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. 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 agric* 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 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>
<thead>
<tr>
<th>Title</th>
<th>First author (last referenced)</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>Health area</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic central nervous system injury and organophosphate poisoning interaction</td>
<td>L. Rosenstock [8]</td>
<td>1991</td>
<td>Retrospective cross-sectional</td>
<td>Neurophysiological testing including nerve conduction velocity, reaction time, sensory perception, mental perception, memory, mental distractibility test, Benton visual analog test, intelligence test, digit span and digit symbol test.</td>
<td>Neurobehavioural</td>
<td>Nigeria</td>
<td>Paired group had lower performance on test battery than controls for both organophosphate exposure classes.</td>
<td>Not statistically significant differences between groups.</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>The relationship between chronic and acute exposure and effects</td>
<td>R. Stephens [11]</td>
<td>1996</td>
<td>Cross-sectional</td>
<td>Neurophysiological testing including isometric strength test and hand muscle strength test.</td>
<td>Neurobehavioural</td>
<td>UK</td>
<td>Deficits of acrobatic effects of organophosphate exposure are independent of acute effects</td>
<td>Absence of immediate negative feedback following exposure is likely to influence measures</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>An investigation into neurological and neurobehavioural effects of long-term agricultural use of neonicotinoid insecticides on farmers in the Western Cape, South Africa</td>
<td>L. Larden [11]</td>
<td>1997</td>
<td>Cross-sectional</td>
<td>Job exposure matrix, Movement battery, Hand-dexterity battery, and Psychological (10 years) test.</td>
<td>Neurobehavioural</td>
<td>Western Cape, South Africa</td>
<td>No significant neurological or psychological deficits were evident with long-term exposure to organophosphates.</td>
<td>Retrospective and well-replicated study shows results. Limited number of subjects, decreasing study power.</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>Organophosphate pesticide exposure and neurobehavioural performance in pregnant women and their non-agricultural Hispanic offspring</td>
<td>J. Rollins [14]</td>
<td>2010</td>
<td>Cross-sectional</td>
<td>Biopsychosocial test including language, tapping, simple reaction time, number and symbol digit span, digit symbol substitution, visual short-term memory, and continuous performance.</td>
<td>Neurobehavioural</td>
<td>Oregon, USA</td>
<td>Correlation between occupant, pesticide exposure, and neurobehavioural performance.</td>
<td>Pesticide exposure cannot be identified from these measures. Individual differences in health status may confound. Non-significant difference in test performance.</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>Neurobehavioural performance of adult and associated agricultural workers</td>
<td>D. Rollins [15]</td>
<td>2007</td>
<td>Cross-sectional</td>
<td>Biopsychosocial test including language, tapping, simple reaction time, and number and symbol digit span.</td>
<td>Neurobehavioural</td>
<td>USA</td>
<td>Significant effect was found with match-to-sample performance and age was a significant predictor of performance.</td>
<td>No exposure-related effect.</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>Neurobehavioural effects of exposure to organophosphate pesticides and organophosphate poisoning among Thai children</td>
<td>N. Hidaka [16]</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>Biopsychosocial test including language, tapping, and simple reaction time.</td>
<td>Neurobehavioural</td>
<td>Thailand</td>
<td>No significant difference between HOC and controls.</td>
<td>Not statistically significant difference.</td>
<td>Medically significant difference in test performance.</td>
<td>WOS</td>
</tr>
<tr>
<td>Cognitive disorders and occupational exposure to organophosphates results from the PHYTOPHOS study</td>
<td>A. Blau [17]</td>
<td>2013</td>
<td>Cohort</td>
<td>Neurophysiological testing including Mini Mental Status, Dartmouth Health and Mental Status.</td>
<td>Neurobehavioural</td>
<td>France</td>
<td>Exposure was associated with low cognitive performance for in-vivo effect relationship found.</td>
<td>Exposure not associated with cognitive performance.</td>
<td>Unacceptable for post-organophosphate studies.</td>
<td>WOS</td>
</tr>
</tbody>
</table>
**Neurobehavioral effects of high-potency organophosphate pesticides: results of a 4-year follow-up of the PROTONE study**

I. Bahill [21]

**Cross-sectional**

Neurobehavioral tests to assess memory, motor speed, sustained attention, verbal learning and visual scanning and processing information. In one having an IFPEE and a matched control was obtained from the Environmental Health Study.

Neurobehavioral 603 USA

Participants: 57 male participants and 61 female participants. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neurobehavioral performance and work experience in farm laborers**

F. Kamei [22]

**Cross-sectional**

Collected information on farm work history and evaluated Neurobehavioral tests to assess memory, motor speed, sustained attention, verbal learning and visual scanning and processing information using a battery of eight tasks.

Neurobehavioral 285 USA

Participants: 211 male participants and 13 female participants. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neurobehavioral effects among workers occupationally exposed to high and low levels of organophosphate pesticides**

T. M. Farzad [23]

**Cross-sectional**

Two groups: those exposed versus those not. Questionnaires, general and neuropsychological test battery, personality assessment and structural analysis of neuropsychological test scores were completed.

Neurobehavioral 192 Egypt

Participants: 120 exposed workers and 120 non-exposed workers. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neuropsychological effects of long-term exposure to organophosphate pesticides: results from the Farming POPCERN Study**

I. Bahill [24]

**Cross-sectional**

Association between neurobehavioral performance and long-term exposure to pesticides.

Neuropsychological 917 France

Participants: 230 participants. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neuropsychological and psychiatric functioning in sheep farmers exposed to low levels of organophosphate pesticides**

B. M. Meckstroth [25]

**Cross-sectional**

Determined if low-level exposure to organophosphate causes neuropsychological or psychiatric impairment. Performance of cognition and mood.

Neurobehavioral 127 UK

Participants: 127 exposed workers and 127 non-exposed workers. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neuropsychological effects of organophosphate pesticides**

I. Ristic [26]

**Cross-sectional**

Cross-sectional survey and high-exposure neurobehavioral deficits using a wide variety of tests to test cognitive and psychological functioning and emotion detection.

Neurobehavioral Neuropsychological Did not specify Spain

Participants: 100 exposed workers and 100 non-exposed workers. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Neurobehavioral effects on Hispanic children’s cognition and behavior in a 9-month follow-up through Standardized neuropsychological testing**

W. Daniel [27]

**Cross-sectional**

Standardized neuropsychological testing in 7th-grade children.

Neuropsychological 89 USA

Participants: 120 children. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.

**Effect of organophosphate pesticides**

P. Lurati [28]

**Cross-sectional**

Battery of cognitive measures administered on the Telephone Card Sorting Test.

Neurobehavioral 48 USA

Participants: 100 exposed workers and 100 non-exposed workers. VAIL (visual analog scale) 2.5 was able to detect a difference in performance in the cognitive tests.
<table>
<thead>
<tr>
<th>Title</th>
<th>Authors</th>
<th>Year</th>
<th>Design</th>
<th>Measures</th>
<th>Findings/Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of suicide with exposure to pesticides in an intensive agricultural area in a 13-year retrospective study</td>
<td>T. Pearson</td>
<td>1995</td>
<td>Cross-sectional</td>
<td>Neuropsychological suicidal. Higher suicide rates in geopraphic regions when compared to other regions of socioeconomic status and geographic features. Mortality from suicide in this region of farmers does not vary compared to other populations.</td>
<td>Retrospective study, Moderate-study, Variables not controlled</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Long-term use of organophosphates and organophosphates on farm residents</td>
<td>N. Fedder</td>
<td>1997</td>
<td>Cross-sectional</td>
<td>Neurocognitive function assessment. No significant changes in the organophosphate-exposed group.</td>
<td>Long-term use of organophosphates showed no significant impact on neurocognitive function.</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>A clinical neuropsychological and neuropsychological study of farm workers</td>
<td>D.A. Ahmad</td>
<td>1992</td>
<td>Case-controlled</td>
<td>Neuropsychological and neuropsychological measures were similar in exposed and non-exposed groups.</td>
<td>No significant differences in exposure to organophosphate and neurocognitive. Three times more reported symptoms among those exposed to pesticides compared to the general population.</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Mental health in Alberta grain farmers using pesticides over many years</td>
<td>N. Ohney</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>Goolph test. Mental health symptoms were related to duration of exposure to phenoxyacetic acid.</td>
<td>Self-reported bias, Selection bias</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Organophosphate-induced multifocal motor neuropathy (COSTNET) results in a survey of farmers</td>
<td>M. Edin</td>
<td>1999</td>
<td>Cross-sectional</td>
<td>No significant difference in multifocal motor neuropathy between exposed and non-exposed groups.</td>
<td>Some evidence of significant differences in multifocal motor neuropathy between exposed and non-exposed groups.</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Depression and pesticide exposure among private pesticide applicators in the Agricultural Health Study</td>
<td>D.E. Brandt</td>
<td>2008</td>
<td>Cross-sectional</td>
<td>Self-reported physician-diagnosed depression.</td>
<td>Self-reported depression was associated with increased odds of depression among applicators.</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Depression and pesticide exposure in a female offspring of licensed pesticide applicators in agricultural health study</td>
<td>C. Beaver</td>
<td>2006</td>
<td>Case-control</td>
<td>Female offspring of farmers exposed to pesticides showed increased risk of depression.</td>
<td>Case-control study design, Self-reported information.</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Title</td>
<td>Author(s)</td>
<td>Year</td>
<td>Study Design</td>
<td>Setting/Population</td>
<td>Exposure</td>
<td>Outcome Measures</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Depression and pesticide exposure in female farmers in Vietnam</td>
<td>Tran Thi et al.</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>Vietnam</td>
<td>DDT exposure</td>
<td>Depression, anxiety, and stress</td>
</tr>
<tr>
<td>Dementia in children of pesticide-exposed farmers</td>
<td>A. C. Miller</td>
<td>2005</td>
<td>Case-control</td>
<td>Mexico</td>
<td>DDT exposure</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Exposure to endocrine-disrupting chemicals and pesticides</td>
<td>A. S. Kim et al.</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>Pesticide exposure</td>
<td>Hormonal disruption</td>
</tr>
<tr>
<td>Astrocytoma in children of pesticide-exposed farmers</td>
<td>J. J. Kim et al.</td>
<td>2015</td>
<td>Cohort</td>
<td>South Korea</td>
<td>Pesticide exposure</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>Neurobehavioral effects among children exposed to pesticides</td>
<td>L. A. Wang et al.</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>Pesticide exposure</td>
<td>Neurobehavioral outcomes</td>
</tr>
<tr>
<td>An epidemiological study of the relationship between exposure to organophosphate and endometriosis in women</td>
<td>A. S. Kim et al.</td>
<td>2020</td>
<td>Cross-sectional</td>
<td>South Korea</td>
<td>Organophosphate exposure</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>Pesticide exposure and endometriosis in women</td>
<td>L. J. Kim et al.</td>
<td>2016</td>
<td>Cross-sectional</td>
<td>South Korea</td>
<td>Pesticide exposure</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>Neurobehavioral effects among children exposed to pesticides</td>
<td>L. A. Wang et al.</td>
<td>2015</td>
<td>Cohort</td>
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<td>Cohort</td>
<td>United States</td>
<td>Pesticide exposure</td>
<td>Neurobehavioral outcomes</td>
</tr>
</tbody>
</table>

An uncommon pattern of polyneuropathy induced by lifetime exposure to drift containing organophosphate pesticides. A. Sopac et al. 2014. Cohort Qualification about self-reported exposure. Neurological examinations: Electroencephalography studies. Neurological 69 Israel Organophosphate-induced polyneuropathy significantly correlated with proximal digital latency in right median nerve and lower nerve amplitudes in right tibial nerve. Small sample size, Self-reported exposure.


Evaluation of potential adverse health effects resulting from chronic domestic exposure to the organophosphate insecticide methyl parathion. W. O. Enn et al. 2005. Cross-sectional Health screening evaluations Neurological 263 USA Pesticide exposure and chronic relationship between symptoms reported, and the physician's assessments of subacute or chronic toxicity between those in the exposed group and control. No significant difference found in growth and development. No significant difference between symptom and neurophysiological evaluations. Recall bias.

Long-term health effects of pesticide exposure: a cohort study from China. L. Gu et al. 2015. Cohort Two rounds of health investigations: including blood tests and neurological examinations conducted by doctors before camp season. Neurological 248 China Long-term exposure found to be associated with increased abnormality of nerve conduction, especially sensory nerve. Decreased the tibial nerve conduction velocity. Neurophysiological findings. Short-term health effects includes affective changes in cognitive blood test. Hepatic and renal function and nerve conduction velocities and amplitudes. Theses effects could not be detected after 2 years of pesticide exposure. Recall bias. Not a longitudinal study.

SFARS, Surveillance for Agricultural Rate and Risks, DAP, daily average pesticide, HPEE, high pesticide exposure event, MME, main mental examination, TDP, test, DAP, daily average pesticide, WOS, Web of Science.
### Table 2: Literature review of respiratory studies 59-67

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [last reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic exposure to chlordecone-induced persistent, adversely affect respiratory health of agricultural workers in India</td>
<td>S. Chanderlal [64]</td>
<td>2010</td>
<td>Cross-sectional</td>
<td>Questionnaire on respiratory sympotms and long function tests and oxidative stress measured</td>
<td>374</td>
<td>India</td>
<td>Agricultural workers had greater prevalence of upper and lower respiratory symptoms and appreciable reduction in spirometric values. Long function test reduced to 45.9%</td>
<td>Clinical absorption not considered as no personal protective equipment used</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Decreased lung function in 7-year-old children with low exposure to organophosphate exposure</td>
<td>R. Hashan [65]</td>
<td>2015</td>
<td>Cross-sectional</td>
<td>CHONACO longitudinal birth cohort. Organophosphate exposure measured by area metabolite (GPx) at 1 year</td>
<td>279</td>
<td>USA</td>
<td>Long function test significantly associated with decline in lung function at age 7 years</td>
<td>Long to follow-up and challenges in exposure assessment function bias No-long term biomarker</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Association of chronic pesticide exposure with serum cholesterol levels and the pulmonary function test</td>
<td>Z. Sudan [66]</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>Questionnaire to estimate exposure and presence of respiratory symptoms Long function tests</td>
<td>50</td>
<td>Turkey</td>
<td>No difference between farmers with low cholesterol levels and lung function test</td>
<td>Small sample size Cross-sectional study design</td>
<td>Medline Scopus</td>
</tr>
<tr>
<td>Pesticide exposure and respiratory health of indigenous women in Costa Rica</td>
<td>N. Pedro [67]</td>
<td>2009</td>
<td>Cross-sectional</td>
<td>Questionnaire to estimate exposure and presence of respiratory symptoms Long function tests</td>
<td>137</td>
<td>Costa Rica</td>
<td>Exposed demonstrated between 20% and short of breath-20% Organophosphate exposure associated with wheeze No correlation between pesticide exposure and ventilatory lung function ratio found</td>
<td>Small sample size</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Pesticides and adult respiratory outcomes in the Agricultural Health Study</td>
<td>J. Hopkins [68]</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>Looking at respiratory outcomes including wheeze, cough, asthma, farmer’s lung and chronic bronchitis</td>
<td>69,000</td>
<td>USA</td>
<td>Strong association between organophosphates and wheeze</td>
<td>Limited to those who underwent the questionnaire</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Organophosphates and respiratory health among adult respiratory workers</td>
<td>C. Callahan [64]</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>10-month study on male adults with occupational history of exposure Long function tests</td>
<td>62</td>
<td>Egypt</td>
<td>Inconsistent results with spirometry</td>
<td>No baseline assessment</td>
<td>Scopus</td>
</tr>
<tr>
<td>Biomarkers of organophosphate exposure in children of a National Health and Nutrition Examination Survey (NHANES) 1999-2000 analysis</td>
<td>M. Petia [69]</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>Used National Health and Nutrition Examination Survey to evaluate GAP and asthma in school children</td>
<td>2777</td>
<td>USA</td>
<td>No association found between GAP and wheeze</td>
<td>Cross-sectional analysis of the data Self-reported residual confounders</td>
<td>WOS</td>
</tr>
<tr>
<td>Low level of exposure to pesticides leads to lung dysfunction in occupationally exposed subjects</td>
<td>A. Hernandez [69]</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>Questionnaire on blood exposure and symptoms Long function tests</td>
<td>114</td>
<td>Spain</td>
<td>Short reduced forced expiratory volume Long forced expiratory flow Suggestion of restrictive lung disease</td>
<td>Use of biomarkers</td>
<td>WOS</td>
</tr>
<tr>
<td>Urinary diethyl phosphate concentrations and lung function parameters in adolescents and adults: results from the Canadian Health Measures Survey</td>
<td>M. Ye [70]</td>
<td>2016</td>
<td>Cross-sectional</td>
<td>Long function tests and urinary DAP were measured, smoking status and other predictors of lung function</td>
<td>4446</td>
<td>Canada</td>
<td>Reduced forced vital capacity, forced expiratory volume and forced expiratory respiratory ratio/capacity with every unit of DAP metabolite found No associations found in adolescents</td>
<td>Not all the Canadian population was included Those with respiratory comorbidities already had comorbidities No metabolites used specifically</td>
<td>Cross-sectional study</td>
</tr>
</tbody>
</table>

DAP, diethyl phosphate; WOS, Web of Science.

### Table 3: Literature review of cancer studies 68-70

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [last reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associations of pesticides, HCV, HBV, and hepatocellular carcinomas in Egypt</td>
<td>S. Edwar [64]</td>
<td>2005</td>
<td>Case control</td>
<td>Questionnaire Blood and hepatitis virus testing</td>
<td>236</td>
<td>Egypt</td>
<td>Exposure to organophosphates and carbamates is additive risk factors to hepatitis infection among rural men</td>
<td>Limited power</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Exploring cancer development in adulthood chronic depressive and genotoxic effect from chronic exposure to organophosphates pesticide among rural farm children</td>
<td>V. How [65]</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>Identify possible associations between the depression in blood cholinesterase level and genotoxic effect among farm children</td>
<td>55</td>
<td>Malaysia</td>
<td>Reduced blood cholinesterase level from organophosphates pesticide exposure is significantly associated with an increase in chromosomal breakage and DNA strand breaks Genotoxicity and pleiotropic effects of organophosphates are not described</td>
<td>Small sample size Blomkamp limited conclusion</td>
<td>Medline WOS</td>
</tr>
<tr>
<td>Lymphoma risk and occupational exposure to pesticides: results of the Epidemiology study</td>
<td>F. Cosco [70]</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>Detailed occupational collected in cases and controls and job titles applied for farm work</td>
<td>2890</td>
<td>Europe</td>
<td>Risk of lymphoma overall and B cell lymphoma not elevated Risk of chronic lymphoid leukemia was elevated amongst those were exposed to organophosphates and organic pesticides</td>
<td>Creation in interpreting results of the study Small-study bias</td>
<td>Medline WOS</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [full reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident diabetes and pesticide exposure amongst licensed pesticide applicators in the Agricultural Health Study</td>
<td>Montgomery [11]</td>
<td>2008</td>
<td>Cohort</td>
<td>Agricultural Health Study comparing diabetes in the cohort against non-pesticide exposed individuals</td>
<td>33,465</td>
<td>USA</td>
<td>Self-reported incidence and lifetime exposure to pesticides</td>
<td>Self-reported diagnosis to control for exercise and diet</td>
<td>Medline, Scopus</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [full reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [full reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic fatigue and organophosphate pesticides in those farming a repetitive study that is currently reporting to a UK pesticide research scheme</td>
<td>N. Tamez [13]</td>
<td>2003</td>
<td>Retrospective case-control cohort</td>
<td>Two questionnaires</td>
<td>178</td>
<td>UK</td>
<td>High prevalence of chronic fatigue amongst those who completed the questionnaire</td>
<td>Higher economic status and higher exposure to pesticides</td>
<td>WOS</td>
</tr>
</tbody>
</table>

### Table 7: Literature review of fertility studies

<table>
<thead>
<tr>
<th>Title</th>
<th>First author [full reference]</th>
<th>Year</th>
<th>Study design</th>
<th>Method</th>
<th>No. of subjects</th>
<th>Location</th>
<th>Findings</th>
<th>Limitations</th>
<th>Database(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational exposure to organophosphate and cyanate pesticides affect sperm motility and reproductive hormones levels amongst Venezuelan farm workers</td>
<td>L. Meandri-Cantore [14]</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>Recruited for clinical evaluation of fertility status, sperm samples collected and analyzed</td>
<td>99</td>
<td>Venezuela</td>
<td>Significant decreases in sperm motility, DNA fragmentation index, and sperm concentration and morphology and looks</td>
<td>Small sample size</td>
<td>WOS</td>
</tr>
<tr>
<td>Changes in male hormone profile after occupational organophosphate exposure: a longitudinal study</td>
<td>C. Agular-Garduno [15]</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>Effect of organophosphate measured by urine metabolites during the agricultural period with different degrees of pesticide exposure</td>
<td>136</td>
<td>Mexico</td>
<td>Exposure associated with increased urinary FSH and prolactin and decreased serum testosterone and inhibin, LH inversely associated with urine metabolite</td>
<td>Univariate model does not provide specific information regarding the pesticide exposure and its effects on male hormones</td>
<td>WOS, Medline</td>
</tr>
</tbody>
</table>

| 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). Attention span was also found to be affected in two studies.

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 no significant association between 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. Zagana 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, and 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 mortality 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.
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.

REFERENCES:


Mackenzie Ross SJ. Neuropsychological and psychiatric functioning in sheep farmers exposed to low levels of organophosphate pesticides. London: University College London, 2011.


workers in a desert country in relation to long-term exposure to... variability, and relationship with child attention and hyperactivity.


Fortenberry GZ, Meeker JD, Sanchez BN, Barr DB, Panuwet P, and girls.

MR. Acetylcholinesterase activity and neurodevelopment in boys

44 Suarez-Lopez JR, Himes JH, Jacobs DR, Alexander BH, Gunnar PMid:21507776


