Chronic Fatigue and Organophosphate Pesticides in Sheep Farming: A Retrospective Study Amongst People Reporting to a UK Pharmacovigilance Scheme

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The Department of Health has recently published a report from the CFS/ME Working Group which concluded that chronic fatigue syndrome (CFS) should be recognized as a chronic illness. Symptoms consistent with CFS are often reported by people who consider their health has been affected by exposure to pesticides, but the Working Group concluded that this type of exposure is not a common trigger for the syndrome. The Veterinary Medicines Directorate (VMD) collects self-assessed reports of ill health in humans associated with veterinary medicines under their Suspected Adverse Reaction Surveillance Scheme. The reporters have mainly been sheep farmers. These reports were used to investigate the possible relationship between chronic fatigue (CF) and exposure to organophosphate pesticides in sheep farming. The overall aim of the study was to investigate a possible association between exposure to organophosphates and the development of CF amongst people who consider their health has been affected by pesticides in sheep farming. The hypothesis investigated was that repeated exposure to organophosphate pesticides in sheep dip may increase the probability of developing CF. A group of mostly sheep farmers who had reported to the VMD surveillance scheme were identified. We planned to use a retrospective case–control study design but the initial symptoms reports were not sufficiently reliable to enable this. The study population was asked to complete two questionnaires. The first questionnaire was designed to identify the history of exposure of subjects to organophosphate pesticides, and their exposure was then reconstructed using a metric specifically developed for this purpose. The second questionnaire collected detailed information to identify whether the subjects had CF when they originally reported to the VMD and at the time of the survey. The questionnaire was sent to a total of 206 subjects, of whom 28 had moved home. A total of 37% of the remaining 178 subjects participated. There was a high prevalence of CF amongst those who completed the questionnaire and this has generally persisted since the subjects reported to the VMD. Higher CF scores were associated with higher exposure to organophosphate pesticides. CF is very common amongst those who consider their health was affected by pesticides and we have shown there is limited evidence of an association between exposure to organophosphates and CF. Further research is needed to investigate the cause of this syndrome amongst farmers exposed to pesticides.

Keywords: chronic fatigue syndrome; dermal exposure; organophosphate pesticides; sheep farming

INTRODUCTION

On the 17 January 2002 the Department of Health published a report from the CFS/ME Working Group in which they concluded that there should be no doubt that chronic fatigue syndrome (CFS) is a chronic illness and that the health and social care professionals should recognize it as such (CFS/ME Working Group, 2002). Although they could not identify a clear etiology and pathogenesis of the syndrome, they suggested a number of possible predisposing factors and triggers, including infections and environmental toxins such as organophosphate compounds. However, the Working Group considered that exposure to pesticides was not a...
common cause of CFS. The main characterizing features of CFS are overwhelming fatigue, related effects on both physical and cognitive functioning and malaise, typically exacerbated after physical or mental exertion. Common symptoms include persistent and excessive tiredness or fatigue, cognitive impairment, post-exertional malaise, pain, sleep disturbance, recurrent sore throat, digestive disturbances, intolerance to alcohol, medicines or foods and other symptoms related to the neurological and/or endocrine systems (CFS/ME Working Group, 2002).

Recent population studies have shown that fatigue is a common symptom associated with modern living. In questionnaire-based community surveys in southern Scotland and southern England, substantial fatigue was reported by ~38% of the respondents (Mounstephen and Sharpe, 1997). A greater or lesser degree of fatigue has been recognized as an inevitable consequence of agricultural work, including sheep farming (Stephens et al., 1995; Beach et al., 1996; Rees, 1996). However, concerns have been expressed that repeated exposure to low levels of organophosphate pesticides over months or years may result in CFS (Stephens et al., 1995).

In the UK, most sheep farmers regularly dip (i.e. totally immerse) all or a proportion of their flock in insecticides to control ectoparasites (scab, blowflies, keds and lice) (Rees, 1996). This is strenuous and dirty work, where it is difficult to avoid skin contamination with the sheep dip. The Veterinary Medicines Directorate (VMD) collects self-assessed reports (SARs) of ill health from farmers who have been exposed to organophosphates while or after being involved in sheep dipping, through their Suspected Adverse Reaction Surveillance Scheme (SARSS). Some reports have been directly contributed by the subject while others are submitted through a third party such as the medicine licence holder. There is no screening of the reports, although they are reviewed by the VMD Appraisal Panel for Human Suspected Adverse Reactions, who have recently identified a number of SARs in which farmers reported three or more symptoms that the panel considered consistent with CFS. The symptoms comprised fatigue, depression, myalgia, headache, arthralgia, disturbance, sore throat, muscle weakness, irritability, pyrexia, memory impairment, sleep disorder, lymphadenopathy, confusion, mental impairment and a reported diagnosis of CFS.

In this study our aim was to investigate a possible association between exposure to organophosphates and the development of chronic fatigue (CF) amongst respondents to the VMD SARSS. We originally planned to carry out a retrospective case–control study using the SARs, with cases having three or more of the identified symptoms and controls with none or one reported symptom. However, we found that the original symptoms reports were an unreliable indicator of CF. We therefore chose to analyse the association between measures of fatigue and exposure to pesticides directly, rather than in a case–control analysis.

**METHODS**

Exposure metric

An exposure metric was developed to estimate the subjects’ dermal exposure to pesticides. This was based on work by Cherrie and Robertson (1995), who proposed a metric for dermal exposure incorporating the concentration of the chemical in the skin contamination layer \( C \) sk, the duration of exposure \( t \) and the area of skin contaminated \( S \). The exposure metric \( E \) sk is obtained by multiplying these terms together:

\[
E_{sk} = C_{sk} \times t_{sk} \times S_{sk}
\]

Theoretically it should be directly related to the mass of the chemical passing through the skin. In this study \( E_{sk} \) is expressed in units of m² days.

The job that the person has undertaken and the length of time he has carried out his job are main determinants of cumulative dermal exposure. The job title will generally determine the long-term average exposure and was used as the main way of estimating the concentration of pesticide in the skin contamination layer and the area of the body exposed. The use of personal protective clothing such as gloves and overalls plays a major role in decreasing the area of skin exposed if used properly. It has been suggested that in the past the equipment may not have been adequate or properly used. We judged that there are six activities carried out by farmers that lead to most exposure: dipping sheep, handling concentrated pesticide, splashing of concentrate while handling concentrate, handling sheep after dipping, inhalation of sheep dip aerosol and falling in the dip bath. The exposure estimate from each of these activities was added together to provide a cumulative exposure estimate, either until the person originally reported to the VMD or to the time of the survey. The first part of the metric, which deals with sheep dipping activity, provides estimates of exposure to the diluted dip, incorporating a protection factor for the personal protective equipment that the subject reported wearing. The second and third parts of the estimate deal with handling and splashing pesticide concentrate. The protection from gloves was separated from the effects of other protective equipment because the concentrate may heavily contaminate the hands while it was expected only to splash on the rest of the body. The fourth and fifth parts of the exposure estimates could have arisen while handling the sheep after dipping and possible inhalation of the dip during dipping. Finally, the sixth part of the estimate dealt

\[E_{sk} = C_{sk} \times t_{sk} \times S_{sk}\]
with whole body exposure from the subject accidentally falling into the dip bath. For convenience we used a relative measure of concentration where the dilute dip was assigned a concentration of unity (i.e. $C_{sk,dip} = 1$) and concentrated pesticide was assigned a concentration of 500 (i.e. $C_{sk,conc} = 500$).

The total surface area of the skin exposed to a contaminant was estimated. The average skin areas ($S_{sk}$) for males and females were taken as 1.94 and 1.69 m², respectively (Health & Safety Executive, 1999). However, in most tasks the total skin area was not exposed because the person may have worn waterproof clothing, gloves or Wellington boots. We judged the area of skin that would have been protected and the efficiency of the protective clothing. The body parts considered to be the most likely to be exposed while sheep dipping were the head, hands, forearms, 50% upper arms, feet, lower legs, 50% of the thighs and 50% of the trunk, including the neck. To estimate the skin area exposed while handling the concentrate, it was assumed that while undertaking the work 25% of the area of the hands could be contaminated, mainly the palms. It was also estimated that an additional 0.1% of the total area of the body, less the palms of the hands, could become contaminated from spills or splashes if the worker was not wearing any type of protective clothing.

We assumed that while dipping, gloves offered 80% protection for 1.5 h on average and, because of the likelihood of being periodically removed, that they would offer no protection thereafter. It was therefore considered that over an 8 h working day gloves would have given ~30% protection (i.e. $\eta_{gloves} = 0.3$). Waterproof overalls, jackets and trousers were all judged to offer ~60% protection per work day (i.e. $\eta_{PPE} = 0.6$). Head covering was assumed to offer 70% protection, face masks 85% protection and Wellington boots 50% protection.

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The exposure from dipping ($E_{sk,dip}$) was estimated using equation (3):

$$E_{sk,dip} = C_{sk,dip} \times t_{dip} \times S_{sk} \times (1 - R_{PPE} \times \eta_{PPE})$$

where $t_{dip}$ was the time spent dipping, either up to reporting to the VMD or until the time the questionnaire was completed and $R_{PPE}$ was the ratio of the skin area covered by protective clothing to the area of the skin in that body part, e.g. legs or torso.

The exposure from handling concentrate was calculated using equation (4), which is made up of one part for contact between the hands and contaminated objects and a second part from splashing.

$$E_{sk,conc} = C_{sk,conc} \times t_{conc} \times \left[ S_{sk,hand} \times (1 - \eta_{gloves}) + S_{sk,splash} \times (1 - R_{PPE} \times \eta_{PPE}) \right]$$

where $t_{conc}$ was the time handling concentrate, $S_{sk,hand}$ the area of the hands, $S_{sk,splash}$ the estimated splash area and $\eta_{gloves}$ and $\eta_{PPE}$ were the assessed efficiency of gloves and clothing excluding gloves, respectively.

Exposure from handling sheep after they had been dipped was estimated using equation (5):

$$E_{sk,handling} = C_{sk,conc} \times S_{sk,hand} \times t_{handling}$$

where $C_{sk,handling}$ was the normalized concentration of pesticide during handling and $t_{handling}$ was the duration of handling wet sheep.

Equation (6) provides for an estimate of inhalation exposure, but expressed in the same units as the dermal exposure (i.e. m² days), with $k_{sk}$ being a constant.

$$E_{sk,inhalation} = k_{sk} \times t_{dip}$$

Finally, we also allowed for exposure from accidentally falling into the dip bath ($E_{sk,falls}$):

$$E_{sk,falls} = C_{sk,dip} \times S_{sk} \times t_{wash} \times N_{falls}$$

where $t_{wash}$ was the estimated time from falling into the bath until washing and $N_{falls}$ was the number of times the person had fallen into the bath.

The questionnaires

Two questionnaires were sent to the subjects. The first aimed to collect information about the history of exposure of the subjects to organophosphate pesticides. It comprised 23 questions that were mainly of closed format. This questionnaire was based on that used by the Institute of Occupational Medicine in a study of the relationship between exposure to organophosphate pesticides and chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers (Sewell et al., 1999). There was
no obvious link between the questions about the circumstances of the person’s exposure and the exposure metric and so we believe that the subjects would have been unaware of how exposure was to be estimated. The second questionnaire aimed to gather information about symptoms related to CF, both when the farmers originally reported to the VMD (between 1985 and 2001) and at the time of the survey (2001). It compromised 41 questions based on the ‘Multidimensional Checklist Individual Strength (CIS) Questionnaire for Measuring Chronic Fatigue’ that was described and validated by Beurskens et al. (2000). A CFS score was calculated from the questionnaire responses, with scores >76 being considered high. It should be noted that the questionnaire provided an assessment of CF and not CFS.

Population studied

We originally identified all those people submitting reports of three or more CFS-type symptoms as cases and all those who reported one CFS-type symptom or less as controls. Reports were contributed between 1985 and 2001. Controls were matched by age, gender, date of reporting and geographic location to the cases. However, as we indicated, the case–control design was abandoned when we discovered that both groups had a similar prevalence of CF as assessed by the CIS questionnaire.

Since the SARSS database is confidential, the VMD made the initial contact with subjects. The VMD prepared a letter introducing the researchers to the farmers, which they sent to all eligible subjects along with a copy of the questionnaires and a pre-addressed prepaid return envelope for the completed questionnaire. After 3 weeks a reminder letter was sent to all non-respondents asking them to respond in 10 days. No further reminders were sent because of a severe foot and mouth disease outbreak affecting the UK during 2001 and the desire of the VMD and the authors not to disturb the farmers during this critical period.

Analysis

The data were analysed using SPSS version 9. Cumulative exposure to pesticides was calculated from first contact with sheep dip until 2001 when the survey was carried out and from first exposure until the time when the subject reported to the VMD. An overall CF score was also calculated for both time points. A number of participants did not have any exposure to organophosphates after they originally reported to the VMD, mostly because of ongoing health problems or retirement. Estimating both cumulative exposure over the individual’s lifetime and until reporting to the VMD also allowed comparisons to be made of the change in CF score with lifetime cumulative exposure and exposure since the original report was sent to the VMD.

RESULTS

The target study population comprised 81 people selected as ‘cases’ and 125 as ‘controls’. Twenty-eight of the subjects could not be contacted because they had moved home and so the total target population was reduced to 178 subjects; 72 ‘cases’ and 106 ‘controls’. Responses were received for 52.8% (n = 94) of the subjects: 70.2% of these completed the questionnaire, 17% did not wish to participate in the study, 7.4% had changed their address and 5.3% had died. Three of the completed questionnaires were excluded because they were incomplete. Eventually we were left with 63 valid responses, of which 26 (32%) were original designated cases and 37 (30%) were controls. The response rate from males and females was similar.

Table 1. Results from the fatigue questionnaire divided into ‘cases’ and ‘controls’

<table>
<thead>
<tr>
<th>Chronic fatigue questions</th>
<th>‘Cases’; more than three symptoms (%)</th>
<th>‘Controls’; one symptom or less (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past (i.e. at the time the subject reported to the VMD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective feeling of fatigue (8)</td>
<td>69</td>
<td>49</td>
</tr>
<tr>
<td>Low concentration (5)</td>
<td>65</td>
<td>54</td>
</tr>
<tr>
<td>Poor motivation (4)</td>
<td>92</td>
<td>78</td>
</tr>
<tr>
<td>Lack of physical activity (3)</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>CF score &gt; 76</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>Present (i.e. 2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective feeling of fatigue (8)</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Low concentration (5)</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>Poor motivation (4)</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>Lack of physical activity (3)</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>CF score &gt; 76</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Had flu in the past month</td>
<td>19</td>
<td>43</td>
</tr>
</tbody>
</table>

*Different subsets of questions in the CIS questionnaire, with numbers of questions in parentheses.*
Table 1 shows that when the subjects originally reported to the VMD, all of the ‘cases’ and 84% of the ‘controls’ were classified as suffering from CF, i.e. a CF score >76 (Bultmann et al., 2002). This suggested to us that the SARRS symptoms reports are not a reliable way of identifying CF. We consider that the CIS questionnaire used in the present study is a more appropriate tool to assess CF since it was originally developed for this purpose (Beurskens et al., 2000). Table 1 also shows average scores for the different subsets of questions contributing to the overall CF score (number of questions in parentheses).

At the time of the survey the CF scores among the study subjects showed that 85% of the cases and 87% of the controls had CF. We classified all those who had a CF score >76 as having a high CF score and the remainder as having a low CF score.

Table 2 shows that the geometric mean (GM) exposure for the high and low CF score categories along with the 95% confidence interval (95% CI). In Table 2 most of the differences between the two reporting periods occur because of some subjects moving from the high to the low CF category, although some subjects also continued to work with pesticides after reporting to the VMD, which added to their cumulative exposure. The difference between high and low CF score groups was not significant for the exposure up to the time of reporting to the VMD ($P = 0.93$), but was highly significant for cumulative exposure over the subject’s lifetime ($P = 0.004$).

Table 2. Geometric mean estimated exposure for high and low CFS categories

<table>
<thead>
<tr>
<th>CF score</th>
<th>n</th>
<th>GM (m² days)</th>
<th>95% CI (m² days)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>until reporting to the VMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>57</td>
<td>550</td>
<td>350–860</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6</td>
<td>520</td>
<td>200–1400</td>
<td>0.930</td>
</tr>
<tr>
<td>Cumulative exposure over lifetime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>54</td>
<td>730</td>
<td>490–1000</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>9</td>
<td>140</td>
<td>30–670</td>
<td>0.004</td>
</tr>
</tbody>
</table>

$n$, number of subjects; GM, geometric mean; CI, confidence interval.

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The main reason for the change in the association between CF score and exposure between the original report and the time of the survey was the reduction in CF score for subjects with lower lifetime exposures. For the subjects in the bottom tertile of the cumulative lifetime exposure (i.e. <400 m² days) the average CF score declined by 26, while the average score for the subjects in the top two tertiles declined by 4. This difference was statistically significant ($P = 0.005$). These data are shown in Fig. 1.

Figure 2 shows the relationship between estimated cumulative exposure to organophosphate pesticides over the subject’s lifetime and CF score at present.

Any person with a total score above 76 is considered to be a probable fatigue case, shown as a horizontal line on the figure. The Pearson correlation coefficient between CF score and cumulative exposure for the whole dataset is 0.24 ($P = 0.058$).

In Fig. 2 each point represents a single subject’s experience, i.e. their exposure and their health status. These are shown separately depending on whether they were originally identified as a ‘case’ or ‘control’ because of possible concerns about the influence of selection on any association. It shows that for most people exposure was relatively low, although some had high CF scores. All of the subjects with high cumulative exposure to organophosphates had high CF scores. Those originally selected as a ‘control’
had slightly higher exposures on average, but the pattern of CF with exposure was similar.

**DISCUSSION**

Anecdotal information suggests that there is a high prevalence of CF amongst sheep farmers who have used organophosphate pesticides. Our results confirm that amongst a group of people who consider that their health has been impaired by using organophosphate pesticides the majority have self-reported symptoms consistent with CFS. However, so far as we are aware, this is the first study to focus on the association between quantitative estimates of organophosphate exposure and CF.

We obtained a response rate of about 40%, which, given the circumstances of the study, we believe to be satisfactory. For reasons of confidentiality we had no direct access to the names and addresses of those who had reported to the VMD and so it was not possible for us to identify non-responders and it was impossible for us to find out why they had not responded. However, the main problem faced during the study was a severe foot and mouth disease outbreak, which coincided with the period when the questionnaires were sent out. A number of farmers had lost their flocks and were distressed. This will have had an effect on the response rate and it could also have biased the CF scores as the outbreak would have added to the stresses experienced by the farmers. However, we do not see any reason why those with higher past exposure would have suffered greater stress in this situation.

We devised an exposure metric that reflects the mass of pesticide absorbed through the skin of the subjects. The exposure metric, although not validated, was based on sound scientific principals and previous experience. A study undertaken by the Institute of Occupational Medicine has shown the importance of exposure to pesticide concentrate, and this is incorporated into the metric (Sewell et al., 1999). The assessment was based on information supplied by the respondents about their past work. This information could have been subject to recall bias, since the dangers of exposure to organophosphate pesticides are well known and individuals whose health has been more seriously affected may be more aware of the issues involved. However, subjects were not asked specifically to rate their own exposure but were asked to describe the circumstances of the exposure. They were unaware of how this information would be used to reconstruct cumulative exposure for this research. Therefore, we think it unlikely that there was a differential response from those with and without CF. For example, subjects would not have been aware of the much greater weight given to work with pesticide concentrate compared to contact with dilute dip.

The identification of ‘cases’ and ‘controls’ using the original symptoms reports to the VMD SARSS was not reliable and we therefore had to adopt an alternative analysis plan. We consider that the more detailed and specific questionnaire that we used in the present study is a better way of identifying CF and so relied on these data rather than the symptoms reports. However, in studying the relationship with exposure it was important to consider whether abandoning the original case–control design would impact on the exposure–response analysis. On general grounds we considered this unlikely, because the original identification based on symptoms reports proved to be poorly related to CF score. However, for definiteness, we looked at exposure–response separately within ‘cases’ and ‘controls’ and found similar results, leading to a positive relationship in both groups. This within strata analysis is free of any biases linked to classifying subjects originally as ‘cases’ or ‘controls’. It may, of course, be sensitive to non-response in either group, but in our experience exposure–response relationships are much less sensitive to non-response than are prevalence rates.

We found some evidence for an association between CF and exposure to organophosphate sheep dip, with a tendency for the relatively few subjects with highest estimated exposure to have higher CF scores. There were also a large number of subjects with low assigned exposure who also had high CF scores. We believe that this may reflect the multi-causal nature of this syndrome and in fact such alternative causes may be the predominant reason for the high prevalence of CF in this group (Bultmann et al., 2002). For example, it may be that the social isolation or the financial pressures often associated with sheep farming may be predominant. Those subjects with the highest cumulative lifetime exposure to pesticides showed a much smaller reduction in CF score in the time between reporting to the VMD and the survey. This may reflect a difference in cause for the subject’s CF, with those who had a high CF score with low pesticide exposure perhaps having a variant of the syndrome where changes in lifestyle or some other personal factor made remission possible. We consider that our study offers limited evidence that exposure to high levels of organophosphate pesticides may be causally related to CF. Further research should be undertaken to identify the causes of CF amongst sheep farmers who have used organophosphate pesticides.

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