraying are much higher (see supplementary, **Error! Reference source not found.**). Overall, the relationship between estimated and measured skin loading of pesticides for all three tasks showed a 'fair' relationship (Spearman's correlation coefficient, r_s = 0.38, p = 0.403) even though the correlation was not statistically significant.

Cumulative pesticide exposure

The estimated total lifetime intake of pesticide for pesticide-exposed workers ranged from 0.006 g to 12,800 g (median = 379, IQR = 131, 794). Exposure via the dermal route accounted the majority of combined estimated total lifetime pesticide intake (median = 369 g, IQR = 128, 772).

Neurobehavioral performance

Table 4 summaries the relationship between estimated lifetime pesticides intakes with neurobehavioral performance based on four main domains that include attention, visual memory, executive function and induction. Even though education status and age were not significant in Table 1, these variables are known as potential confounders for neurobehavioral performance (Ismail et al., 2012; Meyer-Baron et al., 2015; Starks et al., 2012a). In Attention Domain, after adjustment for possible confounders, estimated total lifetime pesticide intake remained significantly associated with Match to Sample Visual Search (MTS) test, as shown in Table 4. Relative to those workers with no pesticide intake, the MTS score of workers who had high pesticide intake was reduced by 1.4% (95% Confidence Interval (CI) = - 2.6 to - 0.1; p = 0.035). Workers with low pesticide intake also performed poorer than workers with no pesticide intake, where they scored 1.2% (95% CI = - 2.5 to 0.03) less correct in the MTS test. However, the result was not statistically significant.

Two out of three tests in the visual memory domain showed a significant relationship with estimated total lifetime pesticide intake after adjusting for potential confounders. The score for Spatial Recognition Memory (SRM) test was significantly lower for those workers with high pesticide intake (adjusted B = - 3.3, 95% CI = - 5.8 to - 0.8). The findings show that total error in the Paired Associated Learning (PAL) test increased in both pesticide-exposed groups relative to the no exposure group; high pesticide intake (adjusted B = 7.4, 95% CI = 2.3 to 12.4, p = 0.005) and low pesticide intake (adjusted B = 8.1, 95% CI = 3 to 13.2, p = 0.002).

In executive function domain, Spatial Span (SSP) scores were significantly lower for workers who had high pesticide intake (adjusted B = - 0.6, 95% CI = - 0.9 to - 0.3; p = 0.001) and low pesticide intake (adjusted B = - 0.5, 95% CI = - 0.8 to - 0.2; p = 0.005) compared to workers with no pesticide intake. Table 4 shows that workers who had low pesticide intake had a significantly greater mean error (adjusted B = 0.9, 95% CI = 0.1 to 1.6; p = 0.027) in Motor Screening Task (MOT) test compared to those workers with no pesticide intake after adjusting for potentially possible confounders.

Discussion

The main findings of our study suggest that occupational lifetime pesticide intake has a significant link with poor neurobehavioral health. Mosquito control workers in Malaysia and many other parts of the world are involved in the use of pesticides to control vector-borne diseases. Unfortunately, there is limited literature characterising either their exposure to pesticides or the health of these workers. There is some evidence from the literature that exposure to pesticides, particularly OP-based pesticides, may be associated with poorer health.

In our study, thermal spraying tasks produced the highest pesticide exposures. This finding agrees with Geer *et al*. (2004) that pesticide applicators experienced higher inhalation exposure to chlorpyrifos. A study by Lozier *et al.* (2013) found that pesticide applicators had high pesticide exposure using either hand-held equipment (manual backpack pump) or vehicle mounted equipment (tractor/boom system). Most exposure measurements from ULV spraying tasks in our study showed low pesticide exposure. This might be because workers who performed the ULV spraying stayed inside vehicles with ‘enclosed’ cabs, with closed windows and air conditioning. The exposure that did occur may have been due to the consequence of air infiltration through cab leaks or during the occasional times that workers had to venture out of the cabin.

Skin wiping analysis demonstrated that the forearms and forehead had the highest contamination of pesticide. It was observed that most of the workers performed pesticide-related tasks with bare forearms, generally wearing short-sleeved shirts, long trousers, and gloves. Previous studies have shown that workers who use hand-held spraying equipment often experience higher dermal exposure to pesticide than those using other techniques such as ULV spraying (Baldi et al., 2006; Cessna & Grover, 2002).

Results from our study cannot be directly compared to other literature - there is only one study that specifically reports lifetime pesticide exposure from both inhalation and dermal reconstruction methods. The study by Dick *et al.* (2007) used the exposure estimation method by Cherrie and Schneider (1999) to estimate airborne concentrations of pesticide exposure and dermal uptake exposure modelling by Semple *et al.* (2001a) to generate both inhalation and dermal task-exposure estimates. They found that high exposure to pesticide may increase risk of having Parkinson’s disease (OR=1.41, 95% CI 1.06 to 1.88), but not for low exposure (OR=1.13, 95% CI 0.82 to 1.57).

The use of a specific dermal exposure model (Brouwer, et al. 2001; Semple et al., 2001a) with some additional modification was considered an efficient method to estimate pesticide intake via the dermal route. In addition to overspray, other factors such as spill, leak and splash during mixing and spraying were also considered in the dermal exposure model used in our study. Dermal exposure was estimated independently from inhalation exposure before intake from both routes were combined to determine the proportion from each route of exposure contributing to the total pesticide body burden.

The present work demonstrated that skin is the primary route of pesticide intake among mosquito control workers in Malaysia. This result supports the notion that the dermal route plays a significant role in terms of total body burden when workers are exposed to pesticides (Semple, 2005; Xu, et al. 2009). Consistent with previous studies (Bekö et al., 2013; Gong et al., 2014; Little et al., 2012; Rauma et al., 2013) the dermal pathway can contribute significantly to the total pesticide intake.

Neurobehavioral or neuropsychological performance tests have been used widely in assessing the cognitive impairments that may be associated with pesticide exposure (Baldi et al., 2011; Rothlein et al., 2006; Starks, et al., 2012b; Wesseling et al., 2002). The results found in the literature have varied, and no consistent effects have been identified. This may be due to methodological differences, particularly in the use of specific questionnaires, industrial hygiene measurement records, and the application of job exposure matrices as the exposure assessment strategies. For example, when using questionnaires, a specific job title may not provide valid and complete information about specific pesticide exposure and may lead to recall bias. It is clearly important to ensure the accuracy of exposure assessment as it is a key issue for epidemiological research on occupational risk. Thus, our study uses a structured and logical approach to exposure estimation as an alternative to this assessment (Semple, et al., 2001b). The findings in our study reported a significant association of pesticide exposure with neurobehavioral performance, which is consistent with previous studies that used similar exposure assessment methods to assess the exposure-response relationship between pesticide exposure and Parkinson disease (Dick et al., 2007).

Specifically on the use of CANTAB® in assessing cognitive impairment caused by OP exposure in occupational settings, Jamal *et al.* (2002) compared three different groups of sheep dippers exposed to OP who were classified based on neuropathy signs (no, possible and probable/definite). They estimated exposure to pesticide based on an exposure model for a single dipping day (OPEXP) (Buchanan et al. 2001). It was reported that those sheep dippers with possible neuropathy had high cumulative pesticide exposure (4364 OPEXP) compared to the other two groups (no = 1349 OPEXP; and probable/definite = 1758 OPEXP).

However in contrast to our study, they found no changes in cognitive functions in the three groups in all test domains such as attention, memory and visual memory. They suggested that non-significant results might be due to errors in the exposure estimates, both from the recall of exposure days and tasks and error in terms of empirical estimates of parameters in the exposure model (Buchanan et al., 2001; Pilkington et al., 2001). In the current study, we are aware that recall bias might be introduced in data collection during the interview. Workers may not recall the details of previous job tasks and pesticide exposure, resulting in differential exposure misclassification. However, this was minimised by cross-checking the results of self-reported descriptions with those reported by long-service employees.

Other studies have reported that poor neurobehavioral performance related to pesticide exposure. These studies used various assessment tools in different domains. In the PHYTONER study of vineyard workers in France (Baldi et al., 2012; Blanc-Lapierre et al., 2013) the researchers used crop-exposure pesticide matrix (PESTIMATE) and pesticide exposure (PESTEXPO) study for dermal contamination (Baldi et al., 2012) to estimate cumulative lifetime OP exposure. They reported that vineyard workers with higher cumulative lifetime OP scores, specifically to mevinphos, were more likely to experience deficits in attention test as measured in the multiple choice (form F) of the Benton Visual Retention Test (BVRT) (OR = 3.26, 95% CI = 1.54 to 6.88). This association was also observed in our study, which indicates workers' attention might be affected if they receive high pesticide intake in their bodies as measured by the MTS test.

The Agricultural Health Study found that pesticide applicators who reported exposure to carbaryl (a carbamate) showed decreased performance on the Continuous Performance Test for sustained attention (Starks, et al., 2012b). Those with five years cumulative exposure also had an impairment in attention when measured using Selective Attention test among Hispanic agricultural workers (Rohlman et al., 2007). These findings are consistent with the results of our study on mosquito control workers assessed using the MTS test. The MTS test used in the CANTAB® may detect a degree of cognitive dysfunction which can be an indicator of Alzheimer disease (Égerházi et al., 2007).

Pesticide exposure has also been associated with visual memory. For instance, instead of assessing attention in the BVRT in the PHYTONER study, it was also used to assess visual memory among workers exposed to pesticides, specifically OP. It was reported that workers with highest OP exposures were at increased risk of performing poorly in the test (Blanc-Lapierre et al., 2013). A study by Rohlman *et al.* (2007) suggested pesticide handlers, especially males, performed poorly in visual memory test (MTS) as compared to non-pesticide handlers by using BARS. Even after adjusting for confounders, the MTS score found in that study was significantly lower (2.04 points) than the score achieved by non-pesticide handlers. This is in line with the results of our study; pesticide-exposed workers experience deficits in visual memory when assessed by the PAL test. However, only workers who had high pesticide intake demonstrated poor performance in the SRM test for visual memory as compared to workers with no pesticide intake.

The SSP test (executive function) used in our study is able to assess working memory capacity and is a visuospatial analogue of the Digit Span test (Fray et al., 1996). This test is also used for detecting schizophrenia conditions as does the SRM test (Deac et al., 2015). As mentioned earlier, pesticide-exposed workers performed worse in this test compared to those workers without pesticide exposure. Findings in previous studies support this result. Pesticide exposure has been correlated with poorer executive function as indicated by Digit Span (Rasoul et al., 2008; Rothlein et al., 2006), Digit Symbol (Rasoul et al., 2008), and Symbol Digit (Rohlman et al., 2007).

The workers' speed of response and accuracy ability were assessed by the MOT in the induction test. It was found that workers with low pesticide intake had impaired accuracy ability. This problem was also found in a study by Dassanayake *et al.* (2009) among farmers exposed to OP pesticide for more than five years as they made more counting errors in the auditory oddball event-related potentials tasks which signified accuracy impairment of stimulus classification.

There was no significant difference for speed response between exposed and non-exposed workers in our study. This was in contrast to previous studies, that found significant associations between pesticide exposure and poorer cognitive speed test performance in tests such as Trail making (Baldi et al., 2011) and finger tapping (Rothlein et al., 2006). The inconsistency of the findings between our study and other studies could be explained by the difference in sensitivity of the battery tests (Kamel & Hoppin, 2004). In particular, different neurobehavioral batteries use different assessments of cognitive and psychomotor function to assess the subjects' performance. When it comes to minimising errors for administering and scoring tests, computerised neurobehavioral test batteries may be preferable to manual versions.

Our study is the first of its kind to characterise the pesticide exposure of mosquito control workers in Malaysia and to use these data to examine the relationship between workers' health and their estimated total lifetime pesticide exposure. An important strength of our study is the detailed information used in the pesticide exposure modelling with specific information regarding pesticide use. The exposure model adapted in our study provides a good template for future work that requires reconstruction of past exposure to pesticides in the absence of recorded exposure measurement data.

The dermal route of exposure was also included in our study to combine with inhalation exposure to estimate workers' lifetime pesticide intake. Our study shows that the dermal route makes the major contribution to estimated total lifetime pesticide intake among these workers. Such a detailed approach has not previously been used to characterise the exposure among mosquito control workers in Malaysia (Masilamani et al., 2014; Samsuddin et al., 2013, 2015).

Our study also has some limitations. Firstly, the study design is cross-sectional and so causal inference cannot be made. However, our study did employ a retrospective exposure assessment method that enables reconstruction of past exposure and so strengthens the case that lifetime pesticide exposure is associated with poorer performance. Also, the generalizability of the result might be limited as the recruitment and sampling process only took place in five vector control units in the Klang Valley area due to time constraints. However, these locations are likely to be representative of all mosquito control workers in vector control units in Malaysia because of the similarity of the work practices and pesticides used.

Our study also confronted the difficulties of characterising exposure from mixed pesticide usage (OP and pyrethroid). It is therefore impossible to attribute the health effects reported here to any single pesticide type. However, each pesticide used in our study has been considered in the estimate of workers' lifetime pesticide intake. Additionally, information on occupational or environmental exposures to other chemicals was not available for analysis, which could produce an imprecise association to estimate risk between the exposure groups. It is likely that such misclassification of exposure would have impacted equally on both the control and pesticide worker groups and this biased out study towards the null hypothesis. In addition, it is possible that workers might be a potential to have experienced early life or *in utero* exposure to pesticides that we did not assess. Again, such exposures are equally likely to be experienced by the control group and pesticide workers so such non-differential misclassification would tend to bias towards the null hypothesis (Sorahan & Gilthorpe, 1994).

Conclusion

In summary, our study provides new insights about estimated total lifetime pesticide intake and health effects among mosquito control workers in Malaysia. This study suggests an association between lifetime pesticide intake and poorer neurobehavioral performance of workers. Our study shows the importance of the dermal route as the major contributor to total lifetime pesticide intake amongst mosquito control workers. Future research is needed to understand more fully the relationship between pesticide exposure and health in these workers and how best to reduce their exposures.

References

Baldi, I., Gruber, A., Rondeau, V., Lebailly, P., Brochard, P., & Fabrigoule, C. (2011). Neurobehavioral effects of long-term exposure to pesticides: results from the 4-year follow-up of the PHYTONER study. *Occupational and Environmental Medicine*, *68*(2), 108–115.

Baldi, I., Lebailly, P., Jean, S., Rougetet, L., Dulaurent, S., & Marquet, P. (2006). Pesticide contamination of workers in vineyards in France. *Journal of Exposure Science and Environmental Epidemiology*, *16*(2), 115.

Baldi, I., Lebailly, P., Rondeau, V., Bouchart, V., Blanc-Lapierre, A., Bouvier, G., Canal-Raffin, M., & Garrigou, A. (2012). Levels and determinants of pesticide exposure in operators involved in treatment of vineyards: results of the PESTEXPO Study. *Journal of Exposure Science and Environmental Epidemiology*, *22*(6), 593.

Bekö, G., Weschler, C. J., Langer, S., Callesen, M., Toftum, J., & Clausen, G. (2013). Children's phthalate intakes and resultant cumulative exposures estimated from urine compared with estimates from dust ingestion, inhalation and dermal absorption in their homes and daycare centers. *PloS One*, *8*(4), e62442.

Berent, S., Giordani, B., Albers, J. W., Garabrant, D. H., Cohen, S. S., Garrison, R. P., & Richardson, R. J. (2014). Effects of occupational exposure to chlorpyrifos on neuropsychological function: a prospective longitudinal study. *Neurotoxicology*, *41*, 44–53.

Blanc-Lapierre, A., Bouvier, G., Gruber, A., Leffondré, K., Lebailly, P., Fabrigoule, C., & Baldi, I. (2013). Cognitive disorders and occupational exposure to organophosphates: results from the PHYTONER study. *American Journal of Epidemiology*, *177*(10), 1086–

1096.

Brouwer, D. H., Semple, S., Marquart, J., & Cherrie, J. W. (2001). A dermal model for spray painters. Part I: subjective exposure modelling of spray paint deposition. *Annals of Occupational Hygiene*, *45*(1), 15–23.

Buchanan, D., Pilkington, A., Sewell, C., Tannahill, S. N., Kidd, M. W., Cherrie, B., & Hurley, J. F. (2001). Estimation of cumulative exposure to organophosphate sheep dips in a study of chronic neurological health effects among United Kingdom sheep dippers. *Occupational and Environmental Medicine*, *58*(11), 694–701.

Cessna, A. J., & Grover, R. (2002). Exposure of ground-rig applicators to the herbicide bromoxynil applied as a 1: 1 mixture of butyrate and octanoate. *Archives of Environmental Contamination and Toxicology*, *42*(3), 369–382.

Cherrie, J. W. (1999). The effect of room size and general ventilation on the relationship between near and far-field concentrations. *Applied Occupational and Environmental Hygiene*, *14*(8), 539–546.

Cherrie, J. W., & Schneider, T. (1999). Validation of a new method for structured subjective assessment of past concentrations. *Annals of Occupational Hygiene*, *43*(4), 235–245.

Chan, Y. H. (2004) Biostatistics 201: linear regression analysis. *Singapore Med J. 45(2),* 55-61.

Dassanayake, T., Gawarammana, I. B., Weerasinghe, V., Dissanayake, P. S., Pragaash, S., Dawson, A., & Senanayake, N. (2009). Auditory event-related potential changes in chronic occupational exposure to organophosphate pesticides. *Clinical Neurophysiology*, *120*(9), 1693–1698.

Deac, C., Popescu, C. A., Armean, S. M., Macrea, R., & Miclutia, I. V. (2015). Spatial Memory

Functioning And Negative Symptoms In Schizophrenia. *Age*, *2*, 5.

Dick, F. D., De Palma, G., Ahmadi, A., Scott, N. W., Prescott, G. J., Bennett, J., Semple, S., Dick, S., Counsell, C., & Mozzoni, P. (2007). Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occupational and Environmental Medicine*, *64*(10), 666–672.

Égerházi, A., Berecz, R., Bartók, E., & Degrell, I. (2007). Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(3), 746–751.

Eller, P. M., & Cassinelli, M. E. (1994). *NIOSH manual of analytical methods*. Diane Publishing.

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuorpsychiatyric applications of CANTAB. *International Journal of Geriatric Psychiatry*, *11*(4), 329–336.

Geer, L. A., Cardello, N., Dellarco, M. J., Leighton, T. J., Zendzian, R. P., Roberts, J. D., & Buckley, T. J. (2004). Comparative analysis of passive dosimetry and biomonitoring for assessing chlorpyrifos exposure in pesticide workers. *Annals of Occupational Hygiene*, *48*(8), 683–695.

Gong, M., Zhang, Y., & Weschler, C. J. (2014). Predicting dermal absorption of gas-phase chemicals: transient model development, evaluation, and application. *Indoor Air*, *24*(3), 292–306.

IBM Corp. (2015). IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Armonk, NY: IBM

Ismail, A. A., Bodner, T. E., & Rohlman, D. S. (2012). Neurobehavioral performance among agricultural workers and pesticide applicators: a meta-analytic study. *Occupational and*

Environmental Medicine, *69*(7), 457–464.

Jamal, G. A., Hansen, S., Pilkington, A., Buchanan, D., Gillham, R. A., Abdel-Azis, M., Julu, P. O. O., Al-Rawas, S. F., Hurley, F., & Ballantyne, J. P. (2002). A clinical neurological, neurophysiological, and neuropsychological study of sheep farmers and dippers exposed to organophosphate pesticides. *Occupational and Environmental Medicine*, *59*(7), 434–441.

Kamel, F., & Hoppin, J. A. (2004). Association of pesticide exposure with neurologic dysfunction and disease. *Environmental Health Perspectives*, *112*(9), 950–958.

Little, J. C., Weschler, C. J., Nazaroff, W. W., Liu, Z., & Cohen Hubal, E. A. (2012). Rapid methods to estimate potential exposure to semivolatile organic compounds in the indoor environment. *Environmental Science & Technology*, *46*(20), 11171–11178.

Lozier, M. J., Montoya, J. F. L., del Rosario, A., Martínez, E. P., Fuortes, L., Cook, T. M., & Sanderson, W. T. (2013). Personal air sampling and risks of inhalation exposure during atrazine application in Honduras. *International Archives of Occupational and Environmental Health*, *86*(4), 479–488.

Masilamani, R., Rasib, A., Darus, A., & Ting, A. S. (2014). Noise-induced hearing loss and associated factors among vector control workers in a Malaysian state. *Asia Pacific Journal of Public Health*, *26*(6), 642–650.

Meyer-Baron, M., Knapp, G., Schäper, M., & van Thriel, C. (2015). Meta-analysis on occupational exposure to pesticides–Neurobehavioral impact and dose–response relationships. *Environmental Research*, *136*, 234–245.

Pilkington, A., Buchanan, D., Jamal, G. A., Gillham, R., Hansen, S., Kidd, M., Hurley, J. F., & Soutar, C. A. (2001). An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. *Occupational and Environmental Medicine*, *58*(11), 702–710.

Rasoul, G. M. A., Salem, M. E. A., Mechael, A. A., Hendy, O. M., Rohlman, D. S., & Ismail, A. A. (2008). Effects of occupational pesticide exposure on children applying pesticides. *Neurotoxicology*, *29*(5), 833–838.

Rauma, M., Boman, A., & Johanson, G. (2013). Predicting the absorption of chemical vapours. *Advanced Drug Delivery Reviews*, *65*(2), 306–314.

Rohlman, D. S., Ismail, A. A., Abdel-Rasoul, G., Lasarev, M., Hendy, O., & Olson, J. R. (2014). Characterizing exposures and neurobehavioral performance in Egyptian adolescent pesticide applicators. *Metabolic Brain Disease*, *29*(3), 845–855.

Rohlman, D. S., Lasarev, M., Anger, W. K., Scherer, J., Stupfel, J., & McCauley, L. (2007). Neurobehavioral performance of adult and adolescent agricultural workers. *Neurotoxicology*, *28*(2), 374–380.

Rothlein, J., Rohlman, D., Lasarev, M., Phillips, J., Muniz, J., & McCauley, L. (2006). Organophosphate pesticide exposure and neurobehavioral performance in agricultural and nonagricultural Hispanic workers. *Environmental Health Perspectives*, *114*(5), 691–696.

Samsuddin, N., Hassan, N. A., Saad, N. W., Abdullah, N. Z., Razali, A., Zakaria, N. A., & Mohamad, M. (2013). Pesticide Handling Practices and Quantitative Sensory Testing among Foggers in Vector Unit, Kuantan. *International Medical Journal*, *20*(1), 2–5.

Samsuddin, N., Rampal, K. G., Ismail, N. H., Abdullah, N. Z., & Nasreen, H. E. (2015). Pesticide exposure and cardiovascular hemodynamic parameters among male workers involved in mosquito control in East Coast of Malaysia. *American Journal of*

Hypertension, *29*(2), 226–233.

Sartorelli, P., Aprea, C., Cenni, A., Novelli, M. T., Orsi, D., Palmi, S., & Matteucci, G. (1998). Prediction of percutaneous absorption from physicochemical data: a model based on data of in vitro experiments. *The Annals of Occupational Hygiene*, *42*(4), 267–276.

Semple, S. (2005). Assessing occupational and environmental exposure. *Occupational Medicine*, *55*(6), 419–424.

Semple, S., Brouwer, D. H., Dick, F., & Cherrie, J. W. (2001a). A dermal model for spray painters. Part II: estimating the deposition and uptake of solvents. *Annals of Occupational Hygiene*, *45*(1), 25–33.

Semple, S., Proud, L., Tannahill, S., & Tindall, S. (2001b). A training exercise in subjectively estimating inhalation exposures. *Scand J Work Environ Health*, *27*(6), 395–401.

Sorahan, T., & Gilthorpe, M. S. (1994). Non-differential misclassification of exposure always leads to an underestimate of risk: an incorrect conclusion. Occupational and environmental medicine, 51(12), 839.

Starks, S. E., Gerr, F., Kamel, F., Lynch, C. F., Alavanja, M. C., Sandler, D. P., & Hoppin, J. A. (2012). High pesticide exposure events and central nervous system function among pesticide applicators in the Agricultural Health Study. *International Archives of Occupational and Environmental Health*, *85*(5), 505–515.

Starks, S. E., Gerr, F., Kamel, F., Lynch, C. F., Jones, M. P., Alavanja, M. C., Sandler, D. P., & Hoppin, J. A. (2012). Neurobehavioral function and organophosphate insecticide use among pesticide applicators in the Agricultural Health Study. *Neurotoxicology and Teratology*, *34*(1), 168–176.

US OSHA. (2008). *OSHA Technical manual: Sampling for surface contamination, Section II,* *Chapter 2: Wipe sampling methodology*. Occupational Safety & Health Administration (OSHA), US Department of Labor. http://www.osha.gov/dts/osta/otm/otm_ii/otm_ii_2.html#wipe_sampling_methodology

Weschler, C. J., & Nazaroff, W. W. (2008). Semivolatile organic compounds in indoor environments. *Atmospheric Environment*, *42*(40), 9018–9040.

Wesseling, C., Keifer, M., Ahlbom, A., McConnell, R., Moon, J.-D., Rosenstock, L., & Hogstedt, C. (2002). Long-term neurobehavioral effects of mild poisonings with organophosphate and n-methyl carbamate pesticides among banana workers. *International Journal of Occupational and Environmental Health*, *8*(1), 27–34.

World Health Organization. (2011). *Global insecticide use for vector-borne disease control: a 10-year assessment [2000-2009]*. Geneva: World Health Organization.

Xu, Y., Cohen Hubal, E. A., Clausen, P. A., & Little, J. C. (2009). Predicting residential exposure to phthalate plasticizer emitted from vinyl flooring: a mechanistic analysis. *Environmental Science & Technology*, *43*(7), 2374–2380.

Conflict of interest

The authors declare that they have no conflict of interest

Ethical review

The College of Life Sciences and Medicine Ethics and Review Board, University of Aberdeen (CERB/2013/9/927) and Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-13-991-16985) approved the research protocol.

Authors' contribution

The authors responsibilities were as follow – MZY, JWC, NS, SS: designed the research plan and oversaw the study; MZY, SS - analysed the data; MZY – wrote the manuscript and had primary responsibility for the final content; and all authors approved the final version of the manuscript.

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Table 1 Socio-demographic characteristics of workers according to their estimated total lifetime pesticide intake

Characteristics	**Estimated total lifetime pesticide intake**						**F**	χ^2	**p-value**
	High intake group (n = 79)		**Low intake group (n=79)**		**No intake group (n = 176)**				
	n (%)	**Mean (SD)**	**n (%)**	**Mean (SD)**	**n (%)**	**Mean (SD)**			
Age (years)		31 (4)		29 (7)		31 (9)	1.773		p=0.172
Education Status								1.855	p=0.396
Low education	27 (34.2)		35 (44.3)		73 (41.5)				
High education	52 (65.8)		44 (55.7)		103 (58.5)				
Smoking status								18.158	p<0.001[*]
No	22 (27.8)		21 (26.6)		88 (50)				
Yes	57 (72.2)		58 (73.4)		88 (50)				

[*] Significant at p<0.05

Table 2 Median (IQR) concentration of airborne pesticide concentration

Tasks	Averaged duration of sampling (minutes)	Median (IQR) of pesticide concentrations (mg/m^3)					
		Organophosphate		Pyrethroids			
		n sample	Pirimiphos-methyl	n sample	Permethrin	n sample	d,d,T-cyphenothrin
Mixing	37	9	0.005 (0.003, 0.055)	2	0.102 (0.096, 0.102)	5	0.026 (0.016, 0.029)
Thermal spraying	36	5	0.569 (0.151, 0.574)	2	0.136 (0.116, 0.157)	3	0.018 (0.018, 0.031)
ULV spraying	84	1	0.001	2	0.109 (0.101, 0.116)	4	0.009 (0.007, 0.013)

Table 3 Median (IQR) pesticide concentration on skin classified according to body part

Body parts	**Organophosphate**						**Pyrethroid**					
	Pirimiphos-methyl			**Fenitrothion**			**Permethrin**			**d,d,T- cyphenothrin**		
	n	**<LoD n (%)**	**Median (IQR) (µg/cm^2)**	**n**	**<LoD (n (%))**	**Median (IQR) (µg/cm^2)**	**n**	**<LoD (n (%))**	**Median (IQR) (µg/cm^2)**	**n**	**<LoD (n (%))**	**Median (IQR) (µg/cm^2)**
Right hand	10	5 (50)	0.12 (0.01, 0.25)	2	1 (50)	0.68 (0.01, -)	6	4 (66.7)	0.01 (0.01, 0.29)	4	3 (75)	0.01 (0.01, 0.13)
Left hand	10	5 (50)	0.08 (0.01, 0.26)	2	0 (0)	0.22 (0.2, -)	6	4 (66.7)	0.01 (0.01, 0.27)	4	2 (50)	0.12 (0.01, 0.24)
Right forearm	10	4 (40)	1.64 (0.11, 1.94)	2	0 (0)	4.94 (3.28, -)	6	6 (100)	0.01*	4	2 (50)	0.81 (0.06, 2.22)
Left forearm	10	5 (50)	0.88 (0.11, 2.03)	2	0 (0)	3.82 (3.24, -)	6	6 (100)	0.01*	4	3 (75)	0.06 (0.06, 1.21)
Neck	10	5 (50)	0.68 (0.11, 3.28)	2	1 (50)	1.55 (0.06, -)	6	4 (66.7)	0.06 (0.06, 2.29)	4	3 (75)	0.06 (0.06, 1.49)
Forehead	3	1 (33.3)	4.04 (0.11, -)	2	2 (100)	0.01*	-	-	-	2	1 (50)	0.89 (0.06, -)

n=number of samples, <LoD = less than Limit of Detection, *only one value, no IQR available

Table 4 Association of lifetime pesticide exposure intake with neurobehavioral performance scores

	Multiple linear regression[a]						
	Neurobehavioral performances test						
	Attention		**Visual memory**			**Executive function**	**Induction**
Total lifetime pesticide intake[b]	**Match To Sample Visual Search (MTS) (% correct)**	**Reaction Time (RT) (millisecond)**	**Pattern Recognition Memory (PRM) (% correct)**	**Spatial Recognition Memory (SRM) (% correct)**	**Paired Associates Learning (PAL) (total error (adjusted))**	**Spatial Span (SSP) (span length)**	**Motor Screening Task (MOT) (mean error (‘Pixel’ unit))**
	B (95% CI)	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**	**B (95% CI)**
Low (n=79)	-1.2 (-2.5, 0.03)	1.8 (-15.6, 19.1)	-2.3 (-5.1, 0.6)	-1.5 (-3.9, 1)	8.1 (3, 13.2)*	-0.5 (-0.8, -0.2)*	0.9 (0.1, 1.6)*
High (n=79)	-1.4 (-2.6, -0.1)*	0.4 (-16.9, 17.6)	-2.4 (-5.2, 0.4)	-3.3 (-5.8, -0.8)*	7.4 (2.3, 12.4)*	-0.6 (-0.9, -0.3)*	0.8 (-0.01, 1.5)

[a] Adjusted for age (years), education (Low/High), Smoking (No/Yes); [b]No pesticide intake act as a reference group; Low was defined as total estimated lifetime pesticide intake of less than 379 g; High intake was defined as total estimated lifetime pesticide intake of 379 g or more. *Significant ($p<0.05$). Adjusted R^2 for all scores and tests are less than 0.2. Note: B=Coefficient; CI=Confidence Interval