Effects of Organophosphate Pesticides on Neurological Impairment

Ajchamon Thammachai and Ratana Sapbamrer*

Department of Community Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

* Corresponding author. E-mail address: lekratana56@yahoo.com; lekratana56@gmail.com

Received: 4 October 2019; Revised: 9 June 2020; Accepted: 22 June 2020

Abstract

Exposure to organophosphate pesticides (OPs) was found to be associated with an increasing prevalence of neurological symptoms, neuropsychological function and involved in postural balance. However, available scientific data is limited. Therefore, the aim of this article was to review scientific evidence published on the effects of OPs on neurological impairment. The topics presented in the article are as follows: 1) organophosphate pesticide use and exposure, 2) mechanism of OPs toxicity on the neurological system 3) tools for assessment of the neurological system 4) effect of exposure to OPs on neurological signs 5) effect of exposure to OPs on neuropsychological functioning and 6) effect of exposure to OPs on postural balance. Considerable evidence suggests that electrophysiological changes include abnormalities point to remodeling of the motor unit, abnormal small and large nerve fiber function, reduced compound muscle action potential (CMAP) amplitude and ulnar F-wave, abnormal ulnar, tibial, peroneal, and sural nerve conduction. OPs exposure has been implicated in cognitive impairment including deficits of memory, attention, perception and visuospatial function, executive function, language, IQ, and other neuropsychological implications include psychiatric disorders, anxiety, insomnia, major depression, and dementia. A greater postural sway with exposure to OPs than in the unexposed. This article recommends future studies and possibilities for incorporating sensitive health outcomes. The measurement of OPs monitoring on a larger scale is warranted.

Keywords: insecticides, neurological impairment, neuropsychological function, organophosphate pesticides, postural balance

Introduction

Organophosphates pesticides (OPs) are widely used in agriculture to control pests (Kim et al., 2018). Intoxication caused by exposure to pesticides is a major public health problem. More than a billion pounds of pesticides are used annually in the United States with 2.5-5.0 million agricultural workers exposed to OPs in the 1990s (Rothlein et al., 2006). Most of the pesticides identified from exposed pesticides are organophosphorus, organochlorine, carbamates and pyrethroids. OPs are among the most acute toxic and commonly used insecticides which are neurotoxins resulting in three million cases of poisoning and more than 250,000 deaths (Jamal et al., 2016). Pesticide use has increased and led to acute intoxication outbreaks in agricultural areas during the spraying season (Corral et al., 2017). Several observational studies published on the effects of long-term low-level exposure show a correlation between exposure and effect, but results have not been as consistent as those after acute poisoning episodes (Jamal et al., 2002; Pilkington et al., 2001). A previous study showed a strong association between exposure to OPs concentrate and neurological symptoms (Pilkington et al., 2001). Other studies have found neurological problems and postural balance concerning OPs exposure (Baldi et al., 2003; Kim et al., 2018). Neurologic symptoms are also associated with chronic exposure. Peripheral neuropathy, demonstrate paresthesia, pain, anesthesia, paresis, and ataxia. These effects are the leading cause of sensory symptoms in the lower extremities and progress to muscular weakness and finally paralysis and muscle wasting. Central nervous system (CNS) effects may occur, involved in both mood and neurobehavioral impairment (Jokanovic, 2018; London et al., 2012). Several studies have demonstrated an association between chronic pesticide exposure and an increased prevalence of cognitive dysfunction, dementia,

parkinsonism, and Alzheimer's disease (Hayden et al., 2010; Norkaew, Lermaharit, Wilaiwan, & Siriwong, 2015; Rothlein et al., 2006; Singh et al., 2013).

Multiple biological markers have been proposed to predict the severity of pesticide exposure. The alkyl phosphates and phenols to which OPs are excreted by the kidneys can be frequently detected in the urine pesticide absorption and up to 48 hours after exposure. Urinary alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than is required to produce symptoms or to depress cholinesterase activities (Crinnion, 2010). Numerous polymorphisms have been identified in the Paraoxonase1 (PON1) gene that associates with high-density lipoprotein (HDL) particles in the plasma (Salehcheh, Kakantari, Javad Khodayar, & Jahangiri, 2014). PON1 hydrolyzes the highly toxic oxon forms of many widely used OPs, including chlorpyrifos and diazinon (Hofmann et al., 2009).

Studies have examined the neurological symptoms and neuropsychological impact of pesticide exposure, with mixed results (Jamal et al., 2002; Pilkington et al., 2001). Specific to postural balance, a few studies have indicated that pesticide exposed groups based on measures derived from static posturography (Sunwook, Nussbaum, Quandt, Laurienti, & Arcury, 2016). To our knowledge, however, they were hardly a few studies on explored potential associations between neurological symptoms, neuropsychological functioning, postural balance and biomarker (i.e., metabolites of OPs, polymorphisms), with the latter considered of importance as a more direct measure of pesticide exposure. Thus, the aim of this review article was to review scientific evidence published on the effects of OPs on neurological impairment. The topics presented in the article are as follows: 1) organophosphate pesticide use and exposure, 2) mechanism of OPs toxicity on neurological system 3) tools for assessment of neurological system 4) effect of exposure to OPs on neurological signs 5) effect of exposure to OPs on neuropsychological functioning and 6) effect of exposure to OPs on postural balance.

Organophosphate Pesticide Use and Exposure

OPs are widely used for agriculture by controlling insects on farms, resulting in environmental pollution and increased health risks effects (Hongsibsong, Sittitoon, & Sapbamrer, 2017). The insecticides were at higher levels in the summer than in winter because the temperatures in the summer were suitable for the growth of insects (Sapbamrer, 2018). The incidence of pesticide poisoning was higher in males than females who worked and did the major tasks on the farms when either mixing or spraying pesticides (Liu, Hanchenlaksh, Povey, & de Vocht, 2015; Rivera, Siriwong, Taneepanichskul, Norkaew, & Robson, 2016). Incidental poisoning has been the result of these activities and routine uses of the pesticide. The risks were arising due to the exposure to farmers with the addition of incorrect application techniques, poorly maintained spraying equipment, inadequate storage and misguided use of personal protective equipment, and often the reuse of old pesticide containers for food and water storage (Rivera et al., 2016). Most poisoning cases were related to the use of OPs, followed by herbicides and carbamates (Sapbamrer & Nata, 2014). OPs exposure may cause both acute and chronic health effects. The acute effects were related to inhibiting the acetylcholinesterase (AChE) enzyme during neurotransmission, and the cholinergic symptoms that also present with dizziness, blurred vision, nausea, vomiting, cramp, muscular weakness, and numbness. Chronic effects were caused by long-term exposure to low levels of OPs both in farmers and consumers. Exposure to OPs occurs through oral, dermal, and inhalation contact. Ingestion route is the main route for consumers, whereas dermal and inhalation routes are the main route for the farmer (Sapbamrer & Hongsibsong, 2014). A long-term low level of exposure was also associated with deficits performance and balance (Kamel et al., 2003; Kim et al., 2018; Pilkington et al., 2001).

Neurobehavioral (NB) changes have been reported in farmworkers in Florida and Hispanic agricultural workers. These studies have found deficits in measures of sustained attention, information processing, and motor speed and coordination (Kamel et al., 2003; Rothlein et al., 2006). Neurological symptoms and sensory tests within all occupational groups autonomic symptoms were most often reported, followed by sensory symptoms, then muscle weakness symptoms (Pilkington et al., 2001). Previous studies that examined the association of clinical neurological outcomes with chronic organophosphate exposure demonstrated CNS manifestations such as headache, fatigue, tension, irritability, insomnia, dizziness, depression, nausea, absentmindedness, difficulty concentrating, loss of appetite and poor balance (Kamel et al., 2005), whereas others demonstrated peripheral nervous system (PNS) manifestations such as abnormalities in the knee and ankle reflexes, coordination abnormalities, numbness, twitches in arms or legs, tremors in hand, blurred vision, and change in smell or taste (Ismail, Bodner, & Rohlman, 2012; Kamel & Hoppin, 2004). The importance of neuropsychologists was the potential brain difficulties associated with exposure to pesticide chemicals. Many other studies have shown that individuals who experience chronic poisoning of OPs may deficits in neurophysiological and psychological also produced memory impairment (Jamal et al., 2002).

Mechanism of Organophosphate Toxicity on the Neurological System

The primary target of organophosphate (OP) toxic action is known to the nervous system. OPs are toxic because their main toxic effect is the inhibition of OPs (Flaskos, 2012). The synapse prevents the efficient with adequate AChE can breakdown of acetylcholine (ACh) molecules (Mangas, Vilanova, Estevez, & Franca, 2016). ACh is known as a neurotransmitter involved in the functioning of the cholinergic nervous system. This neurotransmitter is released in response to nerve stimulation and binds to postsynaptic acetylcholine receptors, plays a key role for a muscle contraction, or a gland secretion. This function is terminated by hydrolysis with the AChE that found in synaptic membranes. OP compounds exert their mechanism toxicity by the covalent organophosphorylation of AChE. The general chemical structure of an OP comprises a central phosphorus atom with a double-bound to sulfur or oxygen, where R1 and R2 are most commonly alkyls or aryl groups, and symbol x represents a variety of groups and is the so-called leaving group, that is removed when the OP phosphorylates AChE and is the most sensitive to hydrolysis. The resulting phosphorylated enzyme is a very slow rate and remains inhibited, but the recovery by spontaneous reactivation may occur at a significant speed or forced by fluoride or oximes as well as nucleophilic reagents. Furthermore, the phosphoryl enzyme can undergo a dealkylating reaction called aging. The negative charge of the aged phosphoryl group can be considered to be irreversibly inhibited and this makes enzyme not reactivable anymore, either spontaneously or a reactivating agent (Costa, 2018). This enzyme inhibition leads to the synaptic accumulation of acetylcholine at both muscarinic and nicotinic receptors in CNS and PNS (Flaskos, 2012). Neuromuscular block and respiratory failure in severe cases caused by the levels of nerve AChE inhibition of approximately over 70% lead to the accumulation of ACh in synaptic clefts of neuromuscular junctions (Mangas et al., 2016).

The secondary mechanisms of activity and the result of chronic exposure to OPs on non-neuronal molecular target tissues and organs in humans. Recent studies have revealed several secondary targets for OPs. The toxic effects of OPs on the immune system are reflected in different immune organ pathologies. Direct immunotoxic effects, OPs can inhibition of serine hydrolases or esterase in the immune system, oxidative damage of immune system organs, and changes in the signal transduction pathway. Besides direct effects on the immune component, OPs can change in the nervous system as an altered cholinergic tone to a lymphoid organ or chronic effects of

altered metabolism on the immune system. All of which may decrease the integrity of physical barriers to infection (Galloway & Handy, 2003). Not only the nicotinic signs alone during type II paralysis result in the AChE inhibition mechanism, but oxidative stress can lead to muscle cell dysfunction. A previous study has revealed that oxidative stress both in acute and subacute intoxication with OPs leads to many organ damages. OPs can induce oxidative stress leading to the generation of free radicals and alteration in the antioxidant system. In acute exposition to OPs, sudden overproduction of reactive oxygen species leads to enhanced lipid peroxidation and reduced level of antioxidant agents and also to chronic exposition to OPs. Whereas in subchronic intoxication, the effect is in contrast because OPs lead to enhance antioxidant capacity (Lukaszewicz-Hussain, 2010). The study conducted to evaluate the oxidative stress in acute human poisoning with OPs found that significant lipid peroxidation accompanied by decreased levels of total antioxidant capacity, total thiols, and cholinesterase activity. Moreover, a significant association between cholinesterase depression and decreased total antioxidant capacity. In concluding the oxygen free radicals and their related interactions like lipid peroxidation are present in acute OPs (Ranjbar et al., 2005).

There are four types of neurological syndromes associated with OPs poisoning in humans: 1) cholinergic phase, 2) intermediate syndrome (IMS), 3) organophosphate induced delayed polyneuropathy (OPIDN), and 4) chronic organophosphate induced neuropsychiatric disorder (COPIND) (Jokanovic, 2018).

The cholinergic phase is the initial phase of acute organophosphate poisoning which was called type I paralysis (Wadia, Sadagopan, Amin, & Sardesai, 1974). The symptoms are either muscarinic or nicotine type. The most severe manifestation is respiratory failure. The accumulation of acetylcholine and overstimulation of postsynaptic muscarinic and nicotinic receptors are known to be directed by inhibition of AChE at synapses and neuromuscular junctions in cholinergic pathways. For OPs having dimethyl radicals, the AChE reactivation is relatively rapid with a half-time of about one to two hours, whereas that for OPs having a diethyl functional group is 31 to 57 hours. The signs and symptoms of indirect inhibitor appear slowly and last longer, but with direct inhibitors appear quickly after exposure (Jokanovic, 2018).

The IMS is call type II paralysis, which develops between 24 to 96 hours after exposure (Wadia et al., 1974). The mechanism of IMS is caused by the nicotinic signs of AChE inhibition (Sedgwick & Senanayake, 1997). It has been linked with exposure to specific OPs having dimethyl phosphate structure but also developed after exposure to parathion and methamidophos (Bird et al., 2016). The clinical presentations of IMS are a weakness of the proximal upper and lower limb muscles and several muscles supplied by motor cranial nerves, other than, the distal upper and lower limb muscles are also affected (Haliga, Morarasu, Ursaru, Irimioaia, & Sorodoc, 2018).

The OPIDN is a common finding following exposure to organophosphates caused by triorthocresyl phosphate with effects after 10 to 20 days or later of exposure. Neuropathy target esterase (NTE) is involved in intracellular membrane trafficking and cell-signaling pathway between neurons and glial cells which was a relationship between NTE activity and axonal maintenance (Glynn, 2006; Read, Li, Chao, Cavanagh, & Glynn, 2009). It is a cause of paralysis with swelling and degeneration of distal parts of long nerves in the legs and spinal cord (Glynn, 2006).

The COPIND is the most occurrence of a chronic consequence of OPs, which may be caused by not only acute OPs poisoning but also chronic low-level exposure to OPs without cholinergic symptoms. COPIND usually occurs with a delay and persists for a long period possibly suggesting the lasting damage of the CNS (Tan

et al., 2009). It has shown impaired neurobehavioral performance including the cognitive deficit, mood change, depression, psychotic symptoms, emotional lability, chronic fatigue, autonomic dysfunction, peripheral neuropathy and extrapyramidal symptoms (Kamel & Hoppin, 2004).

Tools for Assessment of Neurological Symptoms

Some studies of OPs have demonstrated evidence of impaired nerve conduction. Nerve conduction velocities (NCVs) studies were done with standard techniques, normally on the right side. The maximal motor conduction velocity (MCV) was measured on the median and common peroneal nerves, latency, peak to peak muscle action potential amplitude, nerve conduction velocity, and F wave latency and persistence. The sensory conduction velocity (SCV) was measured on the median and sural nerves, peak latency, peak to peak amplitude, and nerve conduction velocity (NCV). Conduction velocity is the amount of time from stimulation to the onset of principal depolarization (latency) divided by distance, i.e. m/s (Kimura et al., 2005). The electromyography (EMG) was measured from the right extensor digitorum brevis, tibialis anterior, and extensor digit communis. Single-fiber EMG (SFEMG) was a selective EMG recording technique that allowed identification of action potentials (APs) from individual muscle fibers. In SFEMG studies of the right extensor digitorum communis muscle, the integrity of the neuromuscular junction was measured. Although few studies found abnormal EMG results of long-term health effects associated with OPs (Jamal et al., 2002).

Neuropsychological testing provides a purpose evaluation of cognitive, behavioral, and emotional manifestations. A comprehensive neuropsychological evaluation explores several cognitive domains commonly used neuropsychological test batteries, with more than one test for each cognitive domain, are highly reliable (cognitive index scores, reliability coefficients > 0.90) (Zucchella et al., 2018). Therefore, neuropsychological evaluation provides general and specific information about cognitive dysfunction (Schroeder, Martin, & Walling, 2019). Similar measures and testing instruments were used in different studies. Neurobehavioral test batteries, including the World Health Organization Neurobehavioral Core Test Battery (NCTB), have been used to evaluate pesticide effects on cognitive and psychomotor function. It consists of a series of interrelated computerized tests of memory, attention, visuospatial processing, and higher brain function. Most studies reported significant positive decrements on neurobehavioral performance in the exposed group as compared to the control group (Farahat et al., 2003; Ismail et al., 2012; Rothlein et al., 2006). Exposure to chronic low-level of OPs is associated with both cognitive and psychomotor function (Farahat et al., 2003; Kamel et al., 2003; Rothlein et al., 2006). The main effects observed in OPs exposure were classified into eight categories: 1) perception and visuospatial function considers the assessment of spatial component of perception and motor execution, visuospatial abilities, visual and memory abilities, and visuospatial planning 2) motor control includes assessment of ability to voluntary perform gestures or copy geometrical models 3) memory includes assessment of short-term memory, working memory, long-term auditory/verbal memory, recall, learning strategy, and visuospatial leaning 4) attention includes considers the assessment of sustained, selective and divided attention, visual search speed and scanning, rate of information processing , complex scanning, visual tracking and speed of processing 5) executive function includes problem solving, planning, visuospatial and praxis abilities, visuospatial planning and retrieval of clock time representation, non-verbal logical reasoning, cognitive flexibility, motor sequencing, and inhibitory control 6) language includes verbal comprehension, verbal naming 7) intelligence quotient (IQ) considers IQ including verbal and performance scale 8) other neuropsychological test includes the assessment of psychomotor retardation, and cognitive impairment.

Postural sway was quantitatively measured as subclinical neurotoxic effects of pesticides on functional aspects of the CNS by using computerized static posturography. Neurotoxic effects of pesticides could be adversely affected by postural balance performance including CNS processing, integration of afferent input from multiple sensory systems (visual, vestibular, and somatosensory), and motor control (Sunwook et al., 2016). The cognition difficulty conditions were with and without a current cognitive task required verbally counting backward by one from a randomly selected three digits number, while the visual conditions were eyes-closed and eyes-open. The medial-lateral and anterior-posterior directions of the body's center of pressure (COP) in the horizontal plane were recorded. Lengths of the displacement of the COP in the medial-lateral and anterior-posterior directions within each sampling time were summed up for each direction and defined as the length of sway path of the COP in the medial-lateral and anterior-posterior directions (Kim et al., 2018; Kimura et al., 2005; Sunwook et al., 2016).

Effect of Exposure for Organophosphate on Neurological Signs

Eleven articles were specific to the effects of OPs on neurological signs, one study was case-control study, three studies were prospective cohort studies, and seven studies were cross-sectional studies. Three articles aimed to study EMG and NCV with OPs exposure, whereas four articles aimed to study only EMG and 4 articles aimed to study only NCV. Five studies found a significant difference between the exposure and non-exposure groups, four studies found no differences. Furthermore, two studies found an association between OPs and electrophysiological changes (Table 1).

Most studies provided evidence that OPs exposure had an effect on neurological signs in farmers and patients with OPs poisoning (7 from 11 studies). Eight studies assessed the impact on farmers, and three studies on patients with OPs poisoning. Of the eight studies in farmers, four studies assessed neurological signs by using EMG, and the results indicated an abnormalities point to remodeling of the motor unit, abnormal small and large nerve fiber function, SFEMG abnormalities, and sensory abnormality of definite neuropathy group (Jamal et al., 2002), but the others found no differences. The study by Peireis-John et al. (2002) found no significant differences in motor amplitude, motor latency, and neuromuscular transmission among farmers and controls group (Peiris-John, Ruberu, Wickremasinghe, Smit, & van der Hoek, 2002) which was the same as a study by Pilkington et al. (2001) which found no difference in mean vibration thresholds of large fiber among chlorpyrifos applicators and control groups (Pilkington et al., 2001). These results are consistent with the findings of a study by Sapbamrer et al. (2019) which assessed electrophysiological changes by using EMG, and found mean compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes were within normal values and none of the CMAP and SNAP amplitude was associated with urinary dialkyl phosphate (DAP) metabolites or deoxyribonucleic (DNA) damage (Sapbamrer, Hongsibsong, Sittitoon, & Amput, 2019). Concerning the three studies for the assessment of neurological signs in patients with OPs poisoning by using EMG, all of these studies found electrophysiological abnormalities. The study by Jayasinghe, Pathirana, and Buckley (2012) found CMAP amplitude and ulnar F-wave occurrence in the patients were significantly reduced compared to the controls (Jayasinghe et al., 2012). These findings are compatible with the two reports (Alahakoon et al., 2018; Jalali, Balali-Mood, Jalali, & Shakeri, 2011). The study by Jalali et al. (2011) found the amplitude of waves (mv) for both sensory and motor nerves was predominantly a distal deficit according to Alahakoon et al. (2018) who found prolonged jitter within the first 24 hours strongly correlates with subsequent occurrence of intermediated syndrome (Alahakoon et al., 2018; Jalali et al., 2011).

Other studies investigated electrophysiological changes by using NCV, six studies assessed the impact on farmers and one study in patients with OPs poisoning. Three studies found abnormal nerve conduction in farmers group was significantly different compared to the control group (Boostani et al., 2014; Jamal et al., 2002; Peiris-John et al., 2002), but the others found no differences. A study by Steenland et al. (2000) found no differences between applicators and the combined un-exposed group for peroneal, ulnar, or sural nerve conduction velocity or amplitude, but identified significant findings between applicators and un-exposed workers for ulnar amplitude and sural nerve conduction (Steenland et al., 2000). Similar findings were noted with a cross-sectional study and cohort study by Albers et al. (2004) that found no difference in sensory and motor nerve conduction measures among chlorpyrifos exposures both at the baseline and after one year of additional exposure when compared with references at baseline (Albers et al., 2004a; Albers et al., 2004b).

The impaired neurophysiological function after exposure to OPs was exposed to higher levels of OPs (Peiris-John et al., 2002). Clinical results of acute OPs poisonings usually reveal cholinergic crises, CNS depression, and IMS. Therefore, patients revealed clinical symptoms of IMS after moderate and severe acute OPs poisoning (Jalali et al., 2011). Most studies demonstrated sensory and motor nerve impairment after acute poisoning but the long-term effect of OPs has been reported only in a few studies (Peiris-John et al., 2002). There is predominant involvement of sensory type both a symptom and neurophysiological are characteristic of distal with chronic axonopathy. Small nerve fibers are affected more than large fibers. In normally the results of long-term effects associated with OPs found increasing reporting of symptoms, minor sensory changes, an abnormal EMG results that all of the symptoms are in the third phase neurological examinations (Jamal et al., 2002). Chronic exposure regularly follows inhalational or dermal absorption, whereas acute OPs poisoning mostly occurs after a suicidal attempt by oral ingestion (Jalali et al., 2011). Reduced amplitude of CMAP on distal stimulation indicates that an axonal is damaged and reduced NCV only in the distal segment may be evidence of distal demyelination with sparing of a proximal segment (Jayasinghe et al., 2012). The mechanism of increasing SCV in sural nerves is stimulated the fast-conducting fibers arrive at the recording electrode faster than the activity in slower fibers. Therefore, the long-term effects of OPs exposure are damage peripheral nerve fibers be able to highly mechanosensitive and spontaneously without stimulation because electrical impulses may spread abnormally from one fiber to another fiber (Peiris-John et al., 2002). However, in the cross-sectional investigation have no found evidence associated with OPs exposure and electrophysiological changes that they did not follow subjects long enough to identify an interval deterioration (Albers et al., 2004a; Pilkington et al., 2001; Sapbamrer et al., 2019).

Table 1 Effect of Exposure to OPs on Neurological Symptoms

Authors/ Country	Study Population	Exposure assessment	Outcome assessment	Findings
Jamal et al. 2002/ United Kingdom[CC]	79 sheep farmers - No neuropathy - Possible neuropathy - Definite neuropathy	- Questionnaire	- Nerve conduction	- Abnormal nerve conduction of definite neuropathy group > Possible neuropathy group and > No neuropathy group (35%, 21%, and 7%, respectively)
			- EMG	- Abnormalities point to remodeling of the motor unit of definite neuropathy group > Possible neuropathy group and > No neuropathy group (52%, 30%, and 21%, respectively)
			- SFEMG	- SFEMG abnormalities of possible neuropathy group > Definite neuropathy group and > No neuropathy group (15%, 4%, and 0%, respectively)
			- Sensory abnormality	- Sensory abnormality of definite neuropathy group > Possible neuropathy group and > No neuropathy group (30%, 18%, and 0%, respectively)
			-Motor abnormality	- Only two subjects (9%) in the definite neuropathy group had an abnormal motor nerve conduction
			- Small fiber Abnormality	- Abnormal small nerve fiber function of definite neuropathy group > Possible neuropathy group and > No neuropathy group (91%, 76%, and 0%, respectively)
			- Large fiber abnormality	- Abnormal large fiber function of definite neuropathy group > Possible neuropathy group and > No neuropathy group (30%, 21%, and 7%, respectively)
Alahakoon et al. 2018/ Sri Lanka[C]	220 patients attended the hospital with suspected OP ingestion	- History - AChE activity	- Sensory abnormality	- Prolong jitter recorded with SFEMG < 24 hours of ingestion of an OP strongly correlates with subsequent occurrence of the intermediate syndrome (IMS)
Peiris-John et al. 2002/ Sri Lanka[CS]	- Farmers who regularly spray OPs (30) - Controls (30)	- AChE activity	- NCVs - Motor conduction velocity - EMG	- Sensory conduction velocity (m/s) in farmers > Controls ($p = 0.04$) - Motor conduction velocity (m/s) in farmers < Controls ($p = 0.04$) - Sensory conduction velocities during the cultivation season > Inter cultivation season in farmer and control ($p < 0.01$ and $p = 0.04$, respectively) - No significant differences in motor amplitude, motor latency, and neuromuscular transmission among groups
Jalali et al. 2011/ Iran[CS]	8 patients with moderate to severe OP poisonings	- History of OP ingestion - AChE activity	- Nerve conduction	- NCVs of both right and left tibial nerve of the patients < The normal values ($p = 0.04$ and 0.023, respectively) - Motor nerve dysfunction α Sensory nerve latency ($r = -0.558$, $p < 0.001$)
			- EMG	- Amplitude of wave (mV) for both sensory and motor nerve < Normal values ($p < 0.001$)
Jayasinghe et al. 2012/ Sri Lanka[C]	- Patients with acute OP poisoning (70) - Controls (70)	- ChE activity	- MNCS - SNCS - EMG	- In the first assessment, MNCV of median, ulnar and common peroneal nerves, SNCV and CMAP amplitude of ulnar nerve and F wave occurrence of the median of patients < Controls ($p < 0.05$) - The area of CMAP of common peroneal nerve and reduction of tibial F wave latency of patients - In the second assessment < In the first assessment ($p < 0.05$) - The area of CMAP of the ulnar nerve α Type of OP ingested ($\beta = -3.0$, $p < 0.05$) - Effects on SNCV of the median nerve, area of CMAP of the median nerve and F-wave latency of tibial nerve α PAM therapy ($\beta = -5.9, -7.3, -3.6$, respectively)

Table 1 (Cont.)

Authors/ Country	Study Population	Exposure assessment	Outcome assessment	Findings
Sapbamrer et al. 2019/ Thailand[CS]	- Pesticide sprayers (153) - Controls (53)	- Six DAP metabolites: DMP, DMTP, DMDTP, DEP, DETP, and DEDTP	- EMG - CMAP - SNAP	- None of the CMAP and SNAP amplitudes were associated with urinary DAP metabolites. - Mean CMAP and SNAP amplitudes were within normal values
Pilkington et al. 2001/ Scotland and England[CS]	- Sheep dipping farmers (612) - Farmers with no sheep dipping experience (53) - Ceramics workers(107)	- Questionnaire - DAP metabolites: DEP, DETP	- Large fiber abnormality	- No difference in mean vibration thresholds among groups
Boostani et al. 2014/ Iran[CS]	- Farm sprayers (100) - Hospital personnel (100) (control)	- Questionnaire	- Nerve conduction	- Abnormal peroneal NCV (m/s) of sprayers > Controls ($p < 0.001$) - Abnormal sural SNAP amplitude (mV) of sprayers > Controls ($p = 0.029$) - Abnormal radial SNAP peak latency (ms) of sprayers > Control ($p < 0.001$) - Abnormal radial NCV (ms) of sprayers > Control ($p < 0.001$)
Steenland et al. 2000/ USA (NC)[CS]	- Chlorpyrifos applicators (191) - Un-exposed friends (106) - Un-exposed NC workers (83)	- TCPy	- Nerve conduction	- No significant differences between applicators and the combined Un-exposed group for peroneal, ulnar, or sural nerve conduction velocity and amplitude - Ulnar amplitude of applicators < Un-exposed NC workers ($p = 0.03$) - Ulnar amplitude of Currently exposed applicators < Unexposed NC workers ($p = 0.03$) - Sural nerve conduction of applicators > Unexposed NC workers ($p = 0.05$)
Albers et al. 2004a/ USA[CS]	- Chlorpyrifos exposures (53) - Referents (60)	- TCPy - BuChE - AChE activity	- Nerve conduction	- No difference in sensory and motor nerve conduction measures (amplitude, conduction velocity, and latency) among groups
Albers et al. 2004b/ USA[C]	- Chlorpyrifos exposures (53) - References (60)	- TCPy - BuChE - AChE activity	- Nerve conduction	- At baseline, no significant group differences existed for any of the nerve conduction measures - At the one-year examination, borderline significant in peroneal motor distal latency of chlorpyrifos exposures < Referents (4.6 v 4.9 ms, $p = 0.07$) - Compare to baseline and one-year, borderline significant in median motor and sural amplitudes of the chlorpyrifos exposures > References (1.5 v 0.6 mv, $p = 0.08$ and 2.1 v 0.1 mv, $p = 0.09$, respectively)

β= beta, α = had an association, < = lower than, > = higher than, p = P value, r = correlation coefficient, AChE = acetylcholinesterase, BuChE = plasma butyrylcholinesterase, CC = case-control study, CS= cross sectional study, C = prospective cohort study, ChE = plasma cholinesterase, CMAP = compound muscle action potential, DAP = dialkyl phosphate, DEP = diethylphosphate, DETP = diethylthiophosphate, DEDTP = diethyldithiophosphate, DMDTP = dimethyldithiophosphate, DMP = dimethylphosphate, DMTP = dimethylthiophosphate, EMG = electromyography, MNCS = motor nerve conduction studies, NC = North Carolina, NCV = nerve conduction velocity, NCVs = nerve conduction velocities, ms = millisecond, m/s= meter per second, mV = millivolt, OP =organophosphate, PAM = pralidoxime, SFEMG = single fiber electromyography, SNAP = sensory nerve action potential, SNCS = sensory nerve conduction studies, TCPy = 3,5,6-trichloro-2-pyridinol, v = versus

Effect of Exposure for Organophosphate on Neuropsychological Functioning

Nine articles were specific to the effects of OPs on neuropsychological function, one study was case-control studies, two studies were prospective cohort studies, and six studies were cross-sectional studies. The major test used for OPs exposure with suspected changes in other neuropsychological (n=8). Other tests used were the attention (n=7), memory (n=6), perception and visuospatial function (n=4), motor control (n=4), IQ (n=3), executive function (n=2), and language (n=2). Five studies found a significant different neuropsychological between exposure and non-exposure group, while three studies found a significantly different mood and psychiatric disorder. Furthermore, one study found an association between OPs and increased risk of clinically defined dementia/ cognitively impaired but no dementia (cognitively impaired but no dementia (CIND)). (Table 2)

OPs exposure has been implicated in a number of health problems, including cognitive outcome such as deficits of memory, attention, perception and visuospatial function, executive function, language, IQ, and other neuropsychological test (Corral et al., 2017; Farahat et al., 2003; Jamal et al., 2002; Jamal et l., 2016; Paul et al., 2018; Rothlein et al., 2006; Serrano-Medina et al., 2019). Exposure to OPs indicates lower performance than controls in IQ (similarities), memory (digit span forward and backward), attention (trail making part A and B, digit symbol, letter cancel), and perception and visuospatial function (Benton Visual Retention Test (BVRT)) (Farahat et al., 2003). These results are consistent with the direct and indirect pesticide exposure groups have significantly lower cognitive score than unexposed group in memory (digit span forward and backward), and perception and visuospatial function (Rey-Osterrieth Complex Figure Test (ROCF)), while the direct pesticide exposure group have significantly lower cognitive score than the indirect pesticide exposure and unexposed group in executive function (frontal Assessment Battery (FAB)), other neuropsychological tests (mini-mental state examination (MMSE)), and language (semantic verbal fluency (SVF)) (Corral et al., 2017). The longer period of exposure to pesticides is increasing performance deficit more than to control, this result may be related to most neuropsychological deficit was markedly among participants with the more years of exposure. Serum AChE is significantly lower in the exposure group than the control group, as a result of long-term enzyme inhibition related to the low-level OPs exposure and cognitive impairment (Farahat et al., 2003). Other investigators have also reported cognitive impairment in attention (digit symbol, selective and divided attention), deficits in psychomotor abilities (finger tapping), psychiatric disorders, anxiety, insomnia, major depression, and clinically defined dementia/CIND in OPs exposure (Jamal et al., 2016; Paul et al., 2018; Rothlein et al., 2006; Serrano-Medina et al., 2019). Delayed neurotoxicity results from afferent fibers of peripheral and central nerves are damaged by the irreversible inhibition of AChE (Serrano-Medina et al., 2019). The neurotoxic function also contributes to harm in the nervous system. Also, acute and chronic exposure to OPs is related to cognitive and motor impairment that can be monitored even several months post-intoxication (Kamel et al., 2003). COPIND usually occurs with a delay and persists for a long period possibly suggesting the lasting damage of the CNS (Tan et al., 2009). It has shown impaired neurobehavioral performance including the cognitive deficit, mood change, depression, and psychotic symptoms (Kamel & Hoppin, 2004).

Table 2 Effect of Exposure to OPs on Neuropsychological Functioning

Authors/ Country	Study Population	Exposure assessment	Outcome assessment	Instruments	Findings
Jamal et al. 2016/ India[CS]	- Pesticide sprayers(187) - Controls (187)	- AChE activity	- Memory - Attention - Others	- GHQ-28 questionnaire[(a)]	- Psychomotor speed of sprayers < Controls ($p < 0.001$) - Selective attention of sprayers < Controls ($p < 0.001$) - Divided attention of sprayers < Controls ($p < 0.001$) - Verbal memory of sprayers < Controls ($p < 0.001$) - Nonverbal memory of sprayers < Controls ($p < 0.001$) - Prospective memory of sprayers < Controls ($p < 0.001$) - Spatial function of sprayers < Controls ($p < 0.001$) - Initiative/energy of sprayers < Controls ($p < 0.001$) - Rates of anxiety and insomnia of sprayers > Controls ($p = 0.030$) - Rates of severe depression of sprayers > Controls ($p < 0.0001$) - Rates of social dysfunction of sprayers < Controls ($p = 0.002$)
Farahat et al. 2003/ Egypt[CS]	- Exposed pesticide workers (52) - Controls (50)	- AChE activity	- Perception and visuospatial function - Memory - Attention - IQ - Others	- Neurobehavioral test battery [(b)]	- Similarities of exposed workers < Controls ($p < 0.003$) - Digit symbol of exposed workers < Controls ($p < 0.001$) - Trail making A (s) of exposed workers > Controls ($p < 0.030$) - Trail making B (s) of exposed workers > Controls ($p = 0.015$) - Letter Cancel (error) Trail making A (s) of exposed workers > Controls ($p = 0.037$) - Digit span forward of exposed workers < Controls ($p = 0.037$) - Digit span backward of exposed workers < Controls ($p = 0.003$) - BVRT of exposed workers < Controls ($p = 0.003$) - Similarities α Duration of exposure ($\beta = -0.66$, $p = 0.001$) - Digit symbol α Duration of exposure ($\beta = -1.82$, $p < 0.001$) - Digit span forward and Backward α Duration of exposure ($\beta = -0.32$, $p = 0.004$ and $\beta = -0.28$, $p < 0.001$, respectively) - BVRT test α Duration of exposure ($\beta = -0.28$, $p = 0.004$) - Trail making A and B α Duration of exposure ($\beta = 2.40$, $p = 0.001$ and $\beta = 4.24$, $p = 0.001$, respectively)

Table 2 (Cont.)

Authors/ Country	Study Population	Exposure assessment	Outcome assessment	Instruments	Findings
Corral et al. 2017/ Chile[CS]	- Direct pesticide exposure group (32) - Indirect pesticide exposure group (32) - Unexposed group (38)	- Questionnaire	- Perception and visuospatial function - Memory - Attention - Executive function - Language - Others	Neuropsychological test: - MMSE - Digit span test - ROCF - Stroop test - D2 test of attention - FAB - SVF	- Scores of MMSE, FAB, and SVF indirect pesticide exposure group < Indirect pesticide exposure group and unexposed group ($p < 0.001$) - Scores of Digit span forward, ROCF memory recall, and digit span backward indirect pesticide exposure group and indirect pesticide exposure < Unexposed group ($p = 0.004$, $p = 0.002$, and $p < 0.001$, respectively)
Rothlein et al. 2006/ Columbia[CS]	- Hispanic immigrant farmworkers (99) - Non-agricultural Hispanic (55)	- Five DAP metabolites: DMP, DMTP, DMDTP, DEP, and DETP	- Motor control - Memory - Attention - Others	- BARS [(c)]	- Neurobehavioral performance of Hispanic immigrant farmworkers < Non-agricultural Hispanic immigrant populations ($p < 0.01$) - Selective attention latency α Level of combined thiomethyl metabolites ($r = 0.251$, $p = 0.011$) - Symbol-digit latency α Level of combined thiomethyl metabolites ($r = 0.281$, $p = 0.005$) - Finger tapping, preferred hand α Level of combined thiomethyl metabolites ($r = -0.252$, $p = 0.012$) -Finger tapping, alternating hand α Level of combined thiomethyl metabolites ($r = -0.208$, $p = 0.029$)
Serrano-medina et al. 2019/ Mexico[CS]	- Exposed pesticide participants (140) - Unexposed participants (100)	- AChE activity	- Others	- MINI	- Psychiatric disorders in Exposed pesticide participants > Unexposed participants ($p < 0.001$) - Among agricultural workers with slightly inhibited enzymatic activity, 25% met the criteria for major depression and no psychiatric diagnosis disorder
Paul et al. 2018/ USA (California)[C]	- Ambient OP exposure (430)	- Metabolic - Inflammatory biomarkers	- Perception and visuospatial function - Attention - Language - Others	- 3MSE - SENAS	- High ambient exposure α Increased risk of clinically defined dementia/CIND
Berent et al. 2014/ USA (Michigan)[C]	- Chlorpyrifos workers (53) - Referent workers (60)	- TCPy - BuChE activity - AChE activity	- Motor control - Memory - Attention - Executive function	- CANTAB [(e)]	- Chlorpyrifos workers scored > Referent workers on the verbal memory domain score ($p = 0.03$) at baseline - No significant changes in verbal memory over time and no significant group-by-time interactions
Steenland et al. 2000/ USA (NC)[CS]	- Chlorpyrifos applicators (191) - Un-exposed friends (106) - Un-exposed NC workers (83)	- TCPy	- Motor control - Memory - Attention - IQ - Others	- NES [(d)]	- No significant differences between the applicator and nonexposed groups on simple reaction time, digit symbol, continuous performance, digit span, forward and backward, pattern memory and vocabulary - The test for depression of applicators > Un-exposed friends ($p = 0.05$)

Table 2 (Cont.)

Authors/ Country	Study Population	Exposure assessment	Outcome assessment	Instruments	Findings
					- The eight men who reported past chlorpyrifos poisoning reported significantly more confusion (p = 0.03)
Jamal et al. 2002/ United Kingdom[CC]	79 sheep farmers - No, possible neuropathy - Probable neuropathy - Definite neuropathy	- Questionnaire	- Perception and visuospatial function - Motor control - Memory - Attention - IQ	- CANTAB [(e)] - RAG	- No significant differences in IQ between the three neuropathy groups - Anxiety and depression in definite neuropathy group > Other two groups

[(a)] GHQ-28 questionnaire = General Health Questionnaire: attention, divided attention, long-term memory, prospective memory, and psychomotor retardation

[(b)] Neurobehavioral test battery: 1) similarities (test of verbal abstraction, 2) digit symbol and trail making part A and B (visuomotor speed), 3) block design (problem solving), 4) paced auditory serial addition test (PASAT), letter cancellation (attention), 5) digit span, Benton Visual Retention Test (BVRT), story recall parts A and B (memory), and 6) Eysenck Personality Questionnaire (EPQ)

[(c)] BARS = behavioral assessment and research system: 1) psychomotor functioning (finger tapping, simple reaction time, progressive ratio) and 2) cognitive functioning (symbol-digit, digit span, selective attention, serial digit learning, and continuous performance)

[(d)] NES = neurobehavioral evaluation system: 1) vocabulary test, 2) mood scales, 3) digit span test, 4) continuous performance, 5) simple reaction, 6) digit symbol test, and 7) pattern memory

[(e)] CANTAB = Cambridge Neuropsychological Test Automated Battery: 1) Intra-Extra Dimensional Shift (IED), Spatial Span (SSP) and Stockings of Cambridge (SOC), 2) ten tasks from Woodcock-Muñoz Achievement Battery, Revised (W-M): Visual-Motor Integration, Verbal Comprehension (Vocabulary, Synonyms, Antonyms, Analogies), Visual-Auditory Comprehension, Concept Formation, Visual Spatial Thinking, Number Inversion and Spatial Relations, 3) Bender Gestalt task, and 4) Weschler block design task

β= beta, α = had an association, < = lower than, > = higher than, p = P value, *r* = correlation coefficient

3MSE = mini-mental state exam, AChE = acetylcholinesterase, BuChE = plasma butyrylcholinesterase, C = prospective cohort study, CC = case-control study, CIND = cognitively impaired but no dementia, CS = cross sectional study, DAP= dialkyl phosphate, DEP = diethylphosphate, DETP = diethylthiophosphate, DMDTP = dimethyldithiophosphate, DMP = dimethylphosphate, DMTP = dimethylthiophosphate, FAB = frontal Assessment Battery, IQ = Intelligence Quotient, MINI = mini international neuropsychiatric interview diagnostic Test, MMSE = mini-mental state examination, NC = North Carolina, OP =organophosphate, RAG = Battery of psychometric test, ROCF = Rey-Osterrieth Complex Figure Test, SENAS = Spanish and English neuropsychological assessment scales, SVF = semantic verbal fluency, TCPy = 3,5,6-trichloro-2-pyridinol, USA = United States of America

Effect of Exposure for Organophosphate on Postural Balance

Five articles were specific to the effects of OPs on postural balance, one study was prospective cohort studies, and four studies were a cross-sectional study. The major test used to assess postural balance was the computerized static posturography (n = 4). Other tests used were the Romberg test, tandem gait, and postural tremor. One study found a significant postural stability performance difference between exposure and four studies found an association between OPs and postural balance impairment. (Table 3)

Not only the length measurement slopes with a hard surface with eyes closed and soft surface with eyes open and eyes closed conditions showed significant urinary 3,5,6-trichloro-*2*-pyridinol (TCPy) effects, but also the area measurement slopes with a hard surface with eyes closed and soft surface with eyes closed conditions showed significant urinary TCPy effects (Dick, Steenland, Krieg, & Hines, 2001). These results are consistent with the findings of the study by Steenland et al. (2000) which assessed postural sway by using a microcomputer-control force platform and varied test condition (eyes open or closed, hard or soft surface, one leg or two legs), and chlorpyrifos exposure groups have more length of sway than unexposed friends and unexposed controls on a hard surface with eyes open and more length of sway than unexposed controls on a hard surface while standing on the left leg only. Furthermore, the TCPy level significantly predicted the length of

sway (hard surface and foam pad) and area of sway (foam pad) for the test conditions with eyes closed (Steenland et al., 2000). The postural sway test conditions used in these two studies were designed to manipulate input from the various afferent sources such as a hard surface with eyes open followed by the hard surface with eyes closed which removes the visual system. In addition a soft surface or form pad with eyes open condition followed by the soft surface with eyes closed condition removes the visual system and modified proprioceptive feedback. Postural balance control is a dynamic process of a complex interaction of three afferent sources that included proprioceptive and kinesthetic, vestibular, and visual system. Therefore, this indicates a possible effect on both the proprioceptive and vestibular system because urinary TCPy effects occur in the eyes closed conditions both on hard and soft surfaces (Dick et al., 2001). Other tests used were the tandem gait, postural tremor, and Romberg test which found that OPs compounds are associated with tandem gait abnormality, postural tremor abnormality and Romberg test (Starks et al., 2012; Steenland et al., 2000). Acetylcholine is also a neurotransmitter in the brain and chlorpyrifos readily crosses the blood-brain barrier with effects on the muscarinic receptors and the nicotinic receptors. Chlorpyrifos, similarly to other OPs compounds, is an accumulation of the chemical transmitter acetylcholine which results in excess cholinergic stimulation. The possibility for this result that the effects of chlorpyrifos may be on the chemical neurotransmitters that are important in proper PNS and CNS control of postural sway (Dick et al., 2001). The studies by Kim et al. (2016) found no significant difference in the conventional COP between farmworkers and non-farmworkers because of the range of OPs exposure levels overlapped between the two groups that may be influenced by a lifetime of pesticide exposure on postural control (Sunwook et al., 2016). Another study found no significance in the level of urinary DAP metabolites between farmworkers and non-farmworkers because the urine samples were collected up to four times at one-month intervals with postural control measures also obtained at these times. Therefore, it may not effects the urinary DAP metabolites when data on postural control are measure (Kim et al., 2018).

Table 3 Effect of Exposure to OPs on Postural Balance

Authors/Country	Study Population	Exposure assessment	Outcome assessment	Findings
Dick et al. 2001/ USA (NC)[cs]	- Applicators using chlorpyrifos (106) - Un-exposed (52)	- TCPy	- Postural stability (sway)	- Length measurement slopes with hard surface-EC, soft surface-EO and soft surface-EC showed significant urinary TCPy effects (b= 0.0122, p= 0.0006, b = 0.0051, p= 0.032 and b= 0.0202, p= 0.0001, respectively) - Area measurement slopes with hard surface-EC and soft surface-EC showed significant urinary TCPy effects (b= 0.0011, p= 0.0372 and b= 0.0035, p= 0.0001, respectively)
Steenland et al. 2000/ USA (NC)[cs]	- Chlorpyrifos applicators (191) - Un-exposed friends (106) - Un-exposed NC workers (83)	- TCPy	- Postural sway - Romberg test	- The length of sway on a hard surface with EO of applicators > Un-exposed friends and Un-exposed NC workers (p = 0.05, and 0.02, respectively) - The length of sway while standing on the left leg only of applicators > Un-exposed NC workers (p = 0.01) - The TCPy level significantly predicted the length of sway for the test conditions with EC (hard surface, p = 0.03; foam pad, p = 0.01) and area of sway for EC on foam pad (p = 0.02)

Table 3 (Cont.)

Authors/Country	Study Population	Exposure assessment	Outcome assessment	Findings
				- The eighteen men in the applicator group had increased abnormal Romberg test (p = 0.04)
Straks et al. 2012/ USA (NC)[CS]	- Pesticide applicators (678)	- Questionnaire	- Romberg test - Tandem gait - Postural tremor	- Ever used 16 OP pesticides not significant for Romberg test - Dichlorvos use was associated with tandem gait abnormality, with mean (95% CI) values = 2.29 (1.41, 3.71) - Dimethoate, disulfoton, ethoprop, and tebupirimfos use α Postural tremor abnormality, with mean (95% CI) values = 1.90 (1.01, 3.54), 1.95 (1.19, 3.18), 2.16 (1.35, 3.47), and 2.17 (1.18, 4.00), respectively
Sunwook et al. 2016/ USA (NC)[CS]	- Farmworkers (235)	- Questionnaire	- Balance performance baseline COP	- No significant differences in the conventional COP between farmworkers and non-farmworkers
	- Non-farmworkers (212)		measure (2 visual × 2 cognitive difficulties)	- A summary of baseline COP measures, sway complexity (CI_{AP} and CI_{ML}) of farmworkers > Non-farmworkers (p = 0.037 and 0.002, respectively) - For the EC without cognitive task condition, CI_{AP} ratio of farmworkers α Years of occupational exposure (β = -0.046, p = 0.038) - For the EC plus cognitive task condition, MV_{ML} and CI_{ML} values of farmworkers > Non-farmworkers (p < 0.05)
Kim et al. 2018/ USA (NC)[C]	- Farmworkers (77) - Non-farmworkers (56)	- Six DAP metabolites: DMP, DMTP, DMDTP, DEP, DETP, and DEDTP	- Postural control from COP	- Not significant in level of urinary DAP metabolites between farmworkers and non-farmworkers - At baseline condition, CI_{ML} α DAP metabolites, specifically DEP, with a corresponding coefficient = 0.013 (95% CI: -0.002, 0.029) - For the EC with or without cognitive condition, MV_{ML} and CI_{ML} α DAP metabolites with a corresponding coefficient (r^2 = 0.21- 0.22)

β= beta, α = had an association, < = lower than, > = higher than, *b* = Slope Coefficient, p = P value, r^2 = coefficient of determination, C = prospective cohort study, CI = confidence interval, COP = center of pressure, CI_{AP} = complexity index antero-Posterior, CI_{ML} = complexity index medio-lateral, CS = cross sectional study, DAP = dialkyl phosphate, DEP = diethylphosphate, DEDTP = diethyldithiophosphate, DETP = diethylthiophosphate, DMDTP = dimethyldithiophosphate, DMP = dimethylphosphate, DMTP = dimethylthiophosphate, EC = eyes-closed, EO = eyes-open, MV_{ML} = mean COP velocity, NC = North Carolina, OPs =organophosphates, TCPy = 3,5,6-trichloro-2-pyridinol, USA = United States of America

Conclusion and Suggestions

Most of the studies revealed an association between neurological symptoms, neuropsychological functioning deficit, postural balance impairment, and exposure to OPs. These articles also have considerable evidence suggesting that the electrophysiological changes include abnormalities that point to remodeling of the motor unit, abnormal small and large nerve fiber function, reduced CMAP amplitude and ulnar F-wave, and abnormal ulnar, tibial, peroneal, and sural nerve conduction. OPs exposure has been implicated in cognitive impairment including deficits of memory, attention, perception and visuospatial function, executive function, language, IQ, and others neuropsychological tests such as psychiatric disorders, anxiety, insomnia, major depression, and dementia. Postural sway of OPs exposure has more length of sway than in the unexposed. However, many of these studies

have limitations in design and do not use biomarkers for exposure analysis. Future studies should more specifically include long-time studies and the use of biomarkers of exposure to assess dose responses.

Acknowledgments

We are grateful to the staff of the Faculty of Medicine, Chiang Mai University for their cooperation and assistance in this study.

References

Alahakoon, C., Dassanayake, T. L., Gawarammana, I. B., Sedgwick, E. M., Weerasinghe, V. S., Abdalla, A., . . . Buckley, N. A. (2018). Prediction of organophosphorus insecticide-induced intermediate syndrome with stimulated concentric needle single fibre electromyography. *PloS One, 13*(9), e0203596. doi:10.1371/journal.pone.0203596

Albers, J. W., Garabrant, D. H., Schweitzer, S., Garrison, R. P., Richardson, R. J., & Berent, S. (2004a). Absence of sensory neuropathy among workers with occupational exposure to chlorpyrifos. *Muscle and Nerve, 29*(5), 677-686. doi:10.1002/mus.20007

Albers, J. W., Garabrant, D. H., Schweitzer, S. J., Garrison, R. P., Richardson, R. J., & Berent, S. (2004b). The effects of occupational exposure to chlorpyrifos on the peripheral nervous system: a prospective cohort study. *Occupational and Environmental Medicine, 61*(3), 201-211. doi:10.1136/oem.2003.008847

Baldi, I., Lebailly, P., Mohammed-Brahim, B., Letenneur, L., Dartigues, J. F., & Brochard, P. (2003). Neurodegenerative diseases and exposure to pesticides in the elderly. *American Journal of Epidemiology, 157*(5), 409-414. doi:10.1093/aje/kwf216

Bird, S. B., Krajacic, P., Sawamoto, K., Bunya, N., Loro, E., & Khurana, T. S. (2016). Pharmacotherapy to protect the neuromuscular junction after acute organophosphorus pesticide poisoning. *Annals of the New York Academy of Sciences, 1374*(1), 86-93. doi:10.1111/nyas.13111

Boostani, R., Mellat, A., Afshari, R., Derakhshan, S., Saeedi, M., Rafeemanesh, E., & Mellat, M. (2014). Delayed polyneuropathy in farm sprayers due to chronic low dose pesticide exposure. *Iran Red Crescent Med J, 16*(5), e5072. doi:10.5812/ircmj.5072

Corral, S. A., de Angel, V., Salas, N., Zuniga-Venegas, L., Gaspar, P. A., & Pancetti, F. (2017). Cognitive impairment in agricultural workers and nearby residents exposed to pesticides in the Coquimbo Region of Chile. *Neurotoxicology and Teratology, 62*, 13-19. doi:10.1016/j.ntt.2017.05.003

Costa, L. G. (2018). Organophosphorus Compounds at 80: Some Old and New Issues. *Toxicological Sciences, 162*(1), 24-35. doi:10.1093/toxsci/kfx266

Crinnion, W. J. (2010). The CDC fourth national report on human exposure to environmental chemicals: what it tells us about our toxic burden and how it assist environmental medicine physicians. *Alternative Medicine Review, 15*(2), 101-109.

Dick, R. B., Steenland, K., Krieg, E. F., & Hines, C. J. (2001). Evaluation of acute sensory--motor effects and test sensitivity using termiticide workers exposed to chlorpyrifos. *Neurotoxicology and Teratology, 23*(4), 381-393.

Farahat, T. M., Abdelrasoul, G. M., Amr, M. M., Shebl, M. M., Farahat, F. M., & Anger, W. K. (2003). Neurobehavioural effects among workers occupationally exposed to organophosphorous pesticides. *Occupational and Environmental Medicine, 60*(4), 279-286. doi:10.1136/oem.60.4.279

Flaskos, J. (2012). The developmental neurotoxicity of organophosphorus insecticides: a direct role for the oxon metabolites. *Toxicol Lett, 209*(1), 86-93. doi:10.1016/j.toxlet.2011.11.026

Galloway, T., & Handy, R. (2003). Immunotoxicity of organophosphorous pesticides. *Ecotoxicology, 12*(1-4), 345-363. doi:10.1023/a:1022579416322

Glynn, P. (2006). A mechanism for organophosphate-induced delayed neuropathy. *Toxicology Letters, 162*(1), 94-97. doi:10.1016/j.toxlet.2005.10.012

Haliga, R. E., Morarasu, B. C., Ursaru, M., Irimioaia, V., & Sorodoc, L. (2018). New insights into the organophosphate-induced intermediate syndrome. *Arhiv Za Higijenu Rada i Toksikologiju, 69*(2), 191-195. doi:10.2478/aiht-2018-69-3121

Hayden, K. M., Norton, M. C., Darcey, D., Ostbye, T., Zandi, P. P., Breitner, J. C., . . . Cache County Study, I. (2010). Occupational exposure to pesticides increases the risk of incident AD: the Cache County study. *Neurology, 74*(19), 1524-1530. doi:10.1212/WNL.0b013e3181dd4423

Hofmann, J. N., Keifer, M. C., Furlong, C. E., De Roos, A. J., Farin, F. M., Fenske, R. A., . . . Checkoway, H. (2009). Serum cholinesterase inhibition in relation to paraoxonase-1 (PON1) status among organophosphate-exposed agricultural pesticide handlers. *Environmental Health Perspectives, 117*(9), 1402-1408. doi:10.1289/ehp.0900682

Hongsibsong, S., Sittitoon, N., & Sapbamrer, R. (2017). Association of health symptoms with low-level exposure to organophosphates, DNA damage, AChE activity, and occupational knowledge and practice among rice, corn, and double-crop farmers. *J Occup Health, 59*(2), 165-176. doi:10.1539/joh.16-0107-OA

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. doi:10.1136/oemed-2011-100204

Jalali, N., Balali-Mood, M., Jalali, I., & Shakeri, M. T. (2011). Electrophysiological changes in patients with acute organophosphorous pesticide poisoning. *Basic & Clinical Pharmacology & Toxicology, 108*(4), 251-255. doi:10.1111/j.1742-7843.2010.00652.x

Jamal, G. A., Hansen, S., Pilkington, A., Buchanan, D., Gillham, R. A., Abdel-Azis, M., . . . 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. doi:10.1136/oem.59.7.434

Jayasinghe, S. S., Pathirana, K. D., & Buckley, N. A. (2012). Effects of acute organophosphorus poisoning on function of peripheral nerves: a cohort study. *PloS One, 7*(11), e49405. doi:10.1371/journal.pone.0049405

Jokanovic, M. (2018). Neurotoxic effects of organophosphorus pesticides and possible association with neurodegenerative diseases in man: A review. *Toxicology, 410*, 125-131. doi:10.1016/j.tox.2018.09.009

Kamel, F., Engel, L. S., Gladen, B. C., Hoppin, J. A., Alavanja, M. C., & Sandler, D. P. (2005). Neurologic symptoms in licensed private pesticide applicators in the agricultural health study. *Environmental Health Perspectives, 113*(7), 877-882. doi:10.1289/ehp.7645

Kamel, F., & Hoppin, J. A. (2004). Association of pesticide exposure with neurologic dysfunction and disease. *Environmental Health Perspectives, 112*(9), 950-958. doi:10.1289/ehp.7135

Kamel, F., Rowland, A. S., Park, L. P., Anger, W. K., Baird, D. D., Gladen, B. C., . . . Sandler, D. P. (2003). Neurobehavioral performance and work experience in Florida farmworkers. *Environmental Health Perspectives, 111*(14), 1765-1772. doi:10.1289/ehp.6341

Kim, S., Nussbaum, M. A., Laurienti, P. J., Chen, H., Quandt, S. A., Barr, D. B., & Arcury, T. A. (2018). Exploring Associations Between Postural Balance and Levels of Urinary Organophosphorus Pesticide Metabolites. *Journal of Occupational and Environmental Medicine, 60*(2), 174-179. doi:10.1097/JOM.0000000000001194

Kimura, K., Yokoyama, K., Sato, H., Nordin, R. B., Naing, L., Kimura, S., . . . Araki, S. (2005). Effects of pesticides on the peripheral and central nervous system in tobacco farmers in Malaysia: studies on peripheral nerve conduction, brain-evoked potentials and computerized posturography. *Industrial Health, 43*(2), 285-294. doi:10.2486/indhealth.43.285

Liu, H., Hanchenlaksh, C., Povey, A. C., & de Vocht, F. (2015). Pesticide residue transfer in Thai farmer families: using structural equation modeling to determine exposure pathways. *Environmental Science & Technology, 49*(1), 562-569. doi:10.1021/es503875t

London, L., Beseler, C., Bouchard, M. F., Bellinger, D. C., Colosio, C., Grandjean, P., . . . Stallones, L. (2012). Neurobehavioral and neurodevelopmental effects of pesticide exposures. *Neurotoxicology, 33*(4), 887-896. doi:10.1016/j.neuro.2012.01.004

Lukaszewicz-Hussain, A. (2010). Role of oxidative stress in organophosphate insecticide toxicity - Short review. *Pesticide Biochemistry and Physiology, 98*(2), 145-150. doi:10.1016/j.pestbp.2010.07.006

Mangas, I., Vilanova, E., Estevez, J., & Franca, T. C. C. (2016). Neurotoxic Effects Associated with Current Uses of Organophosphorus Compounds. *Journal of the Brazilian Chemical Society, 27*(5), 809-825. doi:10.5935/0103-5053.20160084

Norkaew, S., Lermaharit, S., Wilaiwan, W., & Siriwong, W. (2015). An association between organophosphate pesticides exposure and parkinsonism amongst people in and agricutural area in Ubon Ratchthani Province, Thailand. *66*(1), 21-26.

Peiris-John, R. J., Ruberu, D. K., Wickremasinghe, A. R., Smit, L. A., & van der Hoek, W. (2002). Effects of occupational exposure to organophosphate pesticides on nerve and neuromuscular function. *Journal of Occupational and Environmental Medicine, 44*(4), 352-357.

Pilkington, A., Buchanan, D., Jamal, G. A., Gillham, R., Hansen, S., Kidd, M., . . . 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. doi:10.1136/oem.58.11.702

Ranjbar, A., Solhi, H., Mashayekhi, F. J., Susanabdi, A., Rezaie, A., & Abdollahi, M. (2005). Oxidative stress in acute human poisoning with organophosphorus insecticides; a case control study. *Environ Toxicol Pharmacol, 20*(1), 88-91. doi:10.1016/j.etap.2004.10.007

Read, D. J., Li, Y., Chao, M. V., Cavanagh, J. B., & Glynn, P. (2009). Neuropathy target esterase is required for adult vertebrate axon maintenance. *Journal of Neuroscience, 29*(37), 11594-11600. doi:10.1523/jneurosci.3007-09.2009

Rivera, E. P., Siriwong, W., Taneepanichskul, N., Norkaew, S., & Robson, M. G. (2016). Health Risk Related to Pesticide Exposure in the Agriculture System in Thailand: A Systematic Review.pdf>. *J health Res, 30, supplement 1*. doi:10.14456/jhr.2016.69

Rothlein, J., Rohlman, D., Lasarev, M., Phillips, J., Muniz, J., & McCauley, L. (2006). Organophosphate pesticide exposure and neurobehavioral performance in agricultural and non-agricultural Hispanic workers. *Environmental Health Perspectives, 114*(5), 691-696. doi:10.1289/ehp.8182

Salehcheh, M., Kakantari, H., Javad Khodayar, M. J., & Jahangiri, A. (2014). Genotyping Paraoxonase Polymorphism in Iranian Farmers Exposed to Organophosphate Pesticides. *International Journal of Pharmacology, 10*(8), 513-518.

Sapbamrer, R. (2018). Pesticide Use, Poisoning, and Knowledge and Unsafe Occupational Practices in Thailand. *New Solutions: A Journal of Environmental and Occupational Health Policy, 28*(2), 283-302. doi:10.1177/1048291118759311

Sapbamrer, R., & Hongsibsong, S. (2014). Organophosphorus pesticide residues in vegetables from farms, markets, and a supermarket around Kwan Phayao Lake of Northern Thailand. *Archives of Environmental Contamination and Toxicology, 67*(1), 60-67. doi:10.1007/s00244-014-0014-x

Sapbamrer, R., Hongsibsong, S., Sittitoon, N., & Amput, P. (2019). DNA damage and adverse neurological outcomes among garlic farmers exposed to organophosphate pesticides. *Environmental Toxicology and Pharmacology, 72*, 103241. doi:10.1016/j.etap.2019.103241

Sapbamrer, R., & Nata, S. (2014). Health symptoms related to pesticide exposure and agricultural tasks among rice farmers from Northern Thailand. *Environmental Health and Preventive Medicine, 19*(1), 12-20. doi:10.1007/s12199-013-0349-3

Schroeder, R. W., Martin, P. K., & Walling, A. (2019). Neuropsychological Evaluations in Adults. *American Family Physician, 99*(2), 101-108.

Sedgwick, E. M., & Senanayake, N. (1997). Pathophysiology of the intermediate syndrome of organophosphorus poisoning. *Journal of Neurology, Neurosurgery and Psychiatry, 62*(2), 201-202. doi:10.1136/jnnp.62.2.201

Serrano-Medina, A., Ugalde-Lizarraga, A., Bojorquez-Cuevas, M. S., Garnica-Ruiz, J., Gonzalez-Corral, M. A., Garcia-Ledezma, A., . . . Cornejo-Bravo, J. M. (2019). Neuropsychiatric Disorders in Farmers Associated with Organophosphorus Pesticide Exposure in a Rural Village of Northwest Mexico. *International Journal of Environmental Research and Public Health, 16*(5). doi:10.3390/ijerph16050689

Singh, N., Chhillar, N., Banerjee, B., Bala, K., Basu, M., & Mustafa, M. (2013). Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. *Human and Experimental Toxicology, 32*(1), 24-30. doi:10.1177/0960327112456315

Starks, S. E., Hoppin, J. A., Kamel, F., Lynch, C. F., Jones, M. P., Alavanja, M. C., . . . Gerr, F. (2012). Peripheral nervous system function and organophosphate pesticide use among licensed pesticide applicators in the Agricultural Health Study. *Environmental Health Perspectives, 120*(4), 515-520. doi:10.1289/ehp.1103944

Steenland, K., Dick, R. B., Howell, R. J., Chrislip, D. W., Hines, C. J., Reid, T. M., . . . Knott, C. (2000). Neurologic function among termiticide applicators exposed to chlorpyrifos. *Environmental Health Perspectives, 108*(4), 293-300. doi:10.1289/ehp.00108293

Sunwook, K., Nussbaum, M. A., Quandt, S. A., Laurienti, P. J., & Arcury, T. A. (2016). Effects of Lifetime Occupational Pesticide Exposure on Postural Control Among Farmworkers and Non-Farmworkers. *Journal of Occupational and Environmental Medicine, 58*(2), 133-139. doi:10.1097/jom.0000000000000655

Tan, D. H., Peng, S. Q., Wu, Y. L., Wang, Y. M., Lu, C. F., & Yan, C. H. (2009). Chronic organophosphate (OP)-induced neuropsychiatric disorder is a withdrawal syndrome. *Medical Hypotheses, 72*(4), 405-406. doi:10.1016/j.mehy.2008.11.026

Wadia, R. S., Sadagopan, C., Amin, R. B., & Sardesai, H. V. (1974). Neurological manifestations of organophosphorous insecticide poisoning. *Journal of Neurology, Neurosurgery and Psychiatry, 37*(7), 841-847. doi:10.1136/jnnp.37.7.841

Zucchella, C., Federico, A., Martini, A., Tinazzi, M., Bartolo, M., & Tamburin, S. (2018). Neuropsychological testing. *Practical Neurology, 18*(3), 227-237. doi:10.1136/practneurol-2017-001743