Neurobehavioural problems following low-level exposure to organophosphates: Methodological considerations for future research.

S.J. Mackenzie Ross[a*] and V.Harrison[b]

[a] *University College London, London, UK*

[b] *The Open University, Milton Keynes, UK*

17.1 Abstract

Organophosphate pesticides (OPs) are increasingly used around the world, and concerns have been expressed about their effects on human health. The neurotoxic effects of high-level acute poisoning are well established, but the possibility that long-term low-level exposure to OPs in doses below that causing acute toxicity causes ill health is controversial. In this chapter we review the available evidence concerning the neurotoxicity of long-term, low-level exposure to OPs in adult populations and highlight unanswered questions and methodological considerations which future researchers will need to address before firm conclusions can be drawn.

17.2 Introduction

Pesticides are widely used in agriculture throughout the world to ensure sufficient food supplies by eliminating a variety of pests, weeds and pathogens which can spread diseases, damage crops and reduce productivity. The United States Environmental Protection Agency estimates over 5.2 million pounds (2.5 million tons) of pesticides were used worldwide in 2006 and 2007 and this figure has been steadily increasing since then, exceeding 6 billion pounds (3 million tons) in 2011 (EPA Reports, 2011 & 2017).

Organophosphate pesticides (OPs) are one of the most widely used insecticides in the world and are considered by the World Health Organisation (WHO) to be one of the most hazardous pesticides to vertebrate animals. They are responsible for poisoning a large number of people worldwide, particularly in developing countries where adequate protective measures may be lacking (De Silva *et al*, 2006; WHO report 1990). OP pesticides kill insects by interfering with nervous system function and are potentially harmful to humans. Concern about the effects of organophosphates on human health has been growing as they are increasingly used throughout the world for a variety of agricultural, domestic and industrial purposes.

The neurotoxic effects of acute OP poisoning are well established and involve inhibition of the enzyme acetylcholinesterase (AChE) causing changes in peripheral, autonomic and central nervous system function (cholinergic crisis). It is estimated that approximately 3-5 million pesticide poisonings occur annually worldwide and pesticide poisoning is around 13 times more likely in developing countries than highly industrialised ones (Karalliede *et al*, 2001; Rosenstock *et al*, 1991; WHO, 1990). This, coupled with the fact that pesticide

*Email address: s.mackenzie-ross@ucl.ac.uk

ingestion is one of the leading causes of suicide, has meant that a significant amount of research has focused on the relationship between high levels of exposure and acute health effects; and there is a general consensus in the literature about its negative effects on physical, neurological and psychiatric functioning.

However, the impact of long-term, low-level exposure to OPs on human health remains unclear as the findings from previous research are inconsistent. Since many more individuals are likely to be at risk this type of exposure, rather than acute poisoning, establishing whether low-level exposure to OPs causes ill health is of the utmost importance. In this chapter we review the available evidence concerning the neurotoxicity of long-term, low-level exposure to OPs and highlight the methodological issues which need to be addressed before firm conclusions can be drawn. This Chapter will provide a brief overview of some of the key studies which have investigated this issue, before considering the findings from recent systematic reviews of the literature.

17.3 Overview of Individual studies

This review will focus on studies which (1) investigate the neurotoxicity of OP pesticides, (2) use objective measures of exposure (e.g. biomarkers and/or questionnaires about exposure/work history) (3) use sensitive, neurobehavioural outcome measures and (4) are observational group studies of human adults. Studies concerning children and adolescents do not form part of this review, as developmental issues may complicate interpretation of neurobehavioural data. Studies which include participants with a history of acute poisoning and papers which were not written in English are also excluded.

A variety of different methodologies have been used to investigate whether low-level exposure to OPs has an adverse effect on neurobehavioural function, but most studies utilize one of three approaches: (1) cross-sectional epidemiological studies comparing exposed participants with non-exposed groups; (2) studies evaluating neurobehavioural function before and/or after a brief period of exposure (3) correlational studies examining the relationship between exposure metrics and health outcomes in a particular occupational groups exposed to OPs. The latter are not included in this review because correlational studies tell us little about cause-and-effect. Cohort studies, which compare the neuropsychological abilities of exposed and non-exposed groups are more appropriate for identifying the neurotoxic effects of long-term, low-level exposure and are therefore the main focus of this review. Relevant studies published since 1960 were identified using computerized databases, including Medline, Embase and Psychinfo and findings are summarised in Tables 1 and 2.

17.3.1 Cognitive Functioning

As Table 1 illustrates, the literature concerning the neurotoxicity of low-level exposure to OPs is equivocal. Of the 22 studies which met our inclusion/exclusion criteria, 17 found evidence of cognitive deficits associated with chronic OP exposure, while 5 did not. Studies that evaluated participants before and after a brief period of exposure were less likely to report adverse effects than cohort studies which compared exposed and unexposed groups, which suggests long-term cumulative exposure may be more harmful than brief periods of exposure. Indeed, two studies claimed they found no relationship between exposure and cognitive performance using a pre/post design, however when their exposed participants were

compared to controls, they found evidence of cognitive impairment (Daniell *et al*, 1992; Maizlish *et al*, 1987).

However, of the studies that found poorer performance in exposed groups, the picture was not entirely clear, as there was considerable variation in the number and type of deficits identified. Some studies found evidence of subtle deficits in only one or two cognitive domains (e.g. Fiedler *et al*, 1997; London *et al*, 1997; Steenland *et al*, 2000; Stephens *et al*, 2004), whilst others reported more profound deficits across several cognitive domains (e.g. Farahat *et al*, 2003; Mackenzie Ross *et al*, 2010; Roldan-Tapia *et al*, 2005 and 2006; Rothlein *et al*, 2006; Srivastava *et al*, 2000). Furthermore, there is some variability in the cognitive domains reported to be impaired with seven studies identifying deficits in memory; six finding problems with attention; five with motor skills; and four identifying issues with executive functioning and spatial processing. Despite this, some consistency in study findings is also evident as few studies identified verbal/language impairments or global intellectual decline. A commonly reported finding (in 10 of the 22 studies) was a relationship between long-term, low-level exposure to OPs and reduced processing speed.

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17.3.2 Psychiatric symptoms

Psychiatric symptoms have been reported following acute OP poisoning, particularly depression and this is biologically plausible because animal studies have shown that OPs disrupt neurotransmission in a number of neural pathways involved in mood regulation (e.g. serotoninergic, dopaminergic and noradrenergic pathways; for review see Stallones & Beseler, 2016). However, it is unclear whether individuals with a history of low-level exposure to OPs are at increased risk of psychiatric illness, as some studies find evidence of mood disorder following low-level exposure to OPs whilst others do not. For example, 13 of the studies outlined in Table 1 (see asterisks) used different self-report and standardised scales to evaluate mood with varying sensitivity and specificity (see Table 2). Four found evidence an association between low-level exposure to OPs and elevated levels of anxiety and depression (Bazylewicz-Walczak *et al*, 1999; Mackenzie-Ross *et al*, 2007; 2010 and Malekriard *et al*, 2013). Three found this association only existed for anxiety (Roldan-Tapia *et al*, 2005; 2006 and Steenland *et al*, 2000) and Stephens *et al* (1995) found OP-exposed farmers showed greater vulnerability to psychiatric disorder, but did not elaborate further. In contrast, Berent *et al* (2014), Feidler *et al* (1997) and Cole *et al* (1997) found no mood-related differences between exposed and non-exposed cohorts.

While self-report mood scales are often used in clinical research (due to their ease of use and cost-effectiveness), they are only designed to screen for emotional distress, not to diagnose psychiatric disorder. To date, only 3 researchers have used strict diagnostic criteria, considered to be the gold standard of psychiatric diagnoses. Salvi *et al* (2003) assessed 37 tobacco workers immediately after OP use and then again, 3 months following cessation. Diagnoses were made in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV). Almost half of their sample met the criteria for a psychiatric disorder (35% anxiety and 21% major depression) when interviewed soon after exposure; but this prevalence declined once exposure ceased, suggesting a strong association between poor mental health and *recent* exposure to pesticides. However, the impact of *long-term*, low-level exposure to OPs cannot be determined from this study.

Amr *et al* (1997) assessed 208 Egyptian pesticide formulators, 172 pesticide applicators and 223 control subjects using DSM-III-R criteria. Psychiatric disorders were more common in exposed subjects, particularly depression and dysthymic disorder; but this study failed to

provide enough detailed information about exposure history to confirm the exclusion of individuals with a history of acute poisoning.

In 2016 we investigated whether UK sheep farmers with a history of low-level exposure to OPs were more vulnerable to psychiatric symptoms than unexposed controls (Harrison and Mackenzie Ross, 2016). In-depth exposure information was collected from all participants and any with a history of acute exposure were excluded from the study. Several measures of emotional well-being were used including self-report measures and structured clinical interviews (based on the DSM-IV). When using self-report scales, a significant effect of exposure group was found, even after controlling for age and psychosocial risk factors such as ill-health, pain and stressful life events. However, when mood was evaluated using more stringent criteria, this relationship was only found for anxiety disorder, and not depression. This suggests self-report measures may overestimate depressive symptoms in OP exposed cohorts, so findings from studies which only utilise these measures should be interpreted with caution.

The individual studies described in this chapter differ in terms of methodological quality and study populations, and these factors may explain the variability in study findings. Major differences in study design are apparent, such as examination of different occupational groups with different levels and routes of exposure, from different cultural backgrounds; examined over different time periods (e.g. following a single episode of exposure, several years of exposure or over a lifetime) using a variety of different measures which vary in terms of sensitivity and specificity. To complicate matters further, the sample sizes examined were often relatively small and may have lacked power to detect what might be quite subtle effects of low-level exposure to OPs on neurobehavioural function. Although the majority of studies found an association between long-term, low-level exposure and impaired neurobehavioural function, it is unclear which findings are most reliable and valid, and should be relied upon.

Systematic reviews (SRs) of the literature (including meta-analyses) are often used to resolve ongoing controversies such as this, because they enable researchers to address some of the methodological problems identified above. SRs allow researchers to explore the similarities and differences between studies and the possible reasons for variation in study findings; they give researchers criteria to rate the methodological quality of individual studies thus enabling more weight to be given to the findings from studies of higher quality.

Additionally, meta-analysis allows researchers to summarize, quantify and combine the results of different studies thereby increasing the number of participants, reducing random error, narrowing confidence intervals and increasing statistical power to detect small effects that may be missed by individual studies which are too small to yield valid conclusions (Centre for Reviews and Dissemination (CRD), 2009). It represents each study's findings in the form of effect sizes and gives a more reliable estimate of whether a significant association exists between specified variables, than one study alone. Meta-analysis moves discussion away from individual studies towards an overview of a body of literature and is considered to be the method of choice in situations where research findings may be used to inform public policy (CRD, 2009).

17.4 Narrative versus Systematic Reviews of the Literature

SRs use explicit protocols to identify, select, analyse and appraise research findings, to reduce bias, increase transparency and ensure scientifically robust interpretations are made of

the available evidence. SR methodology is routinely used in healthcare and social sciences to evaluate study findings which may be used to determine treatment protocols, health and public policy. However, only recently have SR methods been identified as having a potentially useful role to play in chemical risk assessment (CRA). Prior to this narrative reviews (NRs) were used in CRA and range from reflecting the opinion of a single individual, to the consensus view of a small committee or large organisation. For example, in 1998, the UK Department of Health commissioned an independent scientific committee (*Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment; COT*) to review the available scientific evidence concerning the impact of prolonged or repeated low-level exposure to OPs on human health. COT formed a small working group to undertake this work, but were unable to reach a consensus regarding this issue. COT identified several gaps in knowledge which might be contributing to this uncertainty and recommended the UK government commission further research in this area.

In 2014, COT updated their review incorporating findings from research studies undertaken in the interim. This time they concluded that (1) although there is an excess of neuropsychiatric symptoms in people who have been exposed to low-levels of OPs, it is unclear whether this is a consequence of chemical toxicity or other, unrelated psychological mechanisms, and (2) overall, there is no consistent evidence that low-level exposure to OPs has adverse effects on neuropsychological functioning, but if OPs do cause long-term neuropsychological impairment in the absence of overt poisoning, then the effects, in most cases, must be minor and subtle.

Whilst COT's conclusions appear reassuring, it is difficult to know how much confidence to have in their findings because of the review methodology employed by the working group. COT undertook a NR and relied upon a small panel of experts to form an opinion. However, in the last decade the validity and credibility of NRs has been questioned (Whaley *et al*, 2016; Mackenzie Ross *et al*, 2016). Many factors can influence the conclusions drawn by experts in these circumstances, such as personal biases and subjectivity in the interpretation of scientific evidence, the political context and agenda within which a review is undertaken, and the influence of dominant personalities on the committee. Additionally, the limits of human memory and decision-making can lead some to use heuristics (either consciously or unconsciously) to reduce the effort associated with reviewing large amounts of information, resulting in poorer integration of information, inconsistent treatment of material, and/or examination of fewer alternatives (Shah & Oppenheimer, 2008). These factors can lead to biased interpretations which do not adequately reflect the evidence base. Worryingly, the conclusions reached by COT were the complete opposite of those drawn by several independent research groups who used SR methods to evaluate the same body of literature.

Muñoz-Quezada *et al* (2016) reviewed 33 English and Spanish language studies and found that over two-thirds showed evidence of a link between chronic occupational exposure to OP pesticides and low neuropsychological performance. While the authors made no attempt to statistically group the results of the studies, they put more weight on the outcomes of studies using objective measures of exposure (such as biomarkers and environmental arrays) and those they classified as 'high quality' using a standardised review protocol. From this, they concluded that increased exposure to OPs (and the associated low-levels of AChE) was likely to result in poorer performance in the following domains: motor speed; motor coordination; visuospatial coordination; memory; processing speed and attention.

A further three papers have been published which review the literature using SR techniques incorporating meta-analysis. The first was conducted by Ismail *et al* (2012) and included 17 studies (and 21 cohorts). They found exposed participants showed consistent, significant

decrements in neurobehavioural performance across several cognitive domains (attention, visuomotor integration, verbal abstraction and perception). Significant exposure-related decrements were also seen in one of three memory tests, two of five tests of sustained attention, and four of seven tests of motor speed. While this review suggests a range of neurobehavioural deficits are associated with long-term low-level exposure to OPs, there are some problems with the way it was carried out which limit the conclusions that can be drawn. For example, the papers included in the analysis contained both adult and adolescent samples, with differing exposure histories. This has serious implications for the reliability and validity of the fixed-effects model they used to analyse the data, as this assumes all included studies have exactly the same underlying 'true' effect. Given the heterogeneity of the study participants (not to mention other differing factors, such as exposure, measures, methodologies etc), this is unlikely to be the case. Thus, it is difficult to draw firm conclusions from this analysis.

In 2013, we carried out a meta-analysis using a random-effects model to assimilate the data from 14 studies investigating the association between exposure to OPs and neurobehavioural impairment (Mackenzie Ross *et al*, 2013). Only studies using adult populations were considered, and data from more than 1,600 participants were aggregated. The meta-analysis showed a small, but significant association between exposure to low-levels of OPs and decrements in cognitive function. Working memory/attention, visual memory, psychomotor speed, executive function and visuo-spatial ability were compromised, while other cognitive domains, such as language and general knowledge, appeared intact. However, the statistical approach used in this review has limitations. Effect sizes were averaged across different neuropsychological tests, considered to assess the same cognitive domain. It may have been more appropriate to investigate each test separately as they may differ in terms of sensitivity and specificity. In addition, dose-response relationships were not analysed beyond the exploration of broad differences between exposed and unexposed cohorts.

A recent meta-analysis by Meyer-Baron *et al* (2015) explicitly sought to address the shortcomings of Ismail *et al* (2012) and Mackenzie Ross *et al* (2013). They reviewed 22 studies (including 32 samples; 1758 exposed and 1260 unexposed participants) and looked at the effect of exposure on participants' performance on individual tests. While they included both adult and adolescent samples, the analyses for the different populations were carried out separately. Little consistency was found between the outcomes of adolescent studies, although a negative association was found between exposure and a measure of working memory (digit span backward). In contrast, chronically exposed adults showed a relatively consistent pattern of significantly poorer performance on tests of memory and attention; and somewhat smaller effects (with few non-significant outcomes) on tests of psychomotor speed. Analysis of dose-response relationships suggested lower performance was directly related to cumulative exposure.

Despite the different approaches taken by the four research groups employing SR techniques, similar conclusions were reached regarding the neurotoxicity of long-term, low-level exposure OPs. All of the reviews conclude that a significant association exists between long-term, low-level exposure to OPs and impairments in neurobehavioural function with memory, attention and psychomotor speed appearing uniquely susceptible to neurotoxic damage. This is in complete opposition to the conclusion drawn by COT, who did not utilise SR methodology and failed to incorporate the findings from existing SRs into their review. The next section will explore the methodological issues associated with research in the area which may explain some of the variation seen in different study findings.

17.5 Methodological Issues

17.5.1 Exposure assessment

One of the most difficult challenges faced by researchers investigating the relationship between OP exposure and ill-health is establishing the most reliable measures of exposure. Table 1 gives an overview of the different approaches used by the studies in this review. In an ideal world, biological monitoring techniques (i.e. urine and blood analysis) that can detect the presence of OP-markers would provide researchers with an objective measure of exposure. However, OPs are metabolised quickly by the body, so biological monitoring is of limited value in retrospective studies of long-term health effects as they only provide a measure of recent exposure. They may be useful in prospective studies but unfortunately the costs involved in running longitudinal projects mean few are commissioned.

Often the most that can be achieved in retrospective studies is a rough estimate of lifetime exposure based on proxy measures (e.g. where someone lives, or their occupation) and/or an individual's testimony regarding their exposure history (e.g. using EHQs). However, given the limits of human memory, information collected in this way may be unreliable and critical exposure data may be missed. Furthermore, it remains unclear what the critical aspects of exposure actually are (i.e. whether it is dose, frequency, intensity or duration of exposure, the particular OP compound an individual is exposed to, or the route of exposure, such as oral/dermal/inhalation), so critical measurements may be missed in some studies. There is also little agreement in the literature about whether these dimensions of exposure should be treated separately, or be amalgamated into a single metric that captures multiple aspects of exposure simultaneously. Where exposure metrics have been used, they vary enormously in terms of complexity, the variables included and their weightings. While metrics are often considered to be an improvement over simple measures of exposure (e.g. ever/never been exposed or exposure duration), their validity and reliability remain unclear.

An additional complicating factor is the lack of any agreed definition of low-level exposure, beyond classifying it as *that which does not provoke symptoms of acute toxicity which require medical intervention*. This rather crude definition is likely to encompass a wide range of different populations with different durations, frequencies and modes of exposure with some occupational groups at one end of the continuum, reporting daily exposure for prolonged periods of time (e.g. chemical plant manufacturers and pesticide applicators) and others at the opposite end of the continuum reporting infrequent exposure, maybe as little as twice a year for a couple of days (e.g. many sheep farmers). Furthermore, this definition assumes individuals can determine whether their symptoms reflect pesticide poisoning; and does not address the fact that variables other than severity of illness determine whether individuals consult physicians (Pitts & Phillips, 1991).

Finally, few retrospective studies investigate the potential synergistic effects of exposure to more than one chemical substance at a time, a common occurrence in some professions, such as farming. Metabolism of OPs involves a number of enzyme systems, but several of the enzymes involved in metabolising OPs are involved in metabolising other substances which means their ability to metabolise OPs may be altered if an individual is exposed to compounds that share the same metabolic pathway such as certain prescribed medicines or exposure to other industrial chemicals at the same time as OPs (Abou-Donia *et al*, 1996; Costa & Furlong, 2002; van Himbergen *et al*, 2008).

17.5.2 Vulnerable sub-groups

In the last few decades, subgroups of individuals at increased risk of neurobehavioural impairment following exposure to OPs have been identified. Clearly individuals in particular occupations such as farming, or those involved in applying, manufacturing or transporting OP pesticides may be at greater risk than others; but it has become increasingly apparent that children, adolescents and the elderly may be at greater risk of sustaining neurotoxic damage than adults because the organs involved in metabolising and excreting toxins (e.g. liver and kidneys) may not be fully developed or may be compromised by ageing and the co-existence of other health conditions. Many adolescents in developing countries work as pesticide applicators, and many migrant workers who move to developed countries such as the United States, are adolescents who may end up working in the agricultural industry (Rohlman *et al,* 2007; Meyer-Baron *et al,* 2015) and some researchers attribute the rise in neurodevelopmental and neurodegenerative disorders to increased exposure to industrial and environmental chemicals (Grandjean and Landrigan, 2014).

Studies have also identified individuals who are at greater risk of developing ill health following exposure to toxic substances, because of inter-individual differences in the capacity to metabolise and detoxify certain chemicals, hence an individual's response to exposure may be affected by polymorphisms in genes involved in pesticide metabolism (Cherry *et al*, 2002; Mackness *et al,* 2003) which means level of exposure is not the only biologically critical variable.

17.5.3 Developing vs developed countries

Many of the populations included in this review differ in terms of their country of origin. Some of the largest exposure effects were found in studies from developing nations (Amr *et al,* 1997; Farahat *et al*, 2010; Srivastava *et al*, 2000) where daily exposure is not only more frequent and intense, but workers may not receive pesticide safety training or wear suitable protective clothing (Farahat *et al*, 2010). Heat and humidity may alter the characteristics and toxicity of chemical products and influence decisions regarding the use of personnel protective clothing. Linguistic differences and possible illiteracy may mean instructions for use, storage and other health and safety advice is not followed, and economic factors may mean products that have been banned from other countries due to health and safety concerns may still be in use. This is particularly concerning because chemical manufacturing is expected to grow fastest in developing countries over the next five years, making it imperative that workers, employers, government officials and policy makers are educated about the potential risks involved in working with industrial chemicals.

17.5.4 Outcome measures

Although most studies included in this review find individuals with a history of low-level exposure to OPs show evidence of cognitive impairment there is considerable variation in the number and type of deficits identified. This may reflect the wide variety of test batteries administered (see Table 2) which makes direct comparison of study findings from across the world challenging. Even when similar tests have been used across studies, researchers may have different opinions regarding the cognitive domain they represent, for example, Digit Symbol tests have been considered a measure of processing speed, memory and executive function. What is needed is an internationally agreed consensus on which tests or test batteries to use to enable data to be amalgamated and compared, and common effects

identified. The Neurobehavioural Core Test Battery has been proposed by some researchers, but may not detect neurotoxic effects among people with low-levels of education or among diverse cultures (Anger, 1994).

The variety of different methods used to evaluate mental health may also explain the variance in study findings. Many researchers use self-report symptom questionnaires, with differing degrees of sensitivity and specificity and whilst they may be cost-effective for screening purposes in large populations, they appear to overestimate the prevalence of psychiatric conditions in comparison to clinical interviews undertaken by mental health professionals using internationally agreed diagnostic criteria for mental disorders. Furthermore, many of these measures will misclassify people with physical health complaints as having a mental health condition, because they incorporate cognitive and somatic symptoms in addition to the psychic manifestations of emotional distress. For example, symptom checklists for depression often include irritability, difficulty concentrating, indecision, sleep disturbance, lack of energy and fatigue; while anxiety measures include references to numbness, tingling, dizziness, palpitations and breathing difficulties. These symptoms are often reported by individuals who have been exposed to OPs (e.g. Ahmed & Davies 1997; Mackenzie Ross *et al*, 2007; Tahmaz *et al*, 2003), making it difficult to know whether they are truly psychiatric in nature; or whether they are non-psychiatric effects of exposure. Future research exploring this issue should aim to use more objective diagnostic measures; and modern imaging techniques such as PET scans and MRI diffuse tensor imaging and fMRI may be a useful addition to future study designs.

17.5.5 Confounds

Most of the studies included in this review compared the performance of exposure and unexposed individuals on neurobehavioural measures and did not always take account of all of the factors that might affect the outcomes of both cognitive testing and mood measures such as age, gender, years of education, alcohol and drug consumption, and stressful life events; so unless these factors are controlled for (either by matching the exposed and non-exposed groups, or by factoring out their effects as part of the analyses, e.g. as covariates) firm conclusions regarding causation cannot be drawn. Many studies failed to consider the possible confounding effects of mood disorder or other health-related factors (e.g. pain and fatigue) known to effect performance on cognitive tests. Those that have (e.g. Mackenzie Ross *et al*, 2010), found evidence of cognitive impairment in exposed cohorts, even after controlling for the effects of mood. Researchers also need to ensure they do not control for too many potentially confounding variables at once, as some may be inextricably linked to exposure variables (e.g. age) and statistical control of multiple variables may reduce the likelihood of finding meaningful associations between exposure metrics and neurobehavioural test performance.

17.6 Conclusions

The literature regarding the impact of long-term, low-level exposure to OPs on neurobehavioural functioning in adult populations is often described as equivocal, but recent systematic reviews of the literature find the majority of well-designed studies report a significant association between long-term, low-level exposure to OP pesticides and impaired neurobehavioural function. Cognitive functions such as memory, attention, and psychomotor speed, appear to be particularly vulnerable to the neurotoxic effects of OPs; and individuals

with a history of low-level exposure appear to be at increased risk of developing a mental health condition (particularly anxiety). Thus, it seems reasonable to conclude that long-term, low-level exposure to OPs can have an adverse effect on neurobehavioural function. However, research in this area faces a number of methodological challenges, and several questions remain unanswered. Future research will need to address these issues, including the following points. Identifying the critical exposure variables, and obtaining more precise information about dose-response relationships and the time course over which neurobehavioural problems may develop. Level of exposure is frequently assumed to be the only biologically critical variable, but this review has identified several other variables that may influence toxicity, which need to be evaluated. More rigorous selection of study participants is needed to ensure the human health risks of exposure to OPs are not overestimated by accidental inclusion of individuals with a history of acute poisoning. The profile of cognitive and emotional sequelae needs further elucidation and could be expedited if researchers could agree on which tests to use; and modern imaging techniques may be a useful addition to future study designs. When reviewing the literature on the neurotoxicity of OPs, studies should be grouped according to the populations studied, their countries of origin and the age of participants as some populations appear more vulnerable to the neurotoxic effects of OPs. Finally, researchers need to investigate the long-term prognosis of those who report ill health following exposure to OPs and determine whether there are any treatment protocols that could ameliorate their symptoms.

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Table 1. Summary of studies investigating neurobehavioural function following low-level exposure to organophosphates

Author	Study Number	Research Question	Design	Participants (Exposed/Referent)	Job Title	Developed/ Developing	Exposure Measures	Sig Effect?	Summary of Findings
Rodnitzky et al 1975	1	NB changes following chronic exposure to OPs	Group comparisons	23 (12 farmers; 11 applicators)/23 not exposed in last 2 weeks only	Pesticide Applicators	Developed (USA)	EHQ, AChE	no	No significant differences between groups on cognitive tests; AChE within normal limits, but slightly lower in applicators than controls.
Maizlish et al 1987	2	NB effects of chronic exposure over a single work shift	Pre/Post& Group comparisons	46/56	Pesticide Applicators	Developed (USA)	Urinary metabolites	no/yes	No negative exposure-related changes in pre/post performance on NB tests. But performance on Symbol-Digit was poorer in exposed group overall.
Daniell et al 1992	3	NB effects of chronic exposure over a season of spraying (~6 months)	Pre/Post & Group comparisons	49/40	Fruit Tree Sprayers	Developed (USA)	EHQ, AChE	no/yes	Authors claim no significant decrements in performance were found. But, significantly poorer performance found in applicators on Symbol-Digit when baseline scores taken into account.
Ames et al 1995	4	LTLL exposure to OPs and NB function; does prevention of acute poisoning prevent chronic ill health	Group comparisons	45/90	Pesticide Applicators	Developed (USA)	Clinical records	no	No group differences. Authors conclude preventing acute poisoning prevents chronic sequelae.
Stephens et al 1995*	5	LTLL exposure to OPs & NB function	Group comparisons	146/143	Sheep Dippers	Developed (UK)	EHQ	yes	Farmers slower than controls on all timed tests, impaired attention but memory intact. Farmers with the highest exposure level performed worst on syntactic reasoning (even after controlling for covariates). Farmers were 50% more vulnerable to psychiatric disorder.
Fiedler et al 1997*	6	Effect of LTLL exposure to OPs on NB function	Group comparisons	27/42	Fruit Tree Sprayers	Developed (USA)	EHQ	yes: cog no: mood	Fruit farmers had slower simple RT than controls. Within farmers higher related to slower RT. No differences on mood.

Cole et al 1997*	7	Compared NB performance of farm and non-farm members	Group comparisons	Farm members: 23 consumers, 28 exposed, 123 applicators/72	Farm Members	Developing (Equador)	EHQ, AChE	yes: cog no: mood	Evidence of detrimental performance on visual-spatial tasks, language and attention tasks. No differences on mood scores.
London et al 1997	8	Associations between LTLL exposure and adverse effects on vibration sense and NB function	Group comparisons & correlational	163/84	Fruit Tree Sprayers	Developing (South Africa)	EHQ, BuChE	yes	Small associations found between exposure and Pursuit-Aiming and the Santa Ana (nondominant-hand) subtest.
Bazylewicz-Walczak et al 1999*	9	Behavioural effects of chronic exposure to OPs	Group comparisons & Pre/Post	26/25	Greehouse Workers	Developed (Poland)	Air and clothing concentrations	yes	No change in performance on NB tests pre/post season, but exposure group showed impaired perceptuomotor function and increased anxiety, depression, irritability, fatigue and memory problems on both occasions suggesting cumulative exposure affects NB function more than a single exposure episode.
Steenland et al 2000*	10	Chronic neurological effects of OP exposure	Group comparisons	191/189	Pest Control	Developed (USA)	EHQ, PON1, Urinary metabolites	no: cog yes: mood	Exposed group reported more problems with memory, anxiety, fatigue and strength but few differences on cognitive tests. Exposed group showed impairment on pegboard turning and some postural sway tests but were similar to controls on the other measures. 8 subjects who were acutely exposed had impaired reaction time and continuous performance.
Srivastava et al 2000	11	Health risks associated with the manufacture of OP	Group comparisons	59/17	Manufacturers	Developing (India)	EHQ, AChE	yes	Similar AChE levels in both groups, but exposed had altered reflexes and neurobehavioural deficits, i.e. lower scores on digit span, digit symbol & vigilance task.

Salvi et al 2003**	12	NB outcomes after 3 months with and without OP exposure	Pre/Post	37/25	Tobacco Workers	Developing (Brazil)	EHQ, AChE	no: cog yes: mood	AChE levels normal for exposed cohort. No difference between groups on cognitive tests. But higher anxiety and depression rates following recent exposure.
Stephens & Sreenivasan 2004	13	Effect of LTLL exposure to OPs on NB function	Group comparisons	37 orchard sprayers/26 pig farmers/31 construction workers	Fruit Tree Sprayers	Developed (UK)	EHQ	yes	Orchard workers slower on syntactic reasoning than controls but no relationship with exposure index.
Roldan-Tapia et al 2005*	14	Continuous exposure to OPs (subsymtomatic) and NB effects	Group comparisons	40/26	Greehouse Workers	Developed (Spain)	BuChE, EHQ	yes	Association between cumulative exposure and lower performance on verbal memory, visual memory and increased anxiety. Those exposed for more than 10 years also have lower scores on tests of visuo-spatial ability.
Farahat et al 2005	15	NB effects of pesticide exposure	Group comparisons	52/50	Pesticide Applicators (PA)	Developing (Egypt)	EHQ, AChE	yes	PA performed worse than controls on similarities, tests of attention, visual memory and RT, but this did not correlate with AChE levels (so not due to recent exposure) but did correlate with lifetime exposure.
Roldan-Tapia et al 2006*	16	Association between different levels of exposure to OPs & NB function	Group comparisons	24 acute/40 chronic/26 controls	Greenhouse Workers	Developed (Spain)	BuChE, EHQ	yes	Exposed had reduced visuo-motor, perceptual & constructive abilities, verbal learning, processing speed and increased anxiety. Acutely exposed and those exposed for > 10yrs had similar profile of deficits. Those exposed for <10yrs had similar profiles to controls.
Mackenzie Ross et al 2007*	17	Nature & extent of NB problems in farmers who report chronic ill health	Group comparisons	25/22	Sheep Dippers	Developed (UK)	EHQ	yes	Exposed had lower scores on tests of mental flexibility, verbal memory; 72% reported anxiety and 76% depression (significantly more than the controls).

Mackenzie Ross et al 2010*	18	Does LTLL exposure to OPs cause ill health (NB problems) in sheep farmers	Group comparisons	127/78	Sheep Dippers	Developed (UK)	EHQ, PON1	yes	Exposure group performed poorer on tests of response speed, working, verbal and visual memory, mental flexibility and fine motor control; and reported higher levels of anxiety and depression.
Rothlein et al 2006	19	Relationship between LL exposure and NB performance	Group comparisons & correlational	92/45	Farm Workers	Developed (USA)	EHQ, Urinary metabolites , dust samples	yes	Higher metabolites associated with poorer performance on digit symbol, a selective attention task, finger tapping and continuous performance. Lower backward digit span in exposed group, and finger tapping for females
Starks et al 2012	20	Relationship between high pesticide exposure events (without acute toxicity) and NB outcomes	Group comparisons & correlational	156 HPEE/537 No HPEE	Pesticide Applicators	Developed (USA)	EHQ	yes	History of HPEE (without acute toxicity) was associated with poorer performance on digit-symbol substitution and Sequences A. No effects were observed on any of the other neuropsychological tests. NB - all participants in the study were pesticide applicators, so all have exposure.
Malekirad et al 2013*	21	OP effects on neurocognitive impairment and health status	Group comparisons	187/187	Horticultural workers	Developing (Iran)	EHQ	yes	Exposed group showed significantly poorer psychomotor speed, attention, verbal memory, nonverbal memory, prospective memory, spatial functioning, and initiative/energy; and had higher anxiety and depression scores.
Berent et al 2014*	22	Compare NB function of exposed and non-exposed workers over 1 year period	Group comparisons & Longitudinal	53/60	Chemical factory workers	Developed (USA)	BuCHE, AChE and Urinary	no	Exposed group performed better than controls on verbal memory. No other differences found.

AChE–acetylcholinesterase; BuCHE–butyrylcholinesterase; cog-cognitive tests; HPEE-high pesticide exposure events; LTLL–long-term low-level; EHQ–Exposure History Questionnaire; PON1–serum paraoxonase/arylesterase; NB–neurobehavioural; RT–response time; * included self-report measures of psychiatric function (most commonly mood, anxiety or depression); ** investigated mood disorder using clinical diagnostic interviews.

Table 2: Summary of the study measures used to assess the different cognitive domains

Cognitive domain	**Neuropsychological Measures**	**Study No.**
Attention	Continuous Performance	2,3,8,10,20
	Digit Vigilance	7
	Rapid Visual Information Processing	22
	Selective Attention Trials	19
	Sustained Attention	4
	Vigilance Task	11
Executive Function/Mental Flexibility/Inhibition	CALCAP (Choice)	18
	Category Search	5,13
	Sequences B	20
	Similarities	7,15,17,18
	Stockings of Cambridge	22
	Stroop	6,17,18
	Syntactic Reasoning	5,13
	Trails B	6,7,15,17,18
Working Memory	Arithmetic (WAIS)	17
	Digit Span (Backwards)	4-9,11,14-19
	Letter Number Sequencing	17
	Manipulating Numbers	8
	Paced Auditory Serial Addition Test	15
	WMS (Working Memory Subtests)	18
Processing Speed	CALCAP (Simple)	18
	Digit Symbol/Symbol digit	2-11,14-18,20
	Inspection Time	8
	Letter Cancel	15
	Reaction Time (Simple)	1,4-10,13,14,16,19,22
	Sequences A	20
	Trails A	6,7,15,17,18
Verbal Memory	Associate Learning and Recall	10
	Auditory Verbal Learning Test	20
	California Verbal Learning Test	6
	CogniSyst Story Recall Test	22
	Digit Span (Forward)	4-9,11,14-19
	Sentence Repetition	1
	Serial Digit	10,19
	Short-Term Memory Scanning	8
	Story Recall	15
	Verbal Recall	1
	WMS (Verbal Subtests)	18
	Word Learning	5,13
	Word Span	12

Cognitive domain	Neuropsychological Measures	Study No.
Verbal Abilities/Verbal Reasoning/Language Skills	Comprehension (WAIS)	17,18
	Graded Naming	6,18
	Information (WAIS)	6,7,17,18
	National Adult Reading Test	17
	Picture Completion	17
	Pointing and Speaking Arrows	8
	Semantic Fluency	6
	Token Test	6
	Verbal Fluency	17
	Vocabulary (WAIS)	7,17,18
Visual Memory	AMIPB	17
	Benton Visual Retention Test	7-10,14,16
	Face Recognition	17
	Matching to Sample	22
	Pattern Memory	2-4,10
	Visual memory	5,13
	WMS Visual Subtests	6,18
Visuo-motor abilities/ coordination/fine motor control	Finger Tapping	3,4,10,19,20
	Grooved Pegboard	6,18,20
	Hand–eye Coordination Task	2-4,6
	Motor Performance Series	22
	Proprioception	1
	Pursuit Aiming	4,7-9,14,16
	Santa Ana Pegboard	4,7-9,14,16
Visuoperception/visual spatial skills	Benton Visual Form Discrimination	15
	Block Design (WAIS)	7,15,17,18
	Line Orientation	17
	Pattern Comparison	2,10
	Symbol Search	17
General IQ or Aptitude	Armed Forces Qualifying Test	2
	Matrix Reasoning	17
	MMSE	12
	WAIS-III	18
	WAIS-R	17
	Wide Range Achievement Test	6,22
Other, subjective measures	Subjective Neurocognition Inventory	21
	Symptoms Questionniare	9,14,16

Cognitive domain	Neuropsychological Measures	Study No.
Mood	Profile of Mood States	7,9,10,14,16
	Hospital Anxiety & Depression Scale	17,18
	Neuropsychiatric Interview	12
	MMPI-2	6
	General Health Questionnaire	5,21
	Brief Symptom Inventory	22

CALCAP-California Computerized Assessment Package; MMPI-2-Minnesota Multiphasic Personality Inventory-2; MMSE-Mini Mental State Examiniation; WAIS-Wechsler Adult Intelligence Scale; WMS-Wechsler Memory Scale; For further information about the psychometric tests in this table see Lezak et al, 2012 and Strauss et al, 2006.