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Anxiety and depression following cumulative low-level exposure to organophosphate pesticides

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ABSTRACT

Previous research suggests that individuals with a prior history of pesticide poisoning are at increased risk of psychiatric disorder (Freire and Koifman, 2013), but findings regarding the impact of cumulative low-level exposure are inconsistent. The aim of the current study was to investigate whether sheep farmers with a history of low-level exposure to organophosphate pesticides (1) report a higher level of psychological distress on subjective symptom questionnaires, compared to unexposed controls (2) also meet internationally agreed diagnostic criteria for a psychiatric disorder more often than unexposed controls. 127sheep farmers were evaluated and compared to 78 unexposed controls, matched in terms of gender, education, level of intelligence, working status and area of residence. Both self-report measures and structured clinical interviews were used to assess mental health. The exposed cohort reported significantly higher rates of anxiety and depression when self-report questionnaires were used to evaluate mood, even when stressful life events, demographic and physical health factors were taken into account. However, when diagnostic interviews were used to assess mood, this pattern only held true for anxiety.

1. Introduction

Anxiety and depression are common mental health conditions affecting millions of people around the world. The Psychiatric Morbidity Survey in 2007 estimated 2.28 million people in the UK were suffering from anxiety disorders and 1.24 million people were suffering from depression (McManus et al., 2009). These figures are projected to rise over the next two decades (McCrone et al., 2008). A number of factors have been implicated in the onset and course of these conditions including biological, psychological and social factors. The rate of depression seen in women from western industrialised nations is twice that of men (Patel, 2005) and the reason for this disparity has been much debated. Additionally, individuals who are unemployed, of low socio-economic status, or who have suffered stressful life events are thought to be at increased risk of developing depression (Brown and Harris, 1978, 1986). Disturbances in neurotransmitter functioning and genetic factors have also been implicated in the aetiology of anxiety disorders and depression (Marchand et al., 2005).

Epidemiological studies have also reported higher incidences of anxiety and depression in particular groups of individuals such as those with chronic health conditions (NICE, 2009) and individuals in specific occupations. With regard to the latter, Roberts and Lee (1993) found the highest incidence of depression in farming, fishing and forestry occupations. This was confirmed by a study by Sanne et al. (2003) who found male agricultural workers had the highest incidence of anxiety and depression compared to other occupational groups. Additionally, Gregoire (2002) found farmers account for the largest number of suicides amongst other occupational groups in the United Kingdom (UK) and that suicide is the second most common cause of death in UK farmers after accidents.

The reason behind the elevated risk of mood disorder in farming populations is unclear. Some researchers have reported a link between exposure to pesticides, mood disorder and suicidal behaviour (e.g. Amr et al., 1997; Beard et al., 2011, 2014; Beseler and Stallones, 2008; Lee et al. 2007; Levin et al. 1976; Mackenzie Ross et al., 2010; Meyer et al., 2010; Parron et al. 1996; Roldan-Tapia et al., 2006; Salvi et al., 2003; Stallones, 2006; Steenland et al., 2000; Stephens et al., 1995; Van Wijngaarden 2003; Zhang et al. 2009). Organophosphate pesticides (OPs) in particular are associated with an elevated risk of neuropsychiatric disorder (e.g. Wesseling et al., 2010). They are the most widely used group of pesticides in the world and are considered by the World Health Organisation (WHO) to be one of the most hazardous pesticides to vertebrate animals, responsible for many cases of poisoning worldwide, particularly in developing countries where protective

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measures are lacking (WHO Report, 1990; De Silva et al., 2006). The neurotoxic effects of high level acute poisoning are well established and involve inhibition of the enzyme acetylcholinesterase (AChE) causing changes in peripheral, autonomic and central nervous system function (the cholinergic crisis) resulting in a constellation of physical, cognitive and psychiatric symptoms. However, OPs disrupt many other neurotransmitters and some of these are involved in mood regulation such as serotonin (Aldridge et al., 2006). This could explain the link between pesticide exposure and mood disorder observed in earlier studies.

This association appears strongest in individuals who report previous instances of acute poisonings (Beseler and Stallones, 2008; Beseler et al., 2006, 2008). However, the impact of long-term low-level exposure to OPs (in doses below that causing acute toxicity) on human health is less clear. Some studies have found evidence of ill health, mood disorder and cognitive impairment following low-level exposure to OPs whilst others have not (see reviews by Freire and Koifman, 2013; Mackenzie Ross et al., 2013). These inconsistencies may be the result of methodological differences that exist between the different studies in this field. For example, studies investigating this issue have used a plethora of different methods to explore the role of exposure, investigating different occupational groups with differing levels of contact with OPs, routes and nature of exposure, use of protective clothing, demographic and geographic profiles, and over a wide variety of time frames. What's more, they tend to use different definitions and measures of exposure, further complicated by the fact that there is currently no consensus in the literature over what constitutes acute or chronic exposure. Finally, objective measures of exposure are seldom available making it difficult to establish clear dose-response relationships.

Difficulties also exist when it comes to measuring mood. Methods that have been used to assess the presence of mood disorder in OP exposed populations range from simply asking participants whether or not they have ever been diagnosed with depression/anxiety by a physician (e.g. Beard et al., 2014) to asking participants to complete standardised symptom questionnaires with differing degrees of sensitivity and specificity (e.g. Ames et al., 1995; Farahat et al., 2003; Jamal et al., 2002; Mackenzie Ross et al., 2007, 2010; Roldan-Tapia et al., 2006; Stallones and Beseler, 2002a; Steenland et al., 2000; Stephens et al., 1995). Although self-report measures may be useful for screening purposes in large populations, it is not always clear whether findings are comparable with what would be derived from structured clinical interviews undertaken by mental health professionals using internationally agreed diagnostic criteria for mental disorders. Indeed, previous research with other patient cohorts (including multiple sclerosis, cancer, cardiomyopathy, hepatitis C) has shown that self-report measures may not be good indictors of psychiatric disorder (Golden et al., 2007; Mitchell et al., 2010; Poole et al., 2006; Watson et al., 2014), and a recent study suggests this may be particularly true for research with OP exposed groups (Harrison and Mackenzie Ross, In preparation). Structured interviews standardise the coverage of specific psychiatric issues (thus reducing the possibility of missed diagnoses) and require the systematic appraisal of relevant symptoms, to reduce misdiagnosis. As such, clinical interviews are considered the 'gold standard' for diagnosis.

In the last two decades, only two published studies report evaluations of OP exposed participants using strict diagnostic criteria. First, Amr et al. (1997) examined 208 Egyptian pesticide formulators, 172 pesticide applicators and 223 control subjects. All underwent a full psychiatric interview and diagnoses were made in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-III-R). Psychiatric disorders were found to be more common in exposed subjects, particularly depression and dysthymic disorder. However, as the authors did not collect in-depth information about participants' exposure history, it is impossible to determine whether this is a related to long-term low-level exposure, as the possibility of historic acute poisonings cannot be ruled out.

Second, Salvi et al. (2003) assessed 37 tobacco workers from Brazil who had been exposed to organophosphate pesticides, evaluating them shortly after exposure and then again, following 3 months without exposure. Diagnoses were made in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-IV). Almost half of the sample was found to be suffering from a psychiatric disorder (mostly anxiety and depression) when first interviewed, but after 3 months of not using pesticides, the rate of mental disorder had dropped by nearly 50% suggesting a strong association between mental health and exposure to pesticides. However, as this study used a pre/post exposure study design over a relatively short time frame, it is not possible to tell whether *long-term*, low-level exposure to OPs causes ill health; or how these symptoms may persist. Furthermore, participants with past episodes of acute toxicity may have been included in this study, as exposure screening only took into account the previous 12 months.

Another problem inherent in earlier work has been the failure to take account of possible confounding variables that may be involved in the aetiology of psychiatric symptoms when assessing exposed cohorts. For example, farming is a stressful and physically demanding occupation and some researchers argue that socio-economic and psychosocial factors are to blame for the elevated rates of psychological distress observed in this occupational group (Beard et al., 2011; Deary et al., 1997; Pickett et al., 1998; Simkin et al., 1998). Previous research reporting associations between exposure to pesticides and psychiatric illness have often failed to take these issues into account, and lack detailed evaluations of participants' psychiatric history and background making it difficult to determine whether psychosocial or toxicological factors are involved in the aetiology of farmers' mental health complaints. What's more the effect of participants' physical health is rarely considered, despite poor health being a risk factor for mood disorder result (NICE, 2009). Many studies simply compare rates of anxiety and depression in exposed and unexposed populations (e.g. Ames et al., 1995; Bazylewicz-Walczak et al., 1999; Farahat et al., 2003; Jamal et al., 2002; Reidy et al., 1992; Roldan-Tapia et al., 2006; Steenland et al., 2000; Stephens et al., 1995).

An exception is the work of Stallones and Beseler and colleagues (Stallones and Beseler, 2002a; 2002b; Beseler et al., 2006, 2008) in which the influence of demographic factors such as age, gender, marital status, alcohol use, health status and financial difficulties (known risk factors for depression) were explored in addition to pesticide exposure. They found higher rates of depression in individuals with a history of pesticide poisoning, even after adjustments were made for other risk factors. Pesticide poisoning was more strongly associated with depression than lower levels of exposure. However, they also found a relationship between high cumulative exposure and depression in a subgroup of individuals who did not have a history of acute poisoning.

In 2010 we published the findings of a cross-sectional study of 127 UK sheep farmers which sought to determine the neurotoxicity of low-level exposure to OPs. We examined sheep farmers who had been repeatedly exposed to low levels of OPs during the process of sheep dipping (Mackenzie Ross et al., 2010). Neuropsychological assessment found exposed subjects performed significantly worse than matched controls and standardisation samples on tests of memory, response speed, fine motor control, mental flexibility and strategy making, even after controlling for covariates. In addition, more than 40% of study participants reported via questionnaire that they were suffering from significant levels of anxiety and depression compared to less than 23% of