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REVIEW ARTICLE

Organophosphate exposure and the chronic effects on farmers: a narrative review

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ABSTRACT:

Introduction: Organophosphates are a class of insecticides used globally by the agricultural industry for insect control. Acute consequences of organophosphate exposures are well known, while there has been limited research on their long-term effects.

The objective of this review was to discuss the health effects of chronic organophosphate exposure in farmers.
Methods: Medline, Scopus and Web of Science were searched to find the relevant articles. Articles published only in English and until December 2018 were reviewed. The selected articles were then categorised as neurological (neurobehaviour, neurodevelopmental, neurological signs and symptoms) or non-neurological subheadings.
Results: A total of 53 articles for neurological effects and 17 articles for non-neurological effects were identified. Chronic organophosphates exposure was associated with deficits in the neurobehaviour subsets of attention and short-term memory, increased incidence of neurodegenerative diseases and effects on peripheral nerves and neurodevelopment. However, research to support non-neurological effects such as respiratory symptoms, increased cancer risk, endocrine disruption, cardiac issues, chronic fatigue and infertility was limited.
Conclusion: Chronic organophosphate exposure was found to affect four of the five areas of described neurological effects in the literature. A large proportion of the research in this area was not methodologically strong, therefore few recommendations can be conclusively made. Future research is warranted to investigate the non-neurological effects of chronic exposure to ensure the occupational risks of low-level chronic exposure are clearly communicated to farmers and farm workers.

Keywords:
agricultural, Australia, chemicals, exposure, farm workers, farmers, neurological, organophosphate.

FULL ARTICLE:

Introduction

Agrichemicals are commonly used as a defence against plant and insect pests that reduce production in agricultural industries. These pests can have a significant impact on the yield of crops, pasture and animal production. During 2012–2013, approximately $350 billion was spent on insecticides (the group of agrichemicals targeting insects) by Australian agricultural industries[1]. Pesticide use remains high due to the risks associated with potential loss of production to the cropping industry if farmers did not use insecticides[2].

Organophosphates are one of the most common and effective insecticides in the agricultural industry[3]. Due to the growing resistance of insects and parasites to other forms of pesticide, the use of organophosphate chemicals remains widespread in the agricultural industry due to their broad spectrum efficacy[4].

The mode of action of organophosphates is inhibition of the enzyme acetylcholinesterase. Acetylcholinesterase is essential for the regulation of the nervous system within organisms. Organophosphates lead to the eventual death of insects by irreversibly preventing nervous conduction[2]. The human nervous system is affected by organophosphates in a similar manner.

The acute effects of organophosphates are well researched. High-level acute exposure is known to result in the inactivation of acetylcholinesterase, causing unregulated release of acetylcholine. Acute symptoms include blurred vision, lacrimation, salivation, bronchorrhea, pulmonary oedema, nausea, vomiting, diarrhoea, confusion, convulsions, loss of consciousness and respiratory distress[5].

However, less is known about the chronic health effects of organophosphates and whilst there have been a number of studies examining the chronic effects, few have been conducted using longitudinal studies[6]. The detrimental effect of organophosphates to users was, however, identified as early as 1951. Zuckerman, in a report to the British Minister of Agriculture and Fisheries in that year, recorded that organophosphorus compounds aroused apprehension, and noted that repeated absorption of organophosphate may result in cumulative poisoning[7].

Most of the available research on organophosphates is focused on the issues of acute poisoning and exposure. However, it is important to understand the chronic health effects specifically for the farmers who have been using those agrichemicals for years without being aware of the health hazards. Therefore, the objective of this narrative review was to examine the literature focusing on chronic health effects – both neurological and non-neurological – of prolonged exposure of organophosphates.

Methods

For this narrative literature review, three databases were used to search for relevant articles focusing on the chronic health effects of prolonged exposure of organophosphates: Medline, Web of Science and Scopus. The following key words were used: 'organophosph* AND farm* OR agri* AND chronic OR long term AND health'. Inclusion criteria applied for the search were English language and humans, with no limit for dates. The last search was conducted on 6 December 2018. Most of the articles focused on neurological consequences; however, there are some non-neurological studies. Articles were separated into neurological and non-neurological consequences of chronic exposure of organophosphates. Chronic exposure was defined as exposure to organophosphates for 6 months or more in an agricultural setting.

For the neurological effects, the search term 'AND neuro*' was added to existing search terms. It produced 61 articles in Medline, 166 articles in Web of Science and 51 articles in Scopus. Results of each of these searches were then manually sorted with the following exclusion criteria:

- follow-up after an acute poisoning event study
- study where there was a generic exposure to chemicals – not organophosphates specifically
- subjects who weren't exposed to organophosphate in an agricultural setting
- exposure less than 6 months.

When the duplicates were removed and the grey literature and reference lists of the retrieved articles were reviewed, there were 50 articles in total focusing on neurological effects of organophosphate exposure (Table 1).

Neurological consequences were separated into four categories as identified by common themes in this review:

- *neurobehavioural*: of or relating to the relationship between the action of the nervous system and behaviour
- *neurodegenerative*: relating to or marked by degeneration of nervous tissue
- *neurodevelopmental*: relating to development of the nervous system
- *neurological signs and symptoms*: signs and symptoms relating to the nervous system[8].

For the non-neurological consequences, the previous addition was replaced by 'NOT neuro*' and 89 articles were extracted from Medline, 224 from Web of Science and 51 from Scopus. After de-duplication and careful filtering, there were 17 articles in total focusing on the chronic non-neurological effects of organophosphate exposure (Tables 2–7). The process of article selection for this review is depicted in Figure 1. The non-neurological category was divided into common themes: respiratory symptoms, increased cancer risk, endocrine disruption, cardiac issues, chronic fatigue and infertility.

Table 1: Literature review of neurological studies[9-58]

Title	First author [text reference]	Year	Study design	Method	Health area	No. of subjects	Location	Findings	Limitations	Database(s)
Chronic central nervous system effects of acute organophosphate pesticide intoxication	L. Rosenstock [9]	1991	Retrospective cross-sectional	Neuropsychological testing including WHO battery, simple reaction time, pursuit aiming, Santa Ana manual dexterity test, Benton visual retention test, Wechsler adult intelligence test digit span and digit symbol	Neuropsychological Neurobehavioural	61	Nicaragua	Poisoned group had lower performance in 6 subsets of the WHO battery: visual attention, visual memory and visuomotor and motor function Statistical significance in 5 of the 6 subsets	Inability to identify contributions of pesticide exposure other than clinically acute Insufficient data in relation to specific organophosphate exposure – unable to assess the specific pesticide-related interactions Mismatched bias Sample bias Small sample size	Medline WOS
Organophosphates: the relationship between chronic and acute exposure effects	R. Stephens [10]	1996	Cross-sectional	Neuropsychological testing General health questionnaires Subjective memory questionnaire Simple correlation Multiple regression analysis	Neurobehavioural	146	UK	Deficits demonstrated chronic effects of organophosphates are independent of acute effects	Absence of immediate negative feedback during exposure is likely to influence measures	Medline WOS
An investigation into neurologic and neurobehavioral effects of long-term agrichemical use among deciduous fruit farm workers in the Western Cape, South Africa	L. London [11]	1997	Cross-sectional	Job exposure matrix Vibration testing Neurobehavioural battery test (WHO and Health Psychological Unit)	Neurobehavioural	247	Western Cape, South Africa	No significant neurological effect was evident with long-term exposure of organophosphates	Retrospective and self-reported study skews results Limited number of subjects, decreasing study's power	Medline Scopus WOS
Neuropsychological effects of long-term low-level organophosphate exposure in orchard sprayers in England	R. Stephens [12]	2010	Quasiexperimental cross-sectional	Interview/ questionnaire Subjective memory questionnaire General health questionnaire Neuropsychological testing including simple reaction time, digit span, symbol-digit substitution, location recognition, category search and serial word learning	Neuropsychological	94	UK	Slowed neuropsychological processing with long-term exposure	Small sample size Limited power of study	Medline Scopus
Neurobehavioural performance in preschool children from agricultural and non-agricultural communities in Oregon and North Carolina	DS. Rohlman [13]	2005	Cross-sectional	Neurobehavioural battery including 5 computerised BARS tests and 3 non computerised tests	Neurobehavioural	78	Oregon and North Carolina, USA	Decrease response speed and latency in agricultural children	Exclusion bias for difficult test Selection bias Small sample size	Medline WOS
Organophosphate pesticide exposure and neurobehavioral performance in agricultural and non-agricultural Hispanic workers	J. Rothlein [14]	2006	Cross-sectional	BARS neurobehavioural test including finger tapping, simple reaction, time and progressive ratio, symbol-digit, digit span, selective attention, serial digit learning and continuous performance	Neurobehavioural	151	Oregon, USA	Correlation between occupation, pesticide residue in house dust, biologic indicators of exposure and effect on neurobehaviour performance	Pesticide-specific information cannot be derived from urine metabolites because individual pesticide differs in toxicity then these cumulative measures cannot be viewed Only representative of a single community and cannot be extrapolated to other communities	Medline WOS
Neurobehavioral performance of adult and adolescent agricultural workers	DS. Rohlman [15]	2007	Cross-sectional	BARS test	Neurobehavioural	175	USA	Significant effect was found with match-to-sample performance and years worked in agriculture Significant decrease in performance with symbol-digit and reaction time in females as well as selective attention for male participants Decreased performance with selective attention and age with prolonged exposure in females	No exposures are available other than years of working and self-reported pesticide use Lack of time and exposure level of pesticide Small sample size	Medline Scopus WOS
Neurobehavioral effects of exposure to organophosphates and pyrethroid pesticides among Thai children	N. Fiedler [16]	2015	Cross-sectional	BARS neurobehavioural battery	Neurobehavioural	54	Thailand	No significant difference between RICE versus AQUA No significant association between DAP for motor speed or learning in LOW versus HIGH	Test unaffected to performance differences	Medline Scopus WOS
Cognitive disorders and occupational exposure to organophosphates: results from the PHYTONER study	A. Blanc-Lapierre [17]	2013	Cohort	4-year follow-up Neuropsychological including Mini Mental, Benton Visual Retention, Wechsler Paired Association and Trial Making Test	Neuropsychological Neurobehavioural	614	France	Exposure was associated with low cognitive performance No dose–effect relationship found but an increased risk observed with 50 mg increase in cumulative score	Unspecific to just organophosphate use	Scopus WOS
Auditory event-related potential changes in chronic occupational exposure to organophosphate pesticides	T. Dassanayake [18]	2009	Cohort Cross-sectional	Event-related potentials auditory exam	Neurobehavioural Neuropsychological	73	Sri Lanka	May delay the neurophysiological process underlying early stages of selective attention and late stages of sensory information processing. These include stimulus evaluation and updating of working memory	Technical limitations – only 2 scalp location recordings Electroculography not recorded No method of artefact rejection	WOS
Electroencephalogram, cognitive state, psychological	M. Bayrami [19]	2012	Comparative cross sectional	Lipid peroxidation, superoxide dismute, catalase glutathione peroxidase, DNA	Neurobehavioural	80	Iran	Farmers showed clinical symptoms such as eczema, breathing muscle	Small sample size	WOS

								evaluation and updating of working memory		
Electroencephalogram, cognitive state, psychological disorders, clinical symptom, and oxidative stress in horticulture farmers exposed to organophosphate pesticides	M. Bayrami [19]	2012	Comparative cross sectional	Lipid peroxidation, superoxide dismute, catalase glutathione peroxidase, DNA damage, total antioxidant capacity, total thiol molecules and acetylcholinesterase Clinical exams and blood test of each subject	Neurobehavioural	80	Iran	Farmers showed clinical symptoms such as eczema, breathing muscle weakness, nausea and saliva Cognitive function, orientation, registration, attention and calculation, recall and language were not significantly different in farming and control In examinations of psychological distress, only labelled somatisation was significantly higher in farmers This study shows neuropsychological disorders with a complex multivariate phenomenon that is seen in long-term high-dose exposure situations	Small sample size	WOS
High pesticide exposure events and central nervous system function among pesticide applicators in the Agricultural Health Study	SE. Starks [20]	2012	Cross-sectional	Neurobehaviour tests to assess memory, motor speed, sustained attention, verbal learning and visual scanning and processing Information on ever having an HPEE and pesticide poisoning was obtained from previous Agricultural Health Study interviews	Neurobehavioural	693	USA	Adverse associations were observed between ever having an exposure and two of the nine neurobehavioural test On visual scanning and processing (digit symbol) participants who were exposed were 4.2 s slower Visual scanning and motor speed (sequences A) participants who ever had exposure were 2.5 s slower than those without exposure	Participation rate was low More participants reported having HPEE compared to not Ambiguity of temporal association	WOS
Neurobehavioural effects of long-term exposure to pesticides: results from the 4-year follow-up of the PHYTONER study	I. Baldi [21]	2010	Cross-sectional	Neurobehaviour questionnaire Nine neurobehaviour tests were classified according to lifelong pesticide exposure as directly exposed indirectly exposed or non-exposed	Neurobehavioural	614	France	Exposed subjects had the worst decreases in performance The risk of having two-point lower score on the MMSE was 2.15 in exposed subjects	Did not focus on specific pesticides	WOS
Neurobehavioural performance and work experience in Florida farm workers	F. Kamel [22]	2003	Cross-sectional	Collected information on farm work history and evaluated Neurobehavioural performance using a battery of eight tests	Neurobehavioral	288	USA	Ever having done farm work was associated with poor performance on four tests: digit span, tapping, Santa Ana test and postural sway Little effect on symbol digit, latency, vibrotactile, visual contrast sensitivity and grip strength	Use of indirect exposure measures Small number of tests included in neurobehavioural test battery Controls differed from farm workers	WOS
Neurobehavioual effects among workers occupationally exposed to organophosphorous pesticides	TM. Farahat [23]	2003	Cohort	Two groups – those exposed versus those not. Questionnaires, general and neurological examinations, neurobehavioral test battery, personality assessment and serological analysis of serum acetylcholinesterase were completed	Neurobehavioural	102	Egypt	Exposed participants performed significantly lower on six of the neurobehavioural tests (similarities, digit symbol, trailmaking part A and B, Letter cancellation, digit span and Benton visual retention) compared to controls Serum acetylcholinesterase was found to be lower in exposed group but not significantly correlated with neurological abnormalities	Small sample size Controls difference from farm workers	WOS
Neuropsychologic effects of long-term exposure to pesticides: results from the French PHYTONER study	I. Baldi [24]	2001	Cross-sectional	Association between neuropsychological performances and long-term exposure to pesticides in Bordeaux	Neuropsychological	917	France	The risk of scoring a low performance on the tests was constantly higher in exposed subjects	Further investigations needed Cross-sectional study design	WOS
Neuropsychological and psychiatric functioning in sheep farmers exposed to low levels of organophosphate pesticides	SJ. Mackenzie Ross [25]	2010	Cross-sectional	Determine if low-level exposure to organophosphate causes neuropsychological or psychiatric impairment Performance of cognition and mood	Neurobehavioural	127	UK	Exposed subjects performed significantly worse than controls Cognitive deficits identified cannot be attributed to mood disorder, malingering, a history of acute exposure or genetic vulnerability Results suggest a relationship may exist between low-level exposure to organophosphates and impaired neurobehavioural functioning	Lack of control group	WOS
Neuropsychological effects of long-term exposure to organophosphate pesticides	L. Roldan-Tapia [26]	2005	Cross-sectional	Cross-sectional survey of workers in high exposure Neurobehaviour deficits using a wide variety of tasks to test Neuropsychological functioning and emotion status	Neurobehavioural Neuropsychological	Did not specify	Spain	Findings showed an association between long-term exposure and worse performance in neuropsychological functions	Not blinded Indirect exposure measurements Unknown sample size	WOS
Neuropsychological performance among agricultural pesticide applicators	W. Daniell [27]	1992	Prospective longitudinal cohort	Initial evaluation prior to onset of ~ 6 months of spraying Neuropsychological follow-up about 1 month after	Neuropsychological	89	USA	Only significant difference was across seasonal neuropsychological testing in one subset (symbol digit substitution)	Inconsistent findings	WOS
Effects of organophosphate pesticide exposure on Hispanic children's cognitive and behavioural functioning	PS. Lizardi [28]	2008	Cross-sectional	Battery of cognitive measures Wisconsin Card Sorting Test	Neurobehavioural	48	USA	All children had a detectable level of at least one organophosphate pesticide metabolite Higher organophosphate pesticides metabolite concentration levels were significantly correlated with poorer performance on some subtests	Limited number of children Neurobehavioural battery may not be applicable to children Not being able to define a true non-exposed group	WOS

Effects of organophosphate pesticide exposure on Hispanic children's cognitive and behavioural functioning	PS. Lizardi [28]	2008	Cross-sectional	Battery of cognitive measures Wisconsin Card Sorting Test	Neurobehavioural	48	USA	All children had a detectable level of at least one organophosphate pesticide metabolite Higher organophosphate pesticides metabolite concentration levels were significantly correlated with poorer performance on some subtests However the significance of this inclusion of two samples with noticeable higher organophosphate pesticide metabolite concentrations	Limited number of children Neurobehavioural battery may not be applicable to children Not being able to define a true non-exposed group	WOS
Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides	R. Harari [29]	2010	Cross-sectional	Expanded neurobehavioural battery: finger tapping, motor coordination, continuous performance test, short-term auditory memory function, visual performance function and visual memory function	Neurobehavioural	84	Ecuador	Exposure-related deficits were evident in motor speed, motor coordination, motor coordination, visuospatial performance and visual memory Correlated with a developmental delay of 1.5–2 years Slight increase in blood pressure and decrease in body mass index	Did not assess all functions completely Small sample size	Medline Scopus WOS
Increased risk of suicide with exposure to pesticides in an intensive agricultural area. A 12-year retrospective study	T. Parron [30]	1996	Retrospective epidemiological	251 suicides reviewed in three different areas	Neuropsychological Suicide	251	El Poniente, Paraguay	Higher suicide rates in geographic region when compared to other regions of similar socioeconomic status and demographic features Mortality from suicide in this region of farmers does not vary compared to other populations	Retrospective study Moderate study Variables not controlled	Medline WOS
Neuropsychological effects of long-term exposure to organophosphates in sheep dip	R. Stephens [31]	1995	Cross-sectional	Neuropsychological testing Short-term memory – digit span, visual spatial memory Sustained attention – simple reaction time Information processing speed Symbol digit substitution, syntactic reasoning Long-term memory function – category search Questionnaire Exposure – urine metabolites	Neuropsychological	289	UK	Significantly worse performance in farmers group in sustained attention and information processing speed Greater vulnerability for psychiatric disorders	Moderate sample size Self-reporting bias	Medline Scopus WOS
Long-term use of organophosphates and neuropsychological performance	N. Fiedler [32]	1997	Cross-sectional	Questionnaire about exposure Neuropsychological tests Neurobehaviour Evaluation System battery Simple reaction time Continuous performance Stroop-coloured word task Hand–eye coordination Wechsler Adult Intelligence Scale Digit span Visual reproduction Continuous visual memory test Animal-naming test Revised token test	Neuropsychological	99	New Jersey	Significantly slower reaction time for farmers with prolonged exposure	Selection bias Self-reporting bias Moderate sample size Recruiting bias	Medline WOS
Pesticide poisoning and depressive symptoms among farm residents	L. Stallones [33]	2002	Cross-sectional	Questionnaire Centre for Epidemiologic Studies of Depression Scale	Neuropsychological	761	USA	Lower reported depressive symptoms with prolonged exposure to pesticide although not significant	Self-reporting bias Selection bias	Medline
A clinical neurological, neurophysiological, and neuropsychological study of sheep farmers and dippers exposed to organophosphate pesticides	GA. Jamal [34]	2002	Case-controlled study within a cross-sectional	Questionnaire – neuropathy and neurological Quantitative sensory tests Neurophysiological (nerve conduction studies and electromyography) Neuropsychological: psychomotor performance, learning and memory	Neurological	79	UK	No significant correlation between exposure to organophosphate and neuropathy Three times more reported neurological symptoms when exposed to pesticides Increasing severity of neuropathy as based on symptoms and sensory test was associated with anxiety and depression Neuropsychological findings were not correlated to cumulative organophosphate exposure	Small sample size Limited power Reporting bias	Medline WOS
Mental health in Alberta grain farmers using pesticides over many years	N. Cherry [35]	2012	Cross-sectional	Questionnaire of pesticide exposure, physician diagnosed disease and neuropsychological symptoms	Neuropsychological	10 676	Alberta	Mental illness symptoms score related to duration of exposure to phenoxy compounds	Self-reporting bias Recall bias	Medline Scopus WOS
Chronic organophosphate induced neuropsychiatric disorder (COPIND) results of two postal questionnaire surveys	DR. Davies [36]	1999	Cross-sectional	Two postal surveys on neuropsychiatric symptoms in individuals potentially or actually exposed to organophosphate	Neuropsychological	640	UK	One survey shows significant increased symptomology in exposed versus non-exposed farmers while the second shows identical symptomology associated with exposure	Detection method Missed farm workers	WOS
Depression and pesticide exposures among private pesticide applicators enrolled in the Agricultural Health Study	CL. Beseler [37]	2008	Cross-sectional	Self-reported physician diagnosed depression against control	Neuropsychological	17 585	USA	Pesticide poisoning was associated with depression compared to intermediate and cumulative exposure	Classification of exposure events Self-report and collected cross-sectionally Identification of age Limited data on potential confounders were limited	WOS
Depression and pesticide exposures in female spouses of licensed pesticide applicators in the Agricultural Health	C. Beseler [38]	2006	Case control Cross-sectional	Female spouse enrolled in AHS and had physician diagnosed depression requiring medication.	Neuropsychological	29 074	USA	Significantly associated with pesticide poisoning but not low cumulative pesticide exposure	Cross-sectional study design Self-reported information	WOS

applicators enrolled in the Agricultural Health Study								intermediate and cumulative exposure	sectionally Identification of age Limited data on potential confounders were limited	
Depression and pesticide exposures in female spouses of licensed pesticide applicators in the Agricultural Health Study Cohort	C. Beseler [38]	2006	Case control Cross-sectional	Female spouse enrolled in AHS and had physician diagnosed depression requiring medication.	Neuropsychological	29 074	USA	Significantly associated with pesticide poisoning but not low cumulative pesticide exposure	Cross-sectional study design Self-reported information	WOS
Suicide in Australia pesticide-exposed workers	E. MacFarlane [39]	2011	Case-controlled	Retrospective cohort of pesticide-exposed workers Subject specific biomonitoring records	Neuropsychological Suicide	360	Australia	Suicide risk was not significantly associated with exposure to pesticide class	Retrospective Moderate sample size	Medline
Dementia of Alzheimer type (DAT) in a man chronically exposed to pesticides	A. Cannas [40]	1992	Empirical	Case study Retrospective	Neurodegenerative	1	Italy	Pathogenic roles explain in regards to environmental factor in certain neurodegenerative diseases	Retrospective study Case study One-person sample size	Medline
Morbidity among farm workers in a desert country in relation to long-term exposure to pesticides	J. Gomes [41]	1998	Cross-sectional	Questionnaire Aiming test Digit span test Acetylcholinesterase level measured	Neurodegenerative	318	United Arab Emirates	Farm workers with prolonged exposure score significantly lower in the aiming and digit symbol test	Limited battery test use Self-reporting bias	Medline
Pesticide exposure and screen-positive neuropsychiatric disease in British sheep farmers	AC. Povey [42]	2014	Cohort	Questionnaire	Neuropsychological Depression Dementia Parkinson's disease	1380	UK	Exposure was associated with screen positive neuropathy and Parkinsonism Not associated with depression or dementia	Self-reporting bias	Medline Scopus WOS
Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children	MF. Bouchard [43]	2011	Cohort	Exposure to pesticide – urine metabolites Wechsler Intelligence Scale for Children	Neurodevelopmental	329	California	Average maternal DAP was associated with poorer scores for working memory processing speed, verbal comprehension, perceptual reasoning and full scale intelligence Children in the highest concentration of maternal DAP metabolites with an average deficit of 7 IQ points Children with DAP metabolites did not have associated cognitive deficits	Epidemiological study can be affected by uncontrollable cofounders	Medline WOS
Acetylcholinesterase enzyme activity and neurodevelopment in boys and girls	JR. Suarez-Lopez [44]	2013	Cohort	Neurodevelopment (NEPSY-II) and acetylcholinesterase activity	Neurobehavioural	307	Ecuador	Lower acetylcholinesterase activity was associated with overall lower neurobehavioural development primarily affecting attention, inhibitory control and memory (and perhaps language) among boys	Constrained power Lack of concurrent and prenatal environmental biomarkers of exposure	Medline Scopus WOS
Urinary TCPY in pregnant women from Mexico City: distribution, temporal variability, and relationship with child attention and hyperactivity	GZ. Fortenberry [45]	2014	Cohort	Maternal urinary TCPY Neurodevelopment testing: Conners Parental Rating Scales revised, Conners Continuous Performance Test, Behaviour Assessment System for Children	Neurodevelopmental	187	Mexico	No significant correlation between maternal TCPY levels and attention deficit hyperactivity disorder in children	Small sample size Single urinary measure	Medline
Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators	RG. Ames [46]	1995	Cross-sectional	Cholinesterase activity recorded Exposure related to job exposure and medical records Neurobehavioural test Nerve conduction tests Vibrotactile sensitivity Test of postural sway	Neurological	135	California	One of 27 studies (serial digit performance) was significant	Self-reporting bias Small sample	Medline WOS
Abnormalities on neurological examination among sheep farmers exposed to organophosphorus pesticides	JR. Beach [47]	1996	Cross-sectional	Symptom questionnaire Neurological examination	Neurological	30	UK	Significant difference in two-point discrimination on dorsum of hand and dorsum of foot Significant difference in circumference of calves	Small sample size Reporting bias	Medline WOS
Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers	L. London [48]	1998	Cross-sectional	Vibration test Neurological questionnaire Exposure determined with job-exposure matrix	Neurological	247	South Africa	Sprayers reported significantly more dizziness, sleepiness and headaches plus a higher more overall neurological symptom score Vibration sense was not affected by organophosphate exposure	Misclassification bias Self-reporting bias Moderate sample size	Medline WOS
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	A. Pilkington [49]	2001	Cross-sectional	Exposure reported in questionnaire Standard neuropathy questionnaire Thermal and vibration quantitative sensory tests	Neurological	772	UK	Weak positive association between cumulative exposure to organophosphate and neurological symptoms No association between cumulative exposure and vibration and thermal sensory thresholds	Self-reporting bias for all facets of study Moderate sample size	Medline Scopus WOS
Neurologic symptoms in licensed pesticide applicators in the Agricultural Health Study	F. Kamel [50]	2005	Cross-sectional	Questionnaire including general health, demographic, lifestyle, medical history, neurological symptoms and pesticide use	Neurological	18 782	Iowa and North Carolina, USA	Increased risk of experiencing 10 or more symptoms in previous years was associated with cumulative lifetime use of insecticides with a strong association to organophosphates	Cross-sectional Self-reporting bias Recall bias	Medline Scopus WOS
A study of neurologic symptoms on exposure to organophosphate pesticides in the children of agricultural workers	SK. Rastogi [51]	2010	Cross-sectional	Neurological symptoms Exposure questionnaire	Neurological	225	India	Increased neurological symptoms reported in children with chronic exposure Most self-reported symptoms were headaches, watering eyes and burning sensation in eyes/face	Self-reporting bias Moderate sample size	Medline Scopus WOS
Peripheral nervous system function and organophosphate pesticide use among licensed pesticide applicators in the	SE. Starks [52]	2012	Cohort	Neurological physical exam Electrophysiological tests Self-reported use of pesticide Questionnaire	Neurological	678	Iowa and North Carolina, USA	Significantly increased odds ratios were demonstrated for 10 of 16 organophosphate pesticides with one or more of six	Self-reporting bias Estimated lifetime cumulative exposure to pesticide	Medline Scopus WOS

organophosphate pesticides in the children of agricultural workers								chronic exposure Most self-reported symptoms were headaches, watering eyes and burning sensation in eyes/face		
Peripheral nervous system function and organophosphate pesticide use among licensed pesticide applicators in the Agricultural Health Study	SE. Starks [52]	2012	Cohort	Neurological physical exam Electrophysiological tests Self-reported use of pesticide Questionnaire	Neurological	678	Iowa and North Carolina, USA	Significantly increased odds ratios were demonstrated for 10 of 16 organophosphate pesticides with one or more of six neurological exam finding Six organophosphates associated with toe proprioception Four organophosphates associated with postural tremor	Self-reporting bias Estimated lifetime cumulative exposure to pesticide	Medline Scopus WOS
An uncommon pattern of polyneuropathy induced by lifetime exposures to drift containing organophosphate pesticides	A. Ophir [53]	2014	Cohort	Questionnaires about self-reported exposure Neurological examinations Electrophysiological studies	Neurological	60	Israel	Organophosphate exposure was significantly correlated to prolonged distal latency in right median nerve and lower wave amplitude in right sural nerve	Small sample Self-reported exposure	Medline
Delayed polyneuropathy in farm sprayers due to chronic low-dose pesticide exposure	R. Boostani [54]	2014	Cross-sectional	Systemic and neurological examination Nerve conduction studies Assumed exposure amount in farming population	Neurological	200	Iran	Ophthalmologic complaints 44% Significant difference in mean peroneal compound muscle action potential amplitude and nerve conduction velocity, sural peak latency, radial sensory nerve action potential amplitude, peak latency and nerve conduction velocity	Assumed exposure to pesticide Moderate sample size	Medline
Effect of chronic pesticide exposure in farm workers of a Mexico community	R. Payañ-Rentería [55]	2012	Transverse comparative	Blood tests with blood count and chemistry, lipid profile, liver and kidney function erythrocyte cholinesterase, lipid peroxide profile and free DNA fragments	Neurological	46	USA	Pesticide exposure and diverse alteration of digestive, neurological, respiratory, circulatory, dermatological, renal and reproduction	Not longitudinal study Small study group	WOS
Effects of occupational exposure to organophosphate pesticides on nerve and neuromuscular function	RJ. Peiris-John [56]	2002	Cross-sectional	Comparison between two groups in relation to neurological symptoms and acetylcholinesterase level	Neurological	60	Sri Lanka	Decreased sensory conduction velocity and motor conduction velocity between cultivation seasons Sensory conduction was reduced significantly in farmers and in controls during cultivation seasons Sensory effect on acute exposure and sensory and motor impairment was seen after long-term low-level exposure	Small sample size Cross-sectional study design	WOS
Evaluation of potential adverse health effects resulting from chronic domestic exposure to the organophosphate insecticide methyl parathion	RD. Cox [57]	2005	Cross-sectional	Health screening evaluations	Neurological	353	USA	No significant difference between symptoms reported or by the physician assessment of subacute or chronic toxicity between those in the exposure group and controls No significant difference found in growth and developmental evaluations	Recall bias	WOS
Long- and short-term health effects of pesticide exposure: a cohort study from China	R. Hu [58]	2015	Cohort	Two rounds of health investigations including blood tests and neurological examinations conducted by doctors before crop season	Neurological	246	China	Long-term exposure found to be associated with increased abnormality of nerve conductions especially sensory nerves Decreased the tibial nerve compound muscle action potential amplitudes Short-term health effects included alterations in complete blood count, hepatic and renal functions and nerve conduction velocities and amplitudes These effects could not be detected after 3 days following pesticides exposure	Recall bias Not a longitudinal study	WOS

BARS, Behavioral Assessment and Research System. DAP, dialkyl phosphate. HPEE, high pesticide exposure event. MMSE, mini mental state examination. TCPY, 3, 5, 6-trichloro-2-pyridinol. WOS, Web of Science.

Table 2: Literature review of respiratory studies[59-67]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India	S. Chakraborty [59]	2009	Cross-sectional	Questionnaire on respiratory symptoms and lung function tests and acetylcholinesterase level was measured	376	India	Agricultural workers had greater prevalence of upper and lower respiratory symptoms and appreciable reduction in spirometric result Overall lung function was reduced by 48.9%	Dermal absorption not considered as no personal protective equipment used	Medline Scopus WOS
Decreased lung function in 7-year-old children with early-life organophosphate exposure	R. Raanan [60]	2015	Cross-sectional	CHAMACOS longitudinal birth cohort Organophosphate exposure measure by urine metabolite (DAP) spirometry at 7 years	279	USA	Urine DAP was significantly associated with decrease in lung function at age 7 years	Loss to follow-up and challenges in exposure assessment Selection bias No long-term biomarkers	Medline WOS
Association of chronic pesticide exposure with serum cholinesterase levels and pulmonary functions	Z. Sutoluk [61]	2011	Cross-sectional	Serum cholinesterase levels and the pulmonary functions test	50	Turkey	No difference between farmers with low cholinesterase level and lung function test	Small sample size Cross-sectional study design	Medline Scopus
Pesticide exposure and respiratory health of indigenous women in Costa Rica	KB. Fieten [62]	2009	Cross-sectional	Questionnaire to estimate exposure and presence of respiratory symptoms Lung function tests	137	Costa Rica	Exposed demonstrated wheeze 20% and short of breath 36% Organophosphates strongly associated with wheeze No relation between pesticide exposure and ventilatory lung function was found	Small sample size	Medline WOS
Pesticides and adult respiratory outcomes in the Agricultural Health Study	JA. Hoppin [63]	2006	Cross-sectional	Looking at respiratory outcomes including wheeze, adult asthma, farmer's lung and chronic bronchitis	~89 000	USA	Strong association between organophosphates and wheeze	Limited to those who returned the questionnaire	Medline WOS
Chlorpyrifos exposure and respiratory health among adolescent agricultural workers	CL. Callahan [64]	2014	Cross-sectional	10-month study on male adolescent Urinary metabolites were measured Lung function tests	62	Egypt	Inconsistent results with spirometry	No baseline assessment Small sample size No controls	Scopus
Biomarkers of insecticide exposure and asthma in children: a National Health and Nutrition Examination Survey (NHANES) 1999–2008 analysis	ME. Perla [65]	2014	Cross-sectional	Used National Health and Nutrition Examination Survey to evaluate DAP and asthma in school children	2777	USA	No association found between DAP and asthma	Cross-sectional nature of the data self-reported residual cofounders	WOS
Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects	AF. Hernández [66]	2008	Cross-sectional	Questionnaire about exposure and symptoms Lung function tests	114	Spain	Short: reduced forced expiratory volume Long: forced expiratory flow Suggestive of restrictive lung disease	Use of biomarkers	WOS
Urinary dialkyl phosphate concentrations and lung function parameters in adolescents and adults: results from the Canadian Health Measures Survey	M. Ye [67]	2016	Cross-sectional	Lung function tests and urinary DAP was measured, smoking status and other predictors of lung functions	4446	Canada	Reduced forced vital capacity, forced expiratory volume and forced expiratory volume/forced vital capacity with every unit of DAP metabolite found in the urine No associations found in adolescents	Not the entire Canadian population was included Those with respiratory conditions already were excluded Urine metabolites lack specificity Cross-sectional study	WOS

DAP, dialkyl phosphate. WOS, Web of Science.

Table 3: Literature review of cancer studies[68-70]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Associations of pesticides, HCV, HBV, and hepatocellular carcinoma in Egypt	S. Ezzat [68]	2005	Case control	Questionnaire Blood and hepatitis virus testing	236	Egypt	Exposures to organophosphates and carbamate are additive risk factors to current HCV and HBV infection among rural males	Limited power	Medline WOS
Exploring cancer development in adulthood: cholinesterase depression and genotoxic effect from chronic exposure to organophosphate pesticides among rural farm children	V. How [69]	2014	Cross-sectional	Identify possible associations between the depression in blood cholinesterase level and genotoxic effect among farm children	95	Malaysia	Reduced blood cholinesterase level from organophosphate pesticide exposure is significantly associated with an increase in chromosome breakage and DNA strand breaks Genotoxicity end points suggest that farm children cells experience early DNA damage that may lead to uncontrolled cell proliferations during their adulthood	Small sample size Biomarker limited conclusion	Medline WOS
Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study	P. Cocco [70]	2013	Cross-sectional	Detailed occupational history collected in cases and controls Job modules applied for farm work	2696	Europe	Risk of lymphoma overall and B cell lymphoma not elevated Risk of chronic lymphoid leukaemia was elevated amongst those ever exposed to inorganics and organic pesticides	Caution in interpreting results of this study Self-reported bias	Medline WOS

WOS, Web of Science.

Table 4: Endocrine study in the literature review[71]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993–2003	MP. Montgomery [71]	2008	Cohort	Agricultural Health Study comparing diabetic in the study against non and lifetime exposure to pesticides	33 457	USA	Seven pesticides demonstrated increased odds of diabetes when either ever used or cumulative use of pesticides	Self-reported diagnosis Inability to control for exercise and diet	Medline Scopus WOS

WOS, Web of Science.

Table 5: Cardiac study in the literature review[72]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Pesticides and myocardial infarction incidence and mortality among male pesticide applicators in the Agricultural Health Study	KT. Mills [72]	2009	Cohort	Agricultural Health Study self-reported lifetime use of pesticides, 1993–1997 MI mortality through 2006 Self-reported nonfatal MI through 2003	32 024	USA	Little evidence of an association between having used pesticides individually or by class and myocardial infarction mortality No dose response either	Inability to detect acute sequelae of pesticide exposure and healthy worker effect	Medline WOS

WOS, Web of Science.

Table 6: Chronic fatigue study in the literature review[73]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Chronic fatigue and organophosphate pesticides in sheep farming: a retrospective study amongst people reporting to a UK pharmacovigilance scheme	N. Tahmaz [73]	2003	Retrospective case control cohort	Two questionnaires	178	UK	High prevalence of chronic fatigue amongst those who completed the questionnaire Higher scores were associated with higher exposures Conclusion: offers limited evidence	Reporting bias Moderate sample size	Medline WOS

WOS, Web of Science.

Table 7: Literature review of fertility studies[74,75]

Title	First author [text reference]	Year	Study design	Method	No. of subjects	Location	Findings	Limitations	Database(s)
Occupational exposure to organophosphate and carbamate pesticides affect sperm chromatin integrity and reproductive hormone levels among Venezuelan farm workers	L. Miranda-Contreras [74]	2013	Cross-sectional	Recruited for clinical evaluation of fertility status Fresh semen samples evaluated for sperm quality and analysed for DNA fragmentation Pesticide exposure assessed using blood acetylcholinesterase and butylcholinesterase levels Serum levels of testosterone, FSH and LH and TSH analysed	99	Venezuela	Significant decreases in some semen parameters DNA fragmentation index negatively correlated with butylcholinesterase, sperm concentration, morphology and vitality Thyroid and prolactin normal; however, there was a tendency for increased LH and FSH	Small sample size Cross-sectional design	Medline WOS
Changes in male hormone profile after occupational organophosphate exposure. A longitudinal study	C. Aguilar-Garduno [75]	2013	Cross-sectional	Effect of organophosphates measured by urine metabolites during two agricultural periods with different degrees of pesticides	136	Mexico	Exposure associated with increased serum FSH and prolactin and with decreased serum testosterone and inhibition LH inversely associated with urine metabolite Oestrodiol was only significant positive trend	Urine metabolites do not provide specific information regarding the particular pesticides to which worker were exposed Only one urine sample collected and analysed	Medline Scopus WOS

FSH, follicle-stimulating hormone. LH, luteinising hormone. TSH, thyroid-stimulating hormone. WOS, Web of Science.

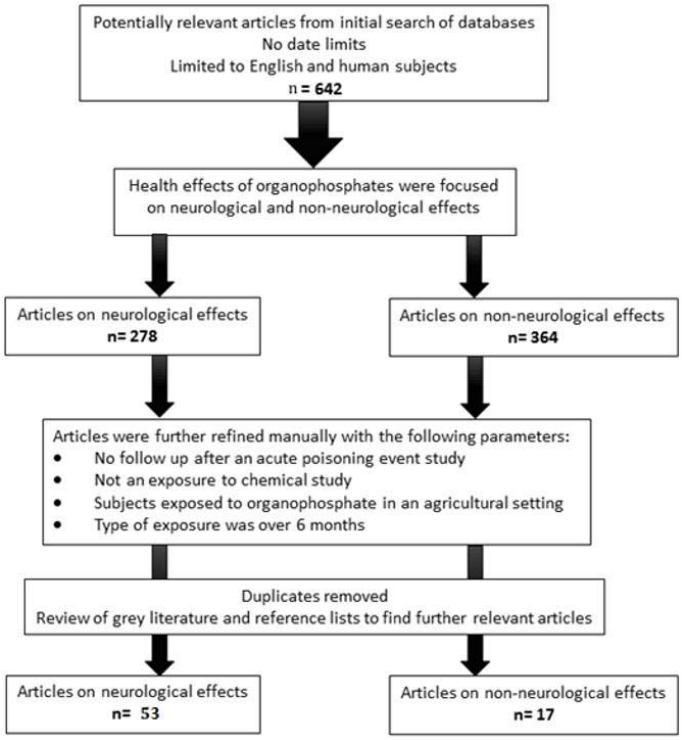

Figure 1: Flow diagram of the selection process of the articles for the narrative literature review.

Results

Neurological changes were the most studied chronic health effects of prolonged exposure to organophosphates. The research was focused on neurobehavioural, neurodegenerative, neurodevelopment and neurological signs and symptoms. The majority of these studies were conducted in the USA and UK, with contributions from South Africa, Mexico, Spain, Thailand, Taiwan and Ecuador.

Neurobehavioural effects

The associations between chronic organophosphate use and neurobehavioural symptoms have been researched in 31 studies[9-29]. Eight of these articles reported a deficit on neurobehavioural batteries (a group of tests performed together for assessment purposes) when there was previous exposure to pesticides [9,10,12-15,17,18,20,21,24-29]. Deficits were found in short-term memory components, with partcipants scoring significntly lower on the Digit Span (forward and reverse recall of digit sequences) and Match-to-Sample tests (matching to previously demonstrated stimuli)[9,10,12-15,17,18,20-22,24-29]. Attention span was also found to be affected in two studies[9,18].

Three studies did not find a significant effect on neurobehaviour with prolonged organophosphate exposure. One study from South Africa showed a slight effect but was explained to most likely be the result of misclassification of exposure[11]. Another study from Iran found no neurobehavioural deficits[19]. The third study, with children from agricultural backgrounds in Thailand, showed no neurobehavioural deficits. However, a negative effect on work performance, although not significant, was demonstrated at times[16].

Ten articles analysed the vulnerability to psychological conditions with chronic exposure to organophosphates, particularly referring to the general health questionnaire[19,25,30,32-38]. Two of the 10 studies noted an association with organophosphate exposure in farmers [25,36]. The remainder did not find a significant relationship[19,30,32-35,37,38]. One study demonstrated a lower percentage of depressive symptoms amongst farm residents (20.6%) in Colorado, USA, compared to the general population (34%)[33]. This was more likely to be related to the healthy worker effect, as the farm population might be healthier due to their nature of work compared to the general population in that study[33]. The relationship of organophosphate pesticide chronic exposure with suicide was also examined[30]. This study reported no significant association between organophosphate exposure and suicide[30].

Vulnerability to specific psychological conditions as a result of chronic exposure is not supported. Further, a 1996 Spanish study on agricultural workers reported that suicides in the farming populations were not caused by chronic exposure to organophosphate, rather it was the result of accessibility to this substance and decreased knowledge of the lethality[30]. This result is consistent within the Australian population, with MacFarlane et al demonstrating in their study a non-significant relationship between exposure and suicide[39]. Nine out of 10 articles reviewed were cross-sectional designs, thus stronger studies need to be conducted to support this theory.

Overall, short-term memory and attention were noted to have a significant difference for those who were chronically exposed to

organophosphate. The levels of evidence according to the National Health and Medical Research Council (NHMRC) of the 21 articles reviewed in terms of short-term memory and attention were NHMRC III-2 and IV[76]. This was because they had a cohort or cross-sectional structure (Table 1). The number of subjects ranged from 48 to 917, which reduces the power of some of the individual studies. Compared to the other sections in this review, the section on neurobehavioural effects of organophosphates has the strongest evidentiary support. However, bias does come into effect as these do not account for educational and cultural backgrounds.

Neurodegenerative diseases

In relation to neurodegenerative diseases, three articles were identified[40-42]. The two disorders described were Alzheimer's disease and Parkinson's disease. Two of the articles related to Alzheimer's disease and both of them showed a positive association between chronic exposure to organophosphates and Alzheimer's disease[40,41]. Zaganas et al described a possible theory for the causal relationship: that excess synaptic acetylcholine leads to chronic excitation of the post-synaptic neurons, which causes excitotoxic damage and degeneration of the cholinergic system[77].

Chronic exposure of organophosphate has been linked to Parkinson's disease. One study investigated the relationship between Parkinson's disease and chronic exposure and found a positive relationship that was not significant (odds ratio (OR) 1.56, 95% confidence interval (CI) 0.95–2.58)[42]. The same article concluded that being acutely poisoned was a more significant indicator for likely development of Parkinson's disease[42].

Short-term memory problems have previously been shown to be associated with chronic exposure to organophosphates[77]. This may explain the increased incidence of Alzheimer's disease in the population, as this disease initially affects short-term memory. The level of evidence of the two articles reviewed was NHMRC IV, which does not provide strength to the theory.

Overall, compared to the Alzheimer's disease articles, the Parkinson's disease article had a clearer design structure and higher number of subjects, making it a powerful study.

Neurodevelopmental diseases

Neurodevelopmental effects from chronic exposure to organophosphate were found in three of four articles[29,43-45]. Three articles described an effect on neurodevelopment when exposed to organophosphates in the prenatal period[29,43]. The effects were on both neurobehaviour and IQ, with one study showing a seven-point decrease in IQ at the age of 7 years when there was a prenatal chronic organophosphate exposure[43]. Another study looked at effects of exposure in the post-natal stage and found neurodevelopment of boys in the group was significantly reduced, by two standard deviations[44]. An article by Fortenberry et al described a relationship between prenatal exposure to organophosphates and the development of attention deficit hyperactivity disorder. The authors found no association but concluded that more research was needed in that area because the study had limited power[45].

Overall, chronically inhibiting the acetylcholinesterase during the prenatal period has been shown to affect nervous system development. The strength of this conclusion was mostly supported by cohort designs, with three of the four studies being of NHMRC level III-2 (Table 1).

Neurological effects

Fourteen articles described neurological symptoms related to chronic exposure of organophosphate pesticides[36,46-58]. Seven studies looked into neurological findings from physical examinations[47-49,52,54,55,57]. A study with a focus on sheep farmers exposed to organophosphates in the UK reported a significant difference (p=0.011) between the most symptomatic farmers, least symptomatic (asymptomatic) farmers and quarry workers (non-farmers) with two-point discrimination (the distance required to determine that two points are separate when pressed on the skin) highest in the symptomatic farmers[47]. Another UK study found the intensity of the concentrate of organophosphate as the significant factor (p=0.005) involved in the development of neurological symptoms, which was independent of the duration of exposure[49]. A study in the USA found toe proprioception (detection of toe movement with eyes closed) to be significantly different between controls and farmers exposed to organophosphate[52]. A South African study found no association between organophosphate pesticide use and neurological deficit in relation to vibration sense or tremor[48].

Some articles reported results of nerve conduction studies performed to assess chronic effects of exposure. Five studies examined this in different areas of the body[46,53,54,56,58]. Four of these studies showed significant differences in nerve conduction results between farmers and controls[53,54,56,58]. These studies demonstrated the difference in distal latencies and wave amplitude of peripheral nerves[53,54].

Neurological symptoms were detailed in four studies[43,48,50,51]. Each of these studies reported that people applying organophosphates were more likely to report neurological symptoms in comparison to controls. These symptoms included dizziness, sleepiness, watering eyes, altered sensation and headache[43,48,50,51]. In one study, organophosphate-induced neurotoxicity was detailed, with described symptoms including insomnia, headache, anorexia and numbness[51].

In the abovementioned studies, chronic organophosphate exposure had some effect on the peripheral nervous system but the symptoms, signs and nerve conduction studies revealed inconsistent results. The level of evidence presented for the 14 articles reviewed were weak in their design as they were mostly cross-sectional studies (Table 1). Further investigations need to be conducted to understand a consistent pattern to chronic health effects of organophosphate pesticides.

Non-neurological effects

Studies involving farmers focusing on the non-neurological health

effects of exposure to organophosphates reported on respiratory symptoms, cancer risk, endocrine disruption, cardiac issues, chronic fatigue and infertility.

Respiratory conditions were detailed in nine articles[59-67]. Six of these articles reported significant associations between respiratory conditions and organophosphate exposure[59,60,62,63,66,67]. Findings included symptoms such as wheeze and a decrease in lung function[59,60,62,63,66,67]. The three remaining articles reported inconsistency, indicating no correlation between prolonged exposure and asthma prevalence or spirometry changes[61,64,65].

Three articles in the databases evaluated cancer risk associated with chronic organophosphate use[68-70]. All of them found positive associations. How et al reported that reduced blood cholinesterase levels from exposure to organophosphate pesticides was significantly associated ($p<0.05$) with an increase in chromosome breakage[69]. This has been linked to increased susceptibility of a person to develop cancer[69]. Another article reported an increased risk of chronic lymphoid leukaemia (OR 2.7, 95%CI 1.2–6.0)[70].

One article reviewed the effects on the endocrine system in relation to diabetes prevalence. It reported a positive association between chronic exposure to organophosphate pesticides and prevalence of diabetes (OR 1.24, 95%CI 1.02–1.52)[72].

One article looked into the incidence of myocardial infarction with exposure of organophosphate pesticides[72]. There was no significant evidence to show a relationship and no dose–response effect of organophosphates in relation to morbidity and fatality of myocardial infarct amongst farmers[72].

There was only one article relating to chronic fatigue met the criteria outlined in the methods[73]. This article showed a high prevalence of chronic fatigue and organophosphate exposure amongst those who were exposed to organophosphates, but that finding was not strong due to the nature of the research conducted[73].

Lastly, fertility was investigated in this review. Two studies showed a significant effect on this system[74,75]. One article demonstrated a significant decrease in the semen parameters, with decreased sperm concentration ($p=0.002$) and vitality ($p<0.0001$)[75]. Both articles highlighted an increase in follicle-stimulating hormones and luteinising hormones[74,75]. Neither study investigated effects on female fertility.

Discussion

The non-neurological health concerns of long-term organophosphate exposure were limited and involved predominantly NHMRC level IV except for the cardiac and endocrine articles, which were cohort studies. Possible areas of concern are respiratory, cancer, endocrine, chronic fatigue and fertility, but further investigations need to be conducted to determine if there is a significant effect due to chronic organophosphate exposure.

Methodological critique of articles reviewed

Summaries of each article, including their limitations, are shown in Tables 1–7. Of the 70 articles reviewed, 73% of articles were designed as cross-sectional studies. This is a weak research design being a level IV NHMRC level of evidence. One study by Fortenberry et al was a progressive study that tracked the progression of results[45]. This is a stronger research design as it excludes the influence of associating a casual relation from retrospective studies.

For the cross-sectional studies reviewed, the majority of the articles included less than 500 subjects, which means a study has minimal power. Six studies included more than 10 000 subjects, which enabled a good representation of study participants, including both farming populations and their controls, and increased the validity of the results[44,45,50,63,71,72].

There were two documented methods, in the articles reviewed, to define organophosphate exposure: self-reporting and by geographical location/occupation. However, these methods allowed for reporting bias. Some articles also used questionnaires to report symptoms, increasing the bias of these studies[47-54,59].

Furthermore, studies did not consistently represent one country, causing inconsistencies with environment and regulations of pesticides. Most represented among the studies were the UK and USA, providing a consistent environment across these studies[9,10,12-15,20,22,25,27,33,34,39-47,49,50,52,55,57,60,63,65,71-73]. However, more research is required for other countries including Australia especially as they have a large farming population.

Overall, the conclusions drawn from this literature review were not well supported – the majority of the studies had weak designs, limited power and confounders.

Applicability to Australia

Organophosphates are widely used in Australian agricultural settings and production methods[1]. Some changes to use and restrictions have occurred over the last decade through the regulatory agency the Australian Pesticide and Veterinary Medicines Authority. For example, a regulatory decision in December 2016 means a ban on the use of omethoate products in the garden at home, on food-producing plants, horticultural crops, pastures, grain legumes or cereals[78].

Whilst no research from Australia fitted the present review's selection criteria, there are still lessons to be taken from this research:

- Organophosphates may result in acute poisoning but have an accumulated exposure effect on human health.
- Chronic exposure to organophosphates appears to particularly affect the neurological system in particular cases.
- Handling organophosphates requires education and appropriate protective equipment to both prevent acute poisoning and reduce the risks associated with chronic accumulated exposure effects.

Limitations

The aforementioned findings are restricted by limitations of a standardised method of testing of organophosphate exposure and the methods of data collection. Only the agricultural population was investigated for this review. Therefore, other areas of population exposure to organophosphate such as fly spray, human head lice treatment, public health, vector control programs and other insect sprays were not included.

Conclusion

This literature review appraised relevant articles concerning the chronic health effects of organophosphate exposure between 1991 and 2016. Internationally, studies have suggested that chronic use of organophosphate affects neurobehaviour, neurodegeneration, neurodevelopment and the peripheral nervous system. Unfortunately, the methodological design of majority of the studies in this review were poor, therefore providing limited support for the results that were reported. Further research should be focused on early identification of an individual's risk of organophosphate exposure and early detection of symptoms.

Global agricultural production continues to use organophosphate pesticides due to both increasing resistance of pests and the increased production pressures to feed and clothe growing populations. The use of organophosphates in Australia continues due to their efficiency as an insecticide in broadacre cropping, horticulture and livestock operations. Whilst restrictions for use have increased for this chemical group, organophosphates are unlikely to be discontinued in the short term. Understanding the consequences of prolonged exposure and establishing safety measures to prevent harm is critical to balance the demands of agricultural productivity with human health.

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