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

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ABSTRACT

The study aim was to determine whether low level exposure to organophosphate pesticides (OPs) causes neuropsychological or psychiatric impairment. Methodological weaknesses of earlier studies were addressed by: recruiting participants who had retired on ill health grounds; excluding participants with a history of acute poisoning, medical or psychiatric conditions that might account for ill health; and exploring factors which may render some individuals more vulnerable to the effects of OPs than others. Performance on tests of cognition and mood of 127 exposed sheep farmers (67 working, 60 retired) was compared with 78 unexposed controls (38 working, 40 retired) and published test norms derived from a cross section of several thousand adults in the general population. Over 40% of the exposed cohort reported clinically significant levels of anxiety and depression compared to less than 23% of controls. Exposed subjects performed significantly worse than controls and standardisation samples on tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for the effects of mood. The pattern was similar for both working and retired groups. The cognitive deficits identified cannot be attributed to mood disorder, malingering, a history of acute exposure or genetic vulnerability in terms of $PON1_{192}$ polymorphisms. Results suggest a relationship may exist between low level exposure to organophosphates and impaired neurobehavioural functioning and these findings have implications for working practice and for other occupational groups exposed to OPs such as aviation workers and Gulf War veterans.

1. Introduction

Organophosphates (OPs) are the most widely used group of pesticides and insecticides in the world and are used for a variety of agricultural and domestic purposes. They are also used by industry as solvents, plasticizers, flame retardants and extreme pressure additives (e.g. lubricants) and by the military as pesticides and nerve agents. This means that a very large number of people will be exposed to these chemicals in some form, during their lifetime. OPs are one of the most common causes of poisoning worldwide [40] and questions have been raised about the long term effects these chemicals may have on human health. The immediate effects of high-level exposure to OPs have been well documented and involve inhibition of the enzyme acetylcholinesterase, causing changes in peripheral, autonomic and central nervous system function (cholinergic crisis). However, the effects of long-term low-level exposure to OPs are less clear [8].

A number of occupational groups are exposed to organophosphates on a regular basis (e.g. agricultural workers, horticulturists, pest control operators, chemical plant workers, military personnel and aviation workers) and many individuals complain of chronic ill health following exposure to OPs. For example, a high incidence of physical and psychological symptoms have been reported by commercial airline pilots and cabin crew exposed to OPs in engine oil fumes [19], Gulf War veterans exposed to OP pesticides [26], and sheep farmers who use OP pesticides [1,7,11,12,15,17,20,32,36,37].

Although evidence exists to support the view that high level/acute OP poisoning can cause ill health, the possibility that long-term low-level exposure to OPs in doses below that causing acute toxicity causes ill health is controversial [8]. Previous research has produced inconsistent findings, with some studies finding evidence of ill health and cognitive impairment following low level organophosphate exposure [6,13,14,20,30,34–36] while others have not [2,3,9,17,18]. Methodological differences may account for these inconsistencies, such as examination of different occupational groups with different levels and routes of exposure, use of protective clothing, differences in cultural backgrounds, and different time periods of examination (e.g. following a single episode of exposure, several years of exposure or over a lifetime). Results are easier to interpret and appear more consistent when studies are grouped by design, occupational group, country and time frame of analysis, enabling like to be compared with like.

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The purpose of the present study was to determine whether long-term, low level exposure to OPs causes ill health in UK sheep farmers because OPs were used routinely following the introduction of compulsory sheep dipping by the British Government in 1976 until 1992. A number of studies of UK sheep farmers appear in the literature utilising different methodologies including case-series analyses, postal questionnaire surveys and clinical evaluations. Different outcomes have been explored including self-reported symptoms of ill health, neurological abnormalities, genetic polymorphisms which influence OP metabolism, and neuropsychological abnormalities. All but one study [17] suggest a link between exposure to sheep dip and the development of ill health and neurobehavioural problems. For example, Ahmed and Davies [1], Davies, Ahmed and Freer [11], Dunn [12], Tahmaz, Soutar and Cherrie [37] and Solomon et al. [32] looked at the incidence and/or nature of self-reported symptoms among different groups of sheep farmers and found that neuropsychiatric symptoms were common in past users of sheep dip.

Beach et al. [5] and Pilkington et al. [24] looked at abnormalities on neurological examination among sheep farmers and found an association between exposure to sheep dip and neurological symptoms such as neuropathy and reduced sensory discrimination.

Cherry et al. [7], Mackness et al. [21] and Povey et al. [25] investigated whether genetic differences in the ability to metabolise OPs rendered some individuals at greater risk of developing ill health following exposure to sheep dip than others. Human serum paraoxonase 1 (PON1) hydrolyzes and detoxifies a number of OPs, including diazinon, one of the most prevalent OP compounds in sheep dip. All three research groups found PON1 polymorphisms in UK sheep farmers who complain of ill health and conclude that OPs contribute to the self-reported ill health of sheep dippers.

Stephens et al. [36] and Mackenzie Ross et al. [20] found sheep farmers performed more poorly than controls on specific cognitive tests. Stephens et al. compared 146 sheep farmers exposed to OPs in sheep dip with 143 unexposed controls (quarry workers) on neuropsychological tests. The farmers performed significantly worse than controls on tests of sustained attention, syntactic reasoning and speed of information processing; and showed greater vulnerability to psychiatric disorder. Memory functioning appeared intact. However, they provided little information about exposure history and only included participants who were fit enough to be in employment at the time of investigation. They did not allow for the fact that individuals with disabling disease may have retired from work. Mackenzie Ross et al. compared 25 farm workers with a history of apparent low level exposure to sheep dip with 22 non-exposed healthy volunteers on neuropsychological tests. Two thirds of farm workers had retired or reduced their workload on ill health grounds and all were involved in litigation. They performed significantly worse than non-exposed healthy volunteers on tests of mental flexibility, response speed and memory; and over 70% suffered from mood disorder. Although this study included participants who had retired on ill health grounds, the sample size was small and self-selected making it unclear how representative they are of the farming community as a whole. Furthermore, many farm workers appeared to have a history of undiagnosed acute poisoning.

The only study of neuropsychological function in UK sheep farmers exposed to OP pesticides which did not find objective evidence of neurobehavioural impairment, was that reported by Jamal et al. [17]. These authors compared three groups of sheep farmers according to whether they had signs of peripheral neuropathy ('no', 'possible' and 'probable/definite' signs) and their performance on neuropsychological tests was related to these groupings. Farmers in the probable/definite group reported more symptoms of emotional distress (anxiety and depression) and showed evidence of reduced processing speed, but no other consistent differences between the groups were found on any of the other neuropsychological measures. The authors conclude that whatever factor was responsible for causing peripheral neuropathy did not cause cognitive impairment. Exposure history was not specified or used as a variable in the analysis and the authors acknowledge that their sample size was too small to allow a meaningful analysis of the relationship between cognitive function and exposure history.

Although the vast majority of earlier studies suggest a link between exposure to sheep dip and the development of neurobehavioural problems, it is unclear whether this is due to a history of acute poisoning or a result of cumulative low level exposure. The present study addresses the methodological weaknesses of earlier studies and sought to determine whether low level exposure to OPs is associated with neuropsychological and psychiatric impairment in UK sheep farmers. Past medical and psychiatric history were taken into account to exclude other possible causes of ill health. This study is the first clinical study to recruit participants who have retired on ill health grounds and to determine in the same cohort of farmers whether variability in PON1 status (plasma level and position 192 functional genotype) renders some individuals more vulnerable to the effects of OPs than others. Participants were expected to show a similar pattern of deficits as that reported by Stephens et al. [36] and Mackenzie Ross et al. [20]. They are hypothesised to show deficits on tests of working and general memory, response speed and mental flexibility with preserved reasoning and general intellectual functioning.

2. Method

2.1. Ethical approval

Ethical approval for this study was granted by the joint University College London (UCL)/UCL Hospital Committee A and by the University of Washington Human Subjects Committee. Written informed consent was provided by all study participants.

2.2. Study design and participants

This study compared the performance of 127 sheep farmers (67 working, 60 retired) to 78 controls (38 working, 40 retired) on measures of cognitive function and mood state. Finding a group of farmers in the UK who do not have a history of exposure to OPs is almost impossible and it was necessary to identify an alternative occupational group that could act as controls. Rural police workers were chosen.

The focus of the project was restricted to the North and South West regions of England which have the highest number of sheep farmers in the UK. Recruitment of the exposed cohort involved writing to farm owners listed on relevant databases (e.g. UK National Business Directory, National Farmers Union membership lists); and telephoning every fifth person on lists held by the Wool Marketing Board. A total of 393 farmers were contacted by telephone and invited to take part and the response rate was 59%. Additionally, some farmers were recruited through advertising or replying to articles in the media.

Controls were recruited by enlisting the help of local constabularies and the National Association of Retired Police Officers (NARPO) who contacted their members by email or newsletter to provide details of our study. Our study was also advertised in Police Press.

Initially 434 farmers came forward (222 retired, 212 working) and 252 police (170 retired, 82 working), however 67% of the farmers and 63% of the controls had to be excluded based on the inclusion/exclusion criteria (Table 1). A further 17 farmers and 4 controls were excluded to in order to establish similar demographic profiles between the groups; 5 farmers' and 1 policeman's data were excluded because they showed evidence of poor effort/malingering on a psychometric test which is insensitive to severe brain injury but which is greatly affected by effort [16].

2.2.1. Exclusion criteria

To ensure that any cognitive and emotional problems identified in this study relate to OP exposure, it was important to exclude individuals