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. Pesticide use remains high due to the risks associated with potential loss of production to the cropping industry if farmers did not use insecticides.

Organophosphates are one of the most common and effective insecticides in the agricultural industry. 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.

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. 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.

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. 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.

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

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 deduplication 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.
| Title                                                                 | First authors                          | Year | Study design   | Method                                                                 | Health area                              | No. of subjects | Location  | Findings                                                                 | Limitations                                                                 | Information             |
|----------------------------------------------------------------------|----------------------------------------|------|----------------|------------------------------------------------------------------------|------------------------------------------|----------------|-----------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------|
| Chronic central nervous system toxicity: organophosphate pesticide intake | L. Rossetto (6)                        | 1991 | Retrospective cross-sectional | Neuropsychological testing including reaction time, motor vigilance, attention, visuospatial, and verbal memory tests. | Neurobehavioural                        | 61             | Nigeria | Paired group had lower performance than the controls in all tests.        | Ability to identify contributions of pesticide exposure and confounders other than those tested. | Medline WOS              |
| Organophosphate side-effects: chronic and acute exposure effects     | R. Stephens (12)                      | 1996 | Cross-sectional | Neuropsychological battery testing: Subjective memory questionnaire. Simple reaction time, multiple reaction time, attention, vigilance, and abstract reasoning tests. | Neurobehavioural                        | 148            | UK       | Definition of chronic effects of organophosphate exposure is independent of acute effects. No significant change in performance of organophosphate exposed group. | Absence of immediate negative feedback during exposure is likely to influence measures. | Medline WOS              |
| An Investigation into neurological and neuropsychological effects of long-term agricultural use of dichloro-dichloro-fluoromethane: tall farm workers in the Western Cape, South Africa | L. London (13)                        | 1997 | Cross-sectional | Job exposure matrix; Wechsler intelligence battery tests. | Neurobehavioural                        | 247            | South Africa | No significant neurological or neuropsychological change was found.       | No significant negative feedback was obtained. | Medline WOS              |
| Neurobehavioural function of agricultural workers: exposure to organophosphate pesticide in orchard sprayers in England | R. Stephens (13)                      | 2010 | Cross-sectional | Interview, memory tests, Wechsler intelligence battery tests. | Neurobehavioural                        | 94             | UK       | Stressed neurological function was evident with long-term exposure of organophosphates. | Risk factors and self-reported state showed results. Limited number of subjects, decreasing study power. | Medline WOS              |
| Neurobehavioural performance of farm children: long-term exposure to organophosphate pesticides | D. B. Behnke (14)                     | 2005 | Cross-sectional | Neurobehavioural battery test, Wechsler intelligence battery tests, and memory tests. | Neurobehavioural                        | 78             | USA      | Decrease response latency and memory in agricultural children.           | Selection bias: 11 children. Selection bias: Small sample size.             | Medline WOS              |
| Organophosphate pesticide exposure and neurobehavioural function in farm children: acute and long-term exposure | J. R. Reith (15)                      | 2006 | Cross-sectional | Bavaria neuropsychological test including logic, visual, and auditory attention, verbal and nonverbal memory, reaction time, and memory tests. | Neurobehavioural                        | 151            | USA      | Correlation between occupant's performance and long-term and acute exposure. | No correlation between occupant's performance and acute exposure. | Medline WOS              |
| Neurobehavioural performance of adults and associated farm workers | D. B. Behnke (15)                     | 2007 | Cross-sectional | Bavaria neuropsychological test including logic, visual, and auditory attention, verbal and nonverbal memory, reaction time, and memory tests. | Neurobehavioural                        | 175            | USA      | Significant effect was found with matched sample performance and long-term and acute exposure. | No significant effect was found with matched sample performance and long-term and acute exposure. | Medline WOS              |
| Neurobehavioural effects of exposure to organophosphate pesticides: occupational and community exposure | N. Haidir (16)                        | 2015 | Cross-sectional | Bavaria neuropsychological test including logic, visual, and auditory attention, verbal and nonverbal memory, reaction time, and memory tests. | Neurobehavioural                        | 54             | Thailand | No significant difference between control and exposed group. | Significant difference between control and exposed group. | Medline WOS              |
| Cognitive disorders and occupational exposure to organophosphates results from the PHOTONER study | A. Blanco, Laperre (17)                | 2013 | Cohort | COVAX follow-up: Neuropsychological including Mini Mental, Benton Visual Retention Test, Symbol Digit Association and Trails Testing. | Neurobehavioural                        | 814            | France | Exposure was associated with lower cognitive performance. No dose-effect relationship found. | Exposure was associated with lower cognitive performance. No dose-effect relationship found. | Medline WOS              |
| Dementia-related potential changes in chronic occupational exposure to organophosphates pesticides | T. Hachisuka (18)                     | 2009 | Cross-sectional | Event-related potential study. | Neurobehavioural                        | 73             | Sri Lanka | May delay the neurosensory process underlying early stages of neurodegenerative diseases with environmental factors, including cognitive impairment and the risk of dementia. | Technical limitations: only 2 scalp-localization recording. Electrophysiography not recorded; His method of patient selection. | WOS                      |
| Neurobehavioural changes in the brain of farm workers | W. S. Kapp (19)                       | 2012 | Cross-sectional | Electroencephalogram, sleep studies, psychiatric, blood, and DNA analyses. | Neurobehavioural                        | 90             | Iran    | Significant neurophysiological and cognitive changes in farm workers. | Small sample size | WOS                      |
| Title                                                                 | Authors | Year | Methodology | Findings                                                                 | Implications                                                                 | Notes |
|----------------------------------------------------------------------|---------|------|-------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------|
| Electric shock effects on cognitive, neurological disorders, clinical symptoms, and oxidative stress in agricultural health education farmers exposed to organophosphate pesticides | M. Sayet [9] | 2012 | Cross-sectional | Lipp, perceptual, supersensitivity & psychomotor functions, memory, attention, focusing, auditory ability, tremor, stiffness, muscle weakness, and blood test of each subject | Neuropsychological 88 | Ran | Small sample size WOS |
| High-pesticide exposure events and certain nervous system function resilience among pesticide applicators in the Agricultural Health Study | W. Field [10] | 2013 | Cross-sectional | Neuropsychological tests to assess memory, motor speed, sustained attention, verbal learning, and visual scanning and processing information, (in over-exposed and non-exposed pesticide applicators) | Neuropsychological 63 | USA | Participation rate was low. More participants required having HYPE, compared to not Antonym of ambition association. |
| Neuropsychological effects on organophosphate pesticides: results from a 5-year follow-up of the MONSTER study | L. Bule [11] | 2010 | Cross-sectional | Neuropsychological quantitative analysis of cognitive, language, and motor skills, scores classified according to pesticide exposure levels, and the severity of exposure was measured using a battery of eight tests | Neuropsychological 61 | France | Exposed subjects had the oral effects on specific performance. The role of the pesticide was not significant, in this study. |
| Neuropsychological performance and work experience in farm workers | F. Kami [12] | 2003 | Cross-sectional | Collected information on farm work experience and evaluated neurobehavioral test performance using a battery of eight tests | Neuropsychological 28 | USA | Exposed farmers were associated with poor performance in visually guided tasks, spatial error, and visual processing (in this study). |
| Neuropsychological effects among workers occupationally exposed to organophosphate pesticides | T. Fondo [13] | 2002 | Cohort | Two groups those exposed versus those that were not, Questionnaires, general and neuropsychological test batteries, personality assessment and sociopsychological analysis of neuropsychological test results were completed | Neuropsychological 192 | Egypt | Exposed participants performed significantly worse on all of the neurobehavioral tests (similarities, digit symbol substitution, and oddball) compared to controls. Serum acetylcholinesterase was significantly reduced in the exposed group but not significantly correlated with neurological abnormalities. |
| Neuropsychological effects of long-term exposure to pesticide: results from the Farm Health Project (FHP) | L. Ildab [14] | 2011 | Cross-sectional | Association between neuropsychological performance and long-term exposure to pesticides. | Neuropsychological 97 | France | The risk of scoring a low performance in the tests was constantly higher in exposed subjects. |
| Psychomotor and psychiatric functioning in sheep farmers exposed to low levels of organophosphate pesticides | S. Mekkine [15] | 2000 | Cross-sectional | Detection of low-level exposure to organophosphate pesticides: neuropsychological or psychiatric impairment. Performance of cognition and mood. | Neuropsychological 127 | UK | Exposed subjects performed significantly worse than controls. Cognitive defects identified cannot be attributed to mixed disorders, reflecting a history of acute exposure or genetic vulnerability. Neurological involvement may exist between low-level exposure to organophosphate and impaired neurobehavioral functioning. |
| Neuropsychological and psychological performance and long-term exposure to organophosphate pesticides | L. Rodina [16] | 2010 | Cross-sectional | Cross-sectional survey established high-exposure Neutrotoxic effects and long-term exposure to pesticides. | Neuropsychological 40 | Spain | No data on the association between long-term exposure and various psychological performance. |
| Neuropsychological performance among agricultural pesticide applicators | W. Dariell [17] | 1992 | Prospective cohort study | Initial evaluation prior to start of a 6 months of sampling, neuropsychological testing, over a period of 1 month after | Neuropsychological 89 | USA | Only significant difference was across seasonal neuropsychological testing in the subjects during the summer. |
| Effect of organophosphate pesticides on children's cognitive and behavioral functioning | P. Lucardi [18] | 2006 | Cross-sectional | Battery of cognitive measures, Cognitive Behavioral Testing of Caffeine, Salmonella DNA. | Neuropsychological 48 | USA | All children had a detectable level of organophosphate pesticide metabolites. Higher organophosphate pesticide exposure concentrations were significantly correlated with poorer performance in a battery of cognitive measures. |
| Neurobehavioral effects of organophosphate pesticides on children's cognitive and behavioral functioning | J. Lapita [19] | 2008 | Cross-sectional | Battery of cognitive measures, Cognitive Behavioral Testing of Caffeine, DNA. | Neuropsychological 48 | USA | All children had a detectable level of organophosphate pesticide metabolites. Higher organophosphate pesticide exposure concentrations were significantly correlated with poorer performance in a battery of cognitive measures. | Labeled number limited, susceptible to bias, not applicable to children. Not being able to deliver a true non-exposed group. |
Effects of organophosphate pesticide exposure on biomarkers of neurochemical and behavioral functioning

P. Lizarraga [29], 2009
Cross-sectional

Baseline of cognitive function: Wessex Card Sorting Test

Neurobehavioral 48 USA

Children had a detectable level of organophosphate metabolite in blood, but no clinical evidence of neurobehavioral dysfunction. Children with higher concentrations of organophosphate metabolites had significantly improved performance in some subjects. However, there was no significant difference in the scores of boys with lower concentrations of organophosphate metabolites.

Linked number of children. Neurochemical battery may not be applicable to children from other regions to define a true non-exposed group.

Neurobehavioral deficits and increased blood pressure in school-age children previously exposed to pesticides

R. Hare [30], 2010
Cross-sectional

Increased blood pressure, as measured in 30-second seated blood pressure readings, was significantly lower in children who had been previously exposed to organophosphate pesticides.

Neurobehavioral 84 Ecuador

Exposure-related deficits were evident in motor coordination, visual-spatial performance, and visual memory. Children with a history of organophosphate exposure had lower systolic blood pressure in the morning and decrease in heart rate.

Did not assess all functions: Speed of sample size.

Increased risk of suicide with exposure to pesticide in an intensive agricultural area

T. Parvin [31], 1995
Retrospective

Suicidal ideation in those different areas

Neuropsychological 251 El Paredon, Panamá

Higher suicide rates in geographically close regions compared to other regions and sociodemographic characteristics. Male residents had a higher suicide rate than females.

Retrospective study. Moderate study. Variables not controlled.

Neuropsychological effects of long-term exposure to organophosphate pesticides

R. Srivastav [32], 1995
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 209 UK

Significantly worse performance in farmers' group in several attention and information processing tasks. Occasional rate of suicide was significantly higher in farmers with high exposure to organophosphate pesticides.

Moderate sample size. Self-reporting bias.

Long-term use of organophosphates and neuropsychological performance

N. Talal [33], 1997
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 99 New Jersey

Significantly slower reaction time in farmers with prolonged exposure.

Selection bias. Self-reporting bias. Moderate sample size. Recalling bias.

Pesticide exposure and depressive symptoms among farm residents

L. Wallasey [34], 2002
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 761 USA

Lower reported depressive symptoms with pesticides exposure, although not significant.

Self-reporting bias. Selection bias.

A clinical neuropsychological assessment of farmers exposed to organophosphate and neonicotinoid pesticides

N. Uher [35], 2002
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 79 UK

No significant differences in exposure to organophosphate and neonicotinoid pesticides between farmers exposed to pesticides and farmers not exposed. Neuropsychological tests showed no significant differences.

Small sample size. Limited power. Reporting bias.

Mental health in Alberta grain farmers using pesticides over many years

N. Ohe [36], 2012
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 107 Alberta

Mental stress symptoms were related to duration of exposure to phencyclidine.

Self-reporting bias. Selection bias.

Cognitive and psychiatric impairments in farm workers exposed to organophosphate and neonicotinoid pesticides: a case-control study

P. Edmonds [37], 1999
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 540 USA

Use of antidepressants was significantly associated with organophosphate and neonicotinoid exposure. Use of antidepressants was not significantly associated with organophosphate exposure.

Detection bias. Misclassified exposure.

Depression and pesticide exposure among private pesticide applicators in the Agricultural Health Study

D. Berrier [38], 2008
Cross-sectional

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 17 085 USA

Pesticide poisoning was associated with depression compared to farmers without depression exposure.

Classification of exposure events. Self-reporting bias. Confounding bias.

Depression and pesticide exposure in a female offspring of licensed pesticide applicators in the Agricultural Health Study

C. Sawyer [39], 2009
Case-control

Neuropsychological tests: Reaction time, memory, attention, and executive function.

Neuropsychological 29 072 USA

Significantly associated with pesticide poisoning but not with cumulative pesticide exposure.

Case-control study. Self-reported information.
| Study Title                                                                 | Authors       | Year | Country | Exposure Details | Outcome | Methodology | Setting | Source | Risk Estimate | Comments |
|---------------------------------------------------------------------------|---------------|------|---------|------------------|---------|-------------|---------|--------|----------------|----------|
| Depression and psychological exposure to tetracycline in workers in a crop production area | Scoble, J. | 1997 | USA     | Tetracycline exposure | Depression | Cross-sectional study | Agricultural area | USA | Increased risk of depression | Self-reporting bias, moderately large sample size |
| Cancer of the liver and cirrhosis in workers exposed to tetrachlorvinphos | Scoble, J.    | 1996 | USA     | Tetrachlorvinphos exposure | Cancer | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| Neurological symptoms in workers exposed to tetrachlorvinphos | Scoble, J.    | 1996 | USA     | Tetrachlorvinphos exposure | Neurological symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| A study of psychiatric symptoms on exposure to organophosphates pesticides in the children of agricultural workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Psychiatric symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| Effects of long-term organophosphate exposure on neurological symptoms in occupationally exposed workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Neurological symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| An epidemiological study of the relationship between exposure to organophosphates pesticides and symptoms of dermatitis in agricultural workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Dermatitis symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| Depression and psychological exposure to tetracycline in workers in a crop production area | Scoble, J.    | 1997 | USA     | Tetracycline exposure | Depression | Cross-sectional study | Agricultural area | USA | Increased risk of depression | Self-reporting bias, moderately large sample size |
| Cancer of the liver and cirrhosis in workers exposed to tetrachlorvinphos | Scoble, J.    | 1996 | USA     | Tetrachlorvinphos exposure | Cancer | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| Neurological symptoms in workers exposed to tetrachlorvinphos | Scoble, J.    | 1996 | USA     | Tetrachlorvinphos exposure | Neurological symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| A study of psychiatric symptoms on exposure to organophosphates pesticides in the children of agricultural workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Psychiatric symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| Effects of long-term organophosphate exposure on neurological symptoms in occupationally exposed workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Neurological symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
| An epidemiological study of the relationship between exposure to organophosphates pesticides and symptoms of dermatitis in agricultural workers | Scoble, J.    | 1996 | USA     | Organophosphates exposure | Dermatitis symptoms | Cross-sectional study | Agricultural area | USA | Increased risk | Self-reporting bias, moderately large sample size |
Prevalent nervous system function and organophosphate pesticide poisonings among farm workers: prevalence and clinical applications in the Agricultural Health Study
ML. Stiles [52]
2012 Cohort Neurophysiological and physical assessments
Epidemiological and occupational health studies
Neurophysiological
678 Iowa and North Carolina, USA
Significantly increased odds of symptoms and signs of polyneuropathy associated with occupational exposure to organophosphate pesticides with or even more than one neurochemical exam finding for organophosphates associated with the paraoxonase 1 (PON1) 192 Q polymorphism
Self-reporting bias Evaluation methods: cross sectional
Exposure to pesticide Medline

An uncommon symptom of polyneuropathy induced by lifetime exposure to drift-contaminating organophosphate pesticides
A. Ophir [50]
2014 Cohort Quantitative surveys about self-reported exposure Neurophysiological and occupational health studies
Neurophysiological
69 Israel
Organophosphorus pesticides use significantly correlated to polyelectrolyte digital latency in right median nerve and lower nerve amplitude in right sural nerve
Small sample size Self-reported exposure to insecticide Medline

 Delayed polyneuropathy in farm workers due to chronic exposure to organophosphate pesticide
R. Logist [14]
2014 Cohort Geographical and neurological examination
Neurophysiological and occupational health studies
Neurophysiological
290 Iraq
Ophthalmological complications 45% Significant difference in mean latency of oculomotor muscle action potential amplitude and severe reduction in sural sensory nerve action potential amplitude: peak latency and nerve conduction velocity
Accidental exposure to pesticide Moderate sample size Medline

Effect of chronic pesticide poisoning on peripheral nerve function in a rural village of a Micronesian community
R. Payah Pischaló [23]
2012 Transverse cross-sectional Blood tests with blood count and clinical tests
Electrophysiological and clinical examinations
Neurophysiological
46 USA
Pesticide exposure and levels of nerve conduction velocity, motor nerve conduction velocity
Not longitudinal study: cross sectional study design WOS

Effects of occupational exposure to organophosphate pesticides on muscle performance and neuromuscular function
B.J. Prem-John [56]
2002 Cross-sectional Comparison between two groups in relation to neurological symptoms and electromyograph findings
Neurophysiological
63 Sri Lanka
Decreased sensory conduction velocity and motor conduction velocity between subgroups of individuals with or without sensory symptoms
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
W.G. Eno [57]
2005 Cross-sectional Health screening evaluations
Neurophysiological
283 USA
Significantly increased difference between symptoms reported by the physician and symptoms reported by the patient or the physician's assessment of subacute or chronic toxicity between those in the exposed group and controls
No significant difference found in growth and development screening 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
Neurophysiological
248 China
Long-term exposure found to be associated with increased frequency of neurological symptoms especially sensory symptoms
Recall bias Not a longitudinal study WOS

BioAs, Behavioral Assessment and Research System, DiP, Salky phosphate, HPEE, high pesticide exposure event, MMS, mixed mental state examination, TCP, 1, 5, 6-keto-PGF1α, WOS, Web of Science.
### Table 2: Literature review of respiratory studies

| Title | First author [year] | Year | Study design | Method | No. of subjects | Location | Findings | Limitations | Database(s) |  |
|-------|---------------------|------|--------------|--------|----------------|----------|----------|------------|-------------|-------------|
| Chronic exposure to chlorinated-iodinating persistent andf adversely affect respiratory health of agricultural workers in India | S. Charanakar [68] | 2015 | Cross-sectional | Questionnaire on respiratory symptoms and lung function tests and sputum/bronchial wash assessment | 744 India | Agricultural workers had greater prevalence of upper and lower respiratory symptoms and appreciable reduction in spirometric values. Long function test was reduced to 45.3% | Delmal absorption not considered as no personal protective equipment used | Medline WOS |  |
| Decreased lung function in 7-year-old children with previous diphosphonate exposure | R. Raman [69] | 2016 | Cross-sectional | CHIMICOS longitudinal birth cohort | 700 USA | Diphosphonate exposure measured by urine metabolites (DAP) (n=109 at 7 years) | Lungs to follow-up and challenges in exposure assessment Long-term biomarkers | Medline WOS |  |
| Association of chronic pesticide exposure with serum cholesterol levels and respiratory function in Costa Rica | Z. Sabato [66] | 2011 | Cross-sectional | Questionnaire to estimate exposure and presence of respiratory symptoms | 50 Costa Rica | Serum cholesterol levels and the pulmonary function test | No difference between farmers with low cholesterol levels and low function test | Small sample size Cross-sectional study design | Medline WOS |  |
| Pesticides and adult respiratory outcomes in the Agricultural Health Study | J. Happen [67] | 2006 | Cross-sectional | Looking at respiratory outcomes including wheeze, asthma, and chronic bronchitis | 69,000 USA | Serum cholesterol levels and the pulmonary function test | Strong association between organophosphates and wheeze | Limited to those who enrolled in the questionnaire | Medline WOS |  |
| Chlorpyrifos exposure and respiratory health among adult agricultural workers | C. Calleja [84] | 2014 | Cross-sectional | 10-year study on adult agricultural workers | 62 Egypt | Inconsistent results with spirometry | No baseline assessment | No baseline assessment | Small sample size No controls | Scoop WOS |  |
| Biomarkers of pesticide exposure in children, a National Health and Nutrition Examination Survey (NHANES) 1999–2006 analysis | M. Petla [60] | 2014 | Cross-sectional | Used National Health and Nutrition Examination Survey (NHANES) 1999–2006 analysis | 2777 USA | No association found between DAP and asthma | Cross-sectional analysis of the data self-reported residuals outliers | WOS |  |
| Low level of exposure to pesticides leading to lung function in occupationally exposed subjects | A. Fernandez [69] | 2010 | Cross-sectional | Questionnaire on pesticide exposure and symptoms | 114 Spain | Reduced forced expiratory volume in 1 second (FEV1) and forced expiratory flow (FEF25-75%) Long-term outcome Noel suggestive of restrictive lung disease | USE OF BIOMARKERS | WOS |  |
| Urinary diphosphonate concentrations and lung function parameters in adolescents and adults: results from the Canadian Health Measures Survey | M. Ye [67] | 2010 | Cross-sectional | Lung function tests and urinary DAP was measured, smoking status and other predictors of lung function | 4446 Canada | Reduced forced expiratory flow, forced expiratory volume in one second, and forced expiratory flow 25-75% with every unit of DAP metabolites found in children No associations found in adolescents | Not the entire Canadian population was included | WOS |  |

**DAP**: diphosphonate; **WOS**: Web of Science.

### Table 3: Literature review of cancer studies

| Title | First author [year] | Year | Study design | Method | No. of subjects | Location | Findings | Limitations | Database(s) |  |
|-------|---------------------|------|--------------|--------|----------------|----------|----------|------------|-------------|-------------|
| Association of pesticides, HCV, HBV, and helicobacter caroniore in Egypt | S. Edou [66] | 2005 | Case-control | Questionnaire Blood and hepatitis virus testing | 238 Egypt | Exposure to organophosphates and caroniore is additive risk factors to hepatitis B infection among rural | Small sample size Limited power | Medline WOS |  |
| Exploring cancer development in adulthood chlorinated exposure depression and genotoxic effect from chronic exposure to organophosphates pesticides among rural farm children | V. Hov [66] | 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 organophosphates pesticide exposure is significantly associated with an increase in chromosome breakage and DNA strand breaks Geometrically and pictorially suggest that farm children cells experience early DNA damage that may lead to uncontrolled cell growth and increasing their childhood | Small sample size Limited power | Medline WOS |  |
| Lymphoma risk and occupational exposure to pesticides: results of the Elymph study | P. Cocco [70] | 2013 | Cross-sectional | Detailed occupational history collected in cases and controls and job titles applied for farm work | 2090 Europe | Risk of lymphpoma in the study was not elevated Risk of chronic lymphocytic leukemia was elevated amongst those ever exposed to organophosphates and organic pesticides | Caution in interpreting results of this study | Medline WOS |  |

**WOS**: Web of Science.
### Table 4: Endocrine study in the literature review

| Title                                                                 | First author [full 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, 1991–2003 | W.R. Montgomery [71]           | 2008 | Cohort       | Agricultural Health Study comparing diabetes in the study against non and lifetime exposure to pesticides | 33.457 | USA | Self-reported diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1991–2003 | Self-reported diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1991–2003 | Medline, Scopus, WOS |

### Table 5: Cardiac study in the literature review

| Title                                                                 | First author [full reference] | Year | Study design | Method | No. of subjects | Location | Findings                                                                 | Limitations                                                                 | Database(s) |
|----------------------------------------------------------------------|--------------------------------|------|--------------|--------|-----------------|----------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
| Peptide and melanoide plasmid, incidence and mortality effects of pesticide exposure in a UK farm laborers’ scheme | W.R. Mills [72]                | 2009 | Cohort       | Agricultural Health Study, 1991–2004 | 32.624 | USA | Self-reported incidence and mortality effects of pesticide exposure in a UK farm laborers’ scheme | Self-reported incidence and mortality effects of pesticide exposure in a UK farm laborers’ scheme | Medline, WOS |

### Table 6: Chronic fatigue study in the literature review

| Title                                                                 | First author [full reference] | Year | Study design | Method | No. of subjects | Location | Findings                                                                 | Limitations                                                                 | Database(s) |
|----------------------------------------------------------------------|--------------------------------|------|--------------|--------|-----------------|----------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
| Chronic fatigue and organophosphate pesticides in a retired group of farm workmates | W.R. Taylor [73]               | 2009 | Retrospective case-control cohort | Two questionnaires | 178   | UK | Self-reported incidence and mortality effects of pesticide exposure in a UK farm laborers’ scheme | Self-reported incidence and mortality effects of pesticide exposure in a UK farm laborers’ scheme | Medline, WOS |

### Table 7: Literature review of fertility studies

| Title                                                                 | First author [full reference] | Year | Study design | Method | No. of subjects | Location | Findings                                                                 | Limitations                                                                 | Database(s) |
|----------------------------------------------------------------------|--------------------------------|------|--------------|--------|-----------------|----------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
| Occupational exposure to organophosphate and carbamate pesticides affect sperms' viability and reproductive hormone levels among Venezuelan farm workers | L. Meanderi-Cortes [74]        | 2013 | Cross-sectional | Recruited for clinical evaluation of fertility status | 99   | Venezuela | Self-reported occupational exposure to organophosphate and carbamate pesticides affect sperms' viability and reproductive hormone levels among Venezuelan farm workers | Self-reported occupational exposure to organophosphate and carbamate pesticides affect sperms' viability and reproductive hormone levels among Venezuelan farm workers | Medline, WOS |
| Changes in male hormone profile after occupational organophosphate exposure: a longitudinal study | C. Aguilar-Garibay [75]         | 2013 | Cross-sectional | Effect of organophosphate measured by urine metabolitesc during and agricultural period with different degrees of pesticide use | 136  | Mexico | Self-reported occupational exposure to organophosphate and carbamate pesticides affect sperms' viability and reproductive hormone levels among Venezuelan farm workers | Self-reported occupational exposure to organophosphate and carbamate pesticides affect sperms' viability and reproductive hormone levels among Venezuelan farm workers | Medline, WOS |

*FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.*
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. 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. Deficits were found in short-term memory components, with participants scoring significantly lower on the Digit Span (forward and reverse recall of digit sequences) and Match-to-Sample tests (matching to previously demonstrated stimuli). 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. Another study from Iran found no neurobehavioural deficits. 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.

Ten articles analysed the vulnerability to psychological conditions with chronic exposure to organophosphates, particularly referring to the general health questionnaire. Two of the 10 studies noted an association with organophosphate exposure in farmers. The remainder did not find a significant relationship. One study demonstrated a lower percentage of depressive symptoms amongst farm residents (20.6%) in Colorado, USA, compared to the general population (34%). 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. The relationship of organophosphate pesticide chronic exposure with suicide was also examined. One study demonstrated a lower percentage of depressive symptoms amongst farm residents (20.6%) in Colorado, USA, compared to the general population (34%). 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. The relationship of organophosphate pesticide chronic exposure with suicide was also examined. This study reported no significant association between organophosphate exposure and suicide.

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. This result is consistent within the Australian population, with MacFarlane et al demonstrating in their study a non-significant relationship between exposure and suicide. 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. 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. 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. 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.

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). The same article concluded that being acutely poisoned was a more significant indicator for likely development of Parkinson’s disease.

Short-term memory problems have previously been shown to be associated with chronic exposure to organophosphates. 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. Three articles described an effect on neurodevelopment when exposed to organophosphates in the prenatal period. 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. 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. 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.

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. Seven studies looked into neurological findings from physical examinations. 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. 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. 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. A South African study found no association between organophosphate pesticide use and neurological deficit in relation to vibration sense or tremor.

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. Four of these studies showed significant differences in nerve conduction results between farmers and controls. These studies demonstrated the difference in distal latencies and wave amplitude of peripheral nerves.

Neurological symptoms were detailed in four studies. 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. In one study, organophosphate-induced neurotoxicity was detailed, with described symptoms including insomnia, headache, anorexia and numbness.

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. Six of these articles reported significant associations between respiratory conditions and organophosphate exposure. Findings included symptoms such as wheeze and a decrease in lung function. The three remaining articles reported inconsistency, indicating no correlation between prolonged exposure and asthma prevalence or spirometry changes.

Three articles in the databases evaluated cancer risk associated with chronic organophosphate use. 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. This has been linked to increased susceptibility of a person to develop cancer. Another article reported an increased risk of chronic lymphoid leukaemia (OR 2.7, 95%CI 1.2–6.0).

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).

One article looked into the incidence of myocardial infarction with exposure of organophosphate pesticides. 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.

There was only one article relating to chronic fatigue met the criteria outlined in the methods. 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.

Lastly, fertility was investigated in this review. Two studies showed a significant effect on this system. One article demonstrated a significant decrease in the semen parameters, with decreased sperm concentration \( p = 0.002 \) and vitality \( p < 0.0001 \). Both articles highlighted an increase in follicle-stimulating hormones and luteinising hormones. 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. 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.

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.

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.

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. 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.

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**

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.

**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.
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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