Acute ill-health in sheep farmers following use of pesticides

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Introduction

Complaints of ill health by sheep dippers emerged after the introduction of organophosphate pesticide (OP) dips to the UK in the 1980s [1,2]. While many of these complaints referred to chronic ill-health, there were also concerns regarding acute ill-health and whether the latter might be an indicator of OP exposure and/or a marker of susceptibility to subsequent chronic ill-health [3]. The term ‘dipper’s flu’ has been used for these episodes of acute ill-health. The causes of dipper’s flu are currently unknown, and while attention has focused on OP exposure, farmers may be exposed to a large number of different environmental agents and physical stressors while treating sheep.

Retrospective studies of farmers who are chronically ill or who belong to groups report a high lifetime prevalence (>60%) of acute health effects [4,5], whereas the prevalence is lower in those farmers without chronic ill-health (18%) or men living in rural areas who report using sheep dip (29% [6]). The incidence of acute ill-health following sheep treatment is unclear, but there were more than 100 cases of acute reactions reported in 1991 to the Appraisal Panel for Human Suspected
Adverse Reactions to Veterinary Medicines [7]. The number of reports has since fallen, and this may be due to changes in both products and methods of treating sheep for ectoparasites [7]. It is widely accepted that there is an underreporting of incidents although there are problems assessing the validity of these reports given that, if any, farmers are evaluated by clinical toxicologists during the critical period immediately after OP exposure. In one small prospective study, approximately 46% of farmers developed new symptoms within 24h of dipping, but none had falls in butyryl or erythrocyte cholinesterase activity indicative of toxicity [8].

While there is no generally agreed definition of what constitutes dipper’s flu, it has been described as a flu-like, febrile illness with symptoms that include fever, cough, headache, dizziness and myalgia [9]. More recently, it was reported that symptoms following sheep dipping included headache, aching limbs, runny nose and muscle weakness [6]. However, in prospective studies of farmers, common patterns of symptoms are not necessarily evident [8], or if present, they do not appear to represent physical illness [10]. There appear to have been few epidemiological studies of dipper’s flu, and the nature and causes of dipper’s flu remain to be determined. In this paper we describe the nature and frequency of symptoms of acute ill health, among farmers treating sheep for ectoparasites.

Methods

A prospective cohort of farmers who were planning to treat their sheep for ectoparasites was identified. The study was based in three distinct areas in the UK: north-west England (Cumbria, Cheshire, Derbyshire, Lancashire, North Yorkshire, Staffordshire and West Yorkshire), south-east England (East Sussex, Hampshire, Kent, Surrey and West Sussex) and Wales (Powys, Ceredigion and Carmarthenshire). These areas were chosen for their closeness to the institutions of the investigators and because farmers in these areas had been less studied than those in other areas (e.g. south-west England) and it was felt would be more likely to participate. The details of sheep farmers were obtained from the National Farmers’ Union (NFU), the British Wool Marketing Board (BWMB) and Cumbrian Shepherd’s Guides as initial pilot studies indicated that recruitment was very poor using only BWMB records. These farmers were sent a letter inviting them to participate in the study, along with an information sheet, consent form and screening questionnaire. Eight weeks later, non-responders were sent a reminder postcard, which was followed up by a reminder telephone call. Farmers were offered up to £100 to compensate any inconvenience the study might cause. Farmers were ineligible if they were either less than 18 or more than 70 years old, did not plan to treat sheep, no longer kept or treated sheep with pesticides (e.g. were organic) or used a contractor to treat sheep. A random sample of farmers who did not respond initially were asked to complete a short telephone questionnaire about their health: responses to this questionnaire were analysed separately from the main study. Ethical approval for the study, including changes in protocol, was obtained from the South East Multicentre Research Ethical Committee (reference 04/1/023).

Farmers were recruited between 2005 and 2006. In order to identify a syndrome of dipper’s flu, they were asked to keep a diary of any symptoms that occurred during 7 days after starting sheep treatment (day 1 being the first day of treatment). On the day before treatment, the farmers were asked whether they felt ill. Participants were also asked to complete a questionnaire, providing information on medical history (including a history of dipper’s flu), lifestyle factors (e.g. alcohol consumption and tobacco use) and occupational history. All recruited farmers were visited by a study nurse prior to the treatment to explain the use of the symptom diary. Farmers were asked to give yes/no answers for any of 10 symptom complexes. Those were (i) feeling generally ill; (ii) feeling unusually tired; (iii) headache; (iv) sweaty, shivery, feverish, hot or cold; (v) pain in muscles or joints; (vi) runny, stuffy, blocked or irritated nose; (vii) hoarse voice or sore throat; (viii) cough, shortness of breath or wheeze; (ix) nausea, poor appetite, vomiting, abdominal pain or diarrhoea and (x) eye irritation. Previously published definitions of dipper’s flu syndromes were matched as closely as possible to the symptom diary complexes prior to any data analysis and hence blind to the results of the study. These definitions were obtained from three different sources; a textbook describing symptoms of headache, pain in muscles or joints and runny, stuffy, blocked or irritated nose [9]; a research report describing symptoms of headache, sweating, shivering, feverishness, feelings of hot or cold, pain in muscles or joints, nausea, poor appetite, vomiting, abdominal pain or diarrhoea [11] and web-based material describing symptoms of feeling generally ill, feeling unusually tired, headache and pain in muscles or joints [12].

The relationships between the data collected from interviewed participants, non-responders and those who did or did not complete the symptom diary were examined by cross tabulation, comparison of means (and medians) where appropriate and calculation of simple univariate statistics (chi square, t-tests, Mann–Whitney’s U-test). \( P \) values less than 0.05 are reported. The numbers of farmers whose symptoms matched the different dipper’s flu definitions were determined firstly using a strict definition that the farmer had to have all the symptom complexes in the definition and secondly using a looser definition in which the farmer had to have any two of the symptom complexes in the definition. Frequencies of different symptom complexes reported at
different days throughout the diary were compared with those values obtained on the seventh day after treatment using a matched McNemar test. The proportions of any new symptom complex recorded on days 1 and 2 were compared with those of symptom complex newly reported on day 7; data from day 7 were included from only those farmers who had not treated their sheep on days 5, 6 and 7 on the assumption that any treatment related effects would have disappeared within 48 h. To explore whether there were any patterns of symptom complexes occurring, a principal component analysis (PCA) of the Pearson correlations was performed: an approach used previously elsewhere [13]. Statistical analysis was carried out using SPSS15.0.

**Results**

To identify a cohort of farmers willing to take part in the study, letters were sent to the addresses of 8747 farmers and an initial response was obtained from 4729 of them (54%). Of the responders, 963 were excluded for reasons including age (194), they did not plan to treat sheep (177), they did not have sheep (312) or they used a contractor (63). Of the 3766 potential participants, 841 agreed to participate and 781 were interviewed before treatment started (and hence defined as an interviewed participant), a response rate of 9% (781/8747). Of the 781 interviewed farmers, 352 (45%) completed symptom diaries following treatment of sheep. There was no response initially from 4018 farmers (46%), but 56 of them did answer a telephone questionnaire: 8% of the latter group reported that they had had dipper’s flu compared to about 22% of interviewed participants (P < 0.01).

The study population is described in Table 1. More than 80% of interviewed participants were men with over 50% of subjects coming from Wales. More than 22% of the participants reported ever having dipper’s flu. There was some evidence that farmers who completed the symptom diary differed from those who did not. In particular, farmers in north-west England were more likely to complete the diary (63%) compared to those in Wales (42%) or south-east England (35%).

On the day before treatment, 7% (23/343) of farmers reported that they felt ill. Following treatment the proportion of farmers complaining of feeling generally ill fell and was approximately 3% on days 1 (11/347), 2 (11/347) and 3 (11/348). It was even lower, but not significantly so, later in the week (Figure 1). The proportion of farmers complaining of the other nine specific symptom complexes varied during the week following treatment. In comparison with day 7, significant increases in symptom reporting were detected especially earlier in the week (Figure 1). The highest proportion of farmers complaining of any of these symptom complexes was on day 2. On day 2 17% of farmers (60/347) complained of pain in muscles or joints, 15% had nasal complaints, 13% had headache, 12% were unusually tired, 12% had a hoarse voice or sore throat, 9% had a cough or shortness of breath or wheeze, 7% had eye irritation, 7% had nausea or poor appetite and 5% felt sweaty, shivery or feverish. Only two farmers (on days 3 and 7), reported all 10 symptom complexes. The number of farmers with 1 or more, 2 or more, 3 or more, 4 or more (but not 6 or more) symptom complexes varied with day after treatment (Table 2) with the highest proportion occurring on day 2. On day 2, approximately 27% of farmers complained of 2 or more symptom complexes.

The number (and proportion) of new symptom complexes reported on day 1 or 2 were compared with those reported on day 7 and are shown in Table 3. On days 1 and 2, the symptom complexes most frequently reported were pain in muscles or joints (15% of all reported symptoms, 67/434), headache (15%) and runny, stuffy, blocked or irritated nose (14%). On day 7 the total number of symptom complexes reported was lower [32] and those most frequently reported were feeling unusually

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interviewed participant</th>
<th>Symptom diary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td></td>
<td>Completed, n = 352</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/female (% male)</td>
<td>662/119 (85)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean ± SD (n)</td>
<td>53.1 ± 10.2 (774)</td>
</tr>
<tr>
<td>Region</td>
<td>Wales (%)</td>
<td>440 (56)</td>
</tr>
<tr>
<td></td>
<td>North-west England (%)</td>
<td>166 (21)</td>
</tr>
<tr>
<td></td>
<td>South-east England (%)</td>
<td>175 (22)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Yes/no/MI (% yes)</td>
<td>111/668/2 (14)</td>
</tr>
<tr>
<td>Current drinker</td>
<td>Yes/no/MI (% yes)</td>
<td>655/124/2 (84)</td>
</tr>
<tr>
<td>Ever had dipper’s flu</td>
<td>Yes/no/DK/MI (% yes)</td>
<td>173/520/84/4 (22)</td>
</tr>
</tbody>
</table>

MI = missing information, DK = don’t know. Significant difference in regional distribution of farmers who did or did not complete the symptom diary. ***P < 0.001 by chi-square test.
tired (28%), headache (25%) and pain in muscles or joints (12.5%). There were no statistically significant differences in the symptom complex reporting except for feeling unusually tired, which was more prevalent on day 7 than on day 1 or 2 ($P < 0.05$; Table 3).

There were few farmers who had dipper’s flu according to the identified definitions. On day 1 there were three and four new cases of dipper’s flu (out of 347 farmers) using the textbook and web-based definitions respectively (an incidence of approximately 1%) and two of these farmers were identified by both definitions. On day 2 the incidence of dipper’s flu using the textbook definition was 2% (7/347) and 1% (3/344) for the web-based definition. No new cases of dipper’s flu were identified using the research report definition on either day 1 or day 2. Using a less restrictive definition of dipper’s flu (i.e. when any two of the symptom complexes in each definition were reported), the number of farmers so identified was higher (Figure 2, panel A). The incidence of dipper’s flu on day 1 was then 7% (25/347) using the textbook definition, 6% using the research report definition and 3% using the web-based definition and decreased over the week (Figure 2, panel A), with most reporting occurring in 2 days after treatment started.

A PCA of new symptom complexes occurring on day 1 or 2 identified two factors (pyrexial and respiratory) that contained more than one symptom complex and that explained 35% of the variance. The pyrexial factor consisted of four symptom complexes (feeling generally ill; sweaty, shivery, feverish, hot or cold; feeling unusually tired; headache), had an eigenvalue of 2.23 and explained 22% of the variance. The respiratory factor consisted of three symptom complexes (runny, stuffy, blocked or irritated nose; cough shortness of breath or wheeze; eye irritation), had an eigenvalue of 1.24 and explained 12% of the variance. Using a strict definition (i.e. the farmer had to have all symptoms), few farmers were identified as having the pyrexial factor (only 1 on days 1, 2 and 5) or the respiratory factor (5 on day 1 and 1 on days 2 and 3). Using a less restrictive definition (i.e. the farmer only had to report two of the symptom complexes in the factor definition) the numbers of farmers identified were higher (Figure 2, panel B) with 5% for the pyrexial factor 1 on day 1 and 5.5% for the respiratory factor. The numbers of farmers so identified then decreased over the following 7 days (Figure 2, panel B).

**Discussion**

In this study, we found little evidence of dipper’s flu as has been defined previously either in textbooks, the scientific literature or on the world wide web [9,11,12].
However, the incidence and prevalence of individual symptom complexes varied during the week after treating sheep with pesticides, with reporting being much higher immediately after treatment rather than later in the week. Furthermore, two factors, a pyrexial and respiratory factor comprising four and three symptom complexes were identified. Few farmers complained of all the symptom complexes in either factor at the same time but approximately 5% of farmers reported having any two of the symptom complexes in either factor on day 1.

Neither the pyrexial nor the respiratory factor have previously been reported in studies of dipper's flu. Certain components of the pyrexial factor have previously been commonly reported such as being sweaty, shivery, feverish, hot or cold [6,10,15], being unusually tired [4] or having a headache [4,6,10,15] but not all at the same time. As for the respiratory factor, only having a runny, stuffy, blocked or irritated nose [7,10] or having a cough [7] have been commonly reported. Muscular problems,

### Table 2. Variation in number of farmers with number of diary symptom complexes with day after treatment

<table>
<thead>
<tr>
<th>Number of symptom complexes</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2</td>
<td>67/280 (19)**</td>
<td>92/255 (27)**</td>
<td>72/276 (21)**</td>
<td>64/283 (18)**</td>
<td>57/288 (17)**</td>
<td>43/301 (13)</td>
<td>40/302 (12)</td>
</tr>
<tr>
<td>≥3</td>
<td>35/312 (10)**</td>
<td>51/296 (15)**</td>
<td>41/307 (12)**</td>
<td>34/313 (10)**</td>
<td>30/315 (9)</td>
<td>23/321 (7)</td>
<td>21/321 (6)</td>
</tr>
<tr>
<td>≥4</td>
<td>24/323 (7)**</td>
<td>27/320 (8)**</td>
<td>26/322 (7)**</td>
<td>23/324 (7)**</td>
<td>17/328 (5)</td>
<td>14/330 (4)</td>
<td>12/330 (4)</td>
</tr>
<tr>
<td>≥6</td>
<td>4/343 (1)</td>
<td>8/339 (2)</td>
<td>7/341 (2)</td>
<td>6/341 (2)</td>
<td>5/340 (1)</td>
<td>4/340 (1)</td>
<td>4/338 (1)</td>
</tr>
<tr>
<td>≥10</td>
<td>0/347 (0)</td>
<td>0/347 (0)</td>
<td>1/347 (&lt;1)</td>
<td>0/347 (0)</td>
<td>0/345 (0)</td>
<td>0/344 (0)</td>
<td>1/341 (&lt;1)</td>
</tr>
</tbody>
</table>

*Symptom complexes from the symptom diary; significantly different when compared to day 7.

*P < 0.05, **P < 0.01, ***P < 0.001 using McNemar’s test.

### Table 3. Number (%) of new symptoms reported on days 1 or 2 and day 7

<table>
<thead>
<tr>
<th>Symptom complex</th>
<th>New on day 1 or 2 (%)</th>
<th>New on day 7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ill</td>
<td>12 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Tired</td>
<td>55 (13)</td>
<td>9 (28)**</td>
</tr>
<tr>
<td>Headache</td>
<td>66 (15)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Sweaty</td>
<td>21 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>67 (15)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Nose</td>
<td>61 (14)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Throat</td>
<td>53 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>36 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Abdo</td>
<td>27 (6)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Eye</td>
<td>36 (8)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

*Analysis of day 7 restricted to those farmers who had not treated sheep on day 5, 6 or 7.

*P < 0.05.
previously identified (e.g. 4, 6, 15) were not part of these two factors. Other previously reported health issues such as thinking problems or difficulty judging distance (e.g. 10) would not necessarily have been detected in the present study because the diary was restricted to the classical flu-like symptoms associated with dipper’s flu [4,6,10,15]. Interestingly, fewer farmers did report feeling generally ill after treatment than before. The reasons for this are as yet unknown, but it is unlikely to be due to any specific exposure or that treating sheep had a positive impact on health given the level of symptom complex reporting.

The study has a number of limitations. Firstly, the response rate was low but is generally consistent with other studies among farming communities. In these the response rate among farmers ranged from 19% to 98% [4,6,8,17–26] with low rates generally in those studies employing blood testing and face-to-face interviewing techniques. This low response rate can be ascribed to a number of reasons including pressure of work, the perceived burden of forms to complete as farmers find form filling particularly stressful [27] and disillusionment with progress in understanding the health concerns of certain sections of the farming community. A low response does not necessarily affect the internal validity of the study but can affect the generalizability of study to the farming population of the UK. Secondly, the sampling frame employed in the study was principally based upon databases held by the NFU and the BWMB. People such as employed farm workers or migrant workers [16] are less likely to have been members of these organizations. It is likely that working practices and awareness of pesticide toxicity may vary between these workers and the study farmers, and the results from this work may not be directly generalized to the former.

When farmers entering the study were compared with non-responders, there was evidence that the study population were more likely to have had dipper’s flu in the past, which might suggest that responders were more likely to report symptoms than the sheep farming community in general. The number of non-responders contacted was small, limiting the value of this observation. However, the reporting of symptom complexes identified in the web-based definitions identified in the research report or textbook definitions. This suggests that over-reporting by farmers based upon widely available information does not appear to have occurred. Within the study, approximately 50% of farmers provided a symptom diary, but there were few differences between this group and the farmers who did not provide a symptom diary. Certainly there was no difference in previous reporting of dipper’s flu. On the whole, the biases described above were unlikely to obscure a commonly occurring syndrome of dipper’s flu. A weakness of the study is that detailed information on baseline symptoms was not collected immediately before treatment for comparison with subsequent complaints. This proved impractical because of farmers’ idiosyncratic working patterns combined with geographical and logistic considerations. The decision to treat sheep for ectoparasites or indeed postpone the treatment is often taken at the last moment. Practically, it then becomes difficult to ask the participant to record symptoms the day before treatment as they do not necessarily know what day that would be.

While the presence or absence of one symptom complex might reflect a chance occurrence or be a normal health experience, the presence of two or more symptom complexes is less likely to occur by chance and may therefore have resulted from an exposure or activity. The symptom complexes used reflect relatively non-specific biological effects, but this is compatible with exposure to agents like infectious pathogens or pesticides that can affect several different organ systems and result in multiple symptoms. It has been suggested that these symptoms are related to perception of risk [6] and may be a non-specific psychological response to OP exposure or alternatively subtle markers of susceptibility to OP poisoning. Many of the symptoms described are also compatible with other environmental exposures and activities during the course of treatment: e.g. physical exertion, other agricultural pesticides, formulation chemicals, infectious pathogens, animal ectoparasites and animal by-products such as faeces and urine. The pyrexial factor is consistent with an infectious illness or an inflammatory response to environmental agents like endotoxin, whereas the respiratory factor is consistent with infection, an inflammatory response and a respiratory irritation caused by exposure to an environmental agent. In contrast, there was evidence to suggest that treatment simply increases the frequency of symptom reporting rather than inducing a new pattern as the relative proportions of new symptom complexes occurring on day 7 were similar to those reported on days 1 and 2. It is thus currently unclear what is the cause of this increased symptom reporting. However, by identifying such new patterns, we are now better placed to identify whether these patterns are associated or not with specific exposures. Further analysis is currently ongoing to ascertain whether these patterns are indeed associated with specific exposures.

Key points

• Reporting of symptoms by farmers is common up to 48 h following sheep treatment.
• There was little evidence of dipper’s flu as currently defined in the literature.
• Two new symptom patterns, pyrexial and respiratory, were identified.
Acknowledgements

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Conflicts of interest

A.C.P. is a current member and H.G.R. a past member of the Advisory Committee on Pesticides. A.C.P. was a member of the Appraisal Panel for Human Suspected Adverse Reactions to Veterinary Medicines (2002-2009). J.P.T. has been a member of the Veterinary Products Committee within the past five years and is a member and past chairman of the Appraisal Panel for Human Suspected Adverse Reactions to Veterinary Medicines.

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