ORIGINAL ARTICLE

Neuropsychiatric symptoms in past users of sheep dip and other pesticides

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Supplementary file containing tables A, B, C and D is available at http://oem.bmj.com/supplemental

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Objectives: To explore the prevalence and pattern of neuropsychiatric symptoms in past users of sheep dip and other pesticides.

Methods: From a postal survey of men born between 1933 and 1977 and resident in three rural areas of England and Wales (response rate 31%), data were obtained on lifetime history of work with pesticides, neurological symptoms in the past month, current mental health and tendency to be troubled by non-neurological somatic symptoms (summarised as a somatising tendency score). Risk factors for current neuropsychiatric symptoms were assessed by modified Cox regression.

Results: Data were available for 9844 men, including 1913 who had worked with sheep dip, 832 with other insecticides but not sheep dip and 990 with other pesticides but never with sheep dip or insecticides. Neurological symptoms were consistently 20–60% more common in past users of sheep dip than in men who had never worked with pesticides, but their prevalence was also higher in men who had worked only with pesticides other than sheep dip or insecticides. They clustered strongly within individuals, but this clustering was not specific to men who had worked with sheep dip. Reporting of three or more neurological symptoms was associated with somatising tendency (prevalence ratio (PR) 15.0, 95% CI 11.4 to 19.5, for the highest vs the lowest category of somatisation) and was more common in users of sheep dip (PR 1.3, 95% CI 1.0 to 1.6), other insecticides (PR 1.4, 95% CI 1.0 to 1.8) and other pesticides (PR 1.3, 95% CI 1.0 to 1.7) than in non-users. Among users of sheep dip, prevalence was higher in men who had dipped most often, but not in those who had worked with sheep dip concentrate. Past use of pesticides was not associated with current anxiety or depression.

Conclusion: Neurological symptoms are more common in men who have worked with sheep dip, but the association is not specific to sheep dip or insecticides. A toxic cause for the excess cannot be ruled out, but several features of our observations suggest that psychological mechanisms have a role.

Organophosphate insecticides have been widely used for >30 years to protect agricultural and horticultural crops, for public hygiene and to control arthropod pests in gardens and homes.[1] In addition, some organophosphates have been licensed as human or veterinary medicines—for example, in the treatment of head lice and in the prevention of scab and other ectoparasitic infestations in sheep. In particular, organophosphates were a major component of sheep dips used in Britain during the 1970s and 1980s, and one, diazinon, continues to be used for this purpose.

The acute toxicity of organophosphate insecticides arises principally from their ability to phosphorylate and thereby inactivate acetyl cholinesterase in cholinergic nerve synapses and at the neuromuscular junction.[1,2] In some cases, acute poisoning may be complicated by the intermediate syndrome, a muscle weakness that typically begins after 1–4 days and lasts for 5–15 days. In addition, some organophosphates can cause a delayed polyneuropathy through inhibition of another enzyme, neuropathy target esterase, but compounds with this property have not been used in the UK for some years. Anecdotally, it has been reported that a flu-like illness (dippers' flu) can occur shortly after dipping sheep, but it is unclear whether the symptoms are caused by a toxic component of sheep dip, by endotoxins, or through some other mechanism.[1]

Follow up of individuals who have been diagnosed with acute organophosphate poisoning has indicated that there may be subtle, long-term neurological sequelae such as impaired attention span and mental agility.[1] However, despite substantial research efforts, doubt remains about the potential for chronic neurotoxicity from exposures to organophosphates insufficient to cause overt, acute toxic effects. Ahmed and Davies[3,4] have postulated that low-level exposures can lead to a syndrome of chronic organophosphate-induced neuropsychiatric disorder (COPIND), characterised by a combination of various neuropsychiatric symptoms, often with a history of acute sensitivity to organophosphates. However, many of the symptoms that they list are common in the general population, and it has not been established whether they cluster unusually among people who have been exposed to organophosphates. If low-level exposure to organophosphates were confirmed to cause chronic neurotoxicity, there might be a need for tighter regulatory controls on their use.

To explore the prevalence and pattern of neuropsychiatric symptoms in past users of sheep dip and other pesticides, we analysed data from a large population-based survey in three rural areas of England and Wales. In particular, we looked for evidence of an increased prevalence and unusual clustering of postulated COPIND symptoms in participants who had worked with sheep dip as compared with those who had never worked with pesticides or had worked only with pesticides other than sheep dip and insecticides. We also examined the association of COPIND symptoms with indices of more intense or extensive exposure to pesticides, and with a general tendency to report concern about somatic symptoms.

Abbreviations: COPIND, chronic organophosphate-induced neuropsychiatric disorder

METHODS

The study population comprised men born between 1933 and 1977 who were resident in defined areas of north Devon, the Welsh borders and south Lincolnshire. Each of the three areas was an aggregate of geographically contiguous electoral wards in which a high proportion of men were employed in agriculture at the time of the 1991 census. Members of the study population were identified from the age–sex lists of local general practitioners (GPs) and were sent a postal questionnaire, followed up if necessary, by a reminder after 10–16 weeks. Because almost everyone in Britain is registered with the National Health Service, general practice lists provide a near-complete enumeration of the general population. The mailings were carried out by local health agencies and the questionnaires, which were identified only by a serial number, were returned directly to the study team. In addition, the study team was provided with the year of birth of all people mailed, which allowed the derivation of response rates by birth cohort.

The study was initiated primarily to investigate acute and chronic symptoms associated with occupational exposure to sheep dip and other pesticides. However, to increase its value, and at the same time reduce the potential for biased participation and reporting of exposures and symptoms, it was designed as a broader investigation of work and health. Among other things, the questionnaire asked about: demographic information; lifetime occupational use of five categories of pesticide (sheep dip, other insecticides, herbicides, fungicides and wood preservatives); the occurrence (ever) of each of 12 listed symptoms within 48 h of using different categories of pesticide; the occurrence in the past month of each of 7 neurological symptoms that have been linked with COPIND (table 1); symptoms of anxiety and depression in the past 7 days; the extent to which the subject had been disturbed or bothered during the past 7 days by each of five somatic symptoms (faintness or dizziness, pains in the heart or chest, nausea or upset stomach, trouble getting breath and hot or cold spells); and lifetime history of consulting a GP for four categories of health problem that have been suggested to occur as a consequence of exposure to organophosphates and which form part of the postulated syndrome of COPIND[3 4] (change in personality, difficulty speaking, difficulty with handwriting and thoughts about self-harm or suicide). The questions about anxiety and depression were taken from the Hospital Anxiety and Depression Scale, and cut-off points for case definition (possible or probable) were defined according to previously published recommendations.[5] The questions about somatic symptoms were taken from the Brief Symptom Inventory,[6] and were used to derive a ''somatising tendency'' score, which was partitioned to four levels. Two other somatic symptoms from the Brief Symptom Inventory (numbness/tingling and feeling weak) were omitted from the score because they were potential manifestations of neurotoxicity.

Statistical analysis was carried out with STATA V.8.2 SE software. Clustering of neurological symptoms within individuals was explored by comparing the number of men who had a given number of symptoms with the number that would have been expected if the occurrence of each symptom were statistically independent (ie, the presence of one symptom did not affect the probability of another). Specific patterns of clustering were investigated by calculating odds ratios (ORs) for the associations between each possible pair of symptoms. The ORs were derived from a simple 2×2 cross-tabulation of one symptom (classed as present or absent) against the other. Associations of neurological and psychiatric symptoms with exposure to pesticides and other possible risk factors were examined by modified Cox regression[7] and the results summarised as prevalence ratios (PRs) with associated 95% CIs.

RESULTS

After two mailings, usable questionnaires were returned by 10 765 (31%) of the men selected for study. The response rate was similar in all three of the areas studied, but higher in older than in younger men (43% in those born during 1933–37). The 23 721 non-responders included 1825 who had died or who had moved to a new address and could not be contacted.

Among the responders, 9844 provided satisfactory information on each of the seven neurological symptoms that were of special interest. Of these, 1913 men had at some time worked with sheep dip, 832 with other insecticides but never with sheep dip, and 990 with other pesticides but never with sheep dip or insecticides. The remaining 6109 had never worked with any type of pesticide. Table 2 summarises various characteristics of these groups, which formed the basis for all further analyses.

Table 1 shows the 1-month prevalence of neurological symptoms (for ''all'', ''most'' or ''a good bit of the time'') according to previous work with pesticides. In comparison with men who had never worked with pesticides, those with occupational exposure to sheep dip had a higher prevalence of each symptom, the largest relative excess being for sensitivity to smells (7.1% vs 4.5%). However, symptoms were also more frequent in those who had worked with other pesticides but not with sheep dip (including those who had never used insecticides occupationally). Table 1 also presents the results of a similar analysis that excluded the 2320 men who might have worked with pesticides in the past year. This was to eliminate possible short-term effects of pesticide exposure. The prevalence of symptoms in pesticide users tended to be somewhat higher than in the full study sample, but the overall pattern was unchanged.

Table 3 illustrates the extent to which neurological symptoms clustered within individuals. Overall, there was strong evidence of clustering. Thus, in comparison with the numbers that would have been expected had the occurrence of each symptom been independent, there was an excess of men with no symptoms (7311 vs 6185.8), a deficit of men with one or two symptoms (2070 vs 3602) and an excess with three or more symptoms (463 vs 56.2). For those with at least four symptoms, the relative excess was even greater (212 vs 2.9). There was no indication, however, that this clustering was specific to work with sheep dip or insecticides. The ratio of observed to expected numbers with at least four symptoms was 48 in men who had worked with sheep dip, 53 in those who had worked with other insecticides but not sheep dip, 48 in those exposed occupationally to other pesticides but not to sheep dip or insecticides and 98 in men who had never worked with pesticides.

In the analysis of pairwise associations between symptoms, ORs among the men who had worked with sheep dip ranged from 3.8 (for the association between sensitivity to smells and difficulty remembering things) to 25.5 (for the association between difficulty speaking and difficulty with handwriting). However, there was no indication of a different pattern of symptom clustering among the men who had worked with sheep dip as compared with those who had worked only with other pesticides or not with pesticides at all (see supplementary table A, supplementary tables are available at http://oem.bmj.com/supplemental). For example, the OR for the association between difficulty speaking and difficulty with handwriting was 18.4 in men who had worked only with pesticides other than sheep dip or insecticides and 21.2 in those who had never worked with any pesticides.

In the study sample as a whole, 1984 (20.2%) men were classed as having symptoms of anxiety and 1161 (11.8%) as having symptoms of depression. Table 4 summarises the associations of neurological and psychiatric symptoms with

Table 1 Prevalence (%) of neurological symptoms according to previous work with pesticides

Symptom*	Never worked with pesticides (n = 6109)	Ever worked with sheep dip: All (n = 1913)	Ever worked with sheep dip: Not worked with pesticides in past year (n = 662)	Ever worked with insecticides, never with sheep dip: All (n = 832)	Ever worked with insecticides, never with sheep dip: Not worked with pesticides in past year (n = 334)	Ever worked with other pesticides, never with sheep dip or insecticides: All (n = 990)	Ever worked with other pesticides, never with sheep dip or insecticides: Not worked with pesticides in past year (n = 419)	All subjects (n = 9844)
Difficulty concentrating	4.4	5.6	8.0	5.9	7.5	5.3	5.3	4.8
Difficulty remembering things	7.4	10.4	11.9	10.8	11.7	9.7	9.1	8.5
Difficulty with handwriting	2.9	3.9	5.1	1.9	3.3	3.2	4.3	3.0
Difficulty speaking	2.6	3.0	4.8	2.9	3.0	2.9	3.3	2.7
Sensitivity to certain smells	4.5	7.1	8.3	7.3	10.8	6.4	6.0	5.4
Increased sensitivity to the effects of alcohol	2.2	3.3	3.8	3.2	1.8	4.0	4.8	2.7
Tiredness and lack of energy	15.4	21.0	24.5	17.3	19.5	17.8	18.6	16.9

*Men were classed as having a symptom if they reported that it had been present for at least ''a good bit of time'' during the past month.

occupational exposure to pesticides and somatising tendency. The neurological symptoms analysed were the same as in table 1. The prevalence of anxiety and depression increased steeply with somatising tendency, and for multiple neurological symptoms the relationship with somatising tendency was even stronger. Thus, reporting of four or more neurological symptoms was >20 times as common among men with a somatising tendency score >1 as in those with a somatising score of 0. The prevalence of anxiety and depression showed no clear relation to work with any category of pesticide, but reporting of multiple neurological symptoms tended to be more frequent among men who had worked with pesticides. The excess was reduced after adjustment for somatising tendency, but was still apparent. No consistent differences were observed in the associations with different classes of pesticide, but for reporting of four or more neurological symptoms, the strongest association was with sheep dip (PR 1.4, 95% CI 1.0 to 2.0).

To look for possible interactions between pesticide exposure and somatising tendency, we repeated the analyses for table 4 separately for each of the four categories of somatising tendency score (see supplementary table B, supplementary tables are available at http://oem.bmj.com/supplemental). Associations between pesticide exposure and COPIND symptoms tended to be strongest in the highest category of somatising tendency, but they were not confined to this group.

Table 5 shows associations with neurological and psychiatric symptoms among the subset of men who had, at some time, worked with sheep dip. All four investigated outcomes were more common among those who reported having experienced multiple symptoms or fever/chills on at least one occasion within 48 h of using sheep dip. None of the outcomes was associated with handling sheep dip concentrate, but the prevalence of multiple neurological symptoms tended to be highest in those who had used sheep dip the most often. To check on the specificity of these findings, we carried out an equivalent analysis for the 990 men who had worked with other pesticides but never with sheep dip or insecticides. Although based on smaller numbers, the patterns were generally similar, with all outcomes occurring more frequently among men who reported acute symptoms within 48 h of using the pesticides

Table 2 Characteristics of participants

Characteristics	Never worked with pesticides (n = 6109)	Ever worked with sheep dip (n = 1913)	Ever worked with insecticides, never with sheep dip (n = 832)	Ever worked with other pesticides, never with sheep dip or insecticides (n = 990)	All subjects (n = 9844)
Age (years)					
Mean	52	49	49	49	51
Median	54	50	51	51	53
Range	24–70	25–69	24–69	24–70	24–70
Smoking habits*					
Never	2718 (44%)	1072 (56%)	396 (48%)	420 (42%)	4606 (47%)
Ever	3325 (54%)	820 (43%)	429 (52%)	562 (57%)	5136 (52%)
Average weekly alcohol consumption (units)*					
0	915 (15%)	392 (20%)	128 (15%)	152 (15%)	1587 (16%)
1–7	1847 (30%)	697 (36%)	325 (39%)	312 (32%)	3181 (32%)
8–21	2321 (38%)	595 (31%)	267 (32%)	358 (36%)	3541 (36%)
>21	1004 (16%)	226 (12%)	111 (13%)	165 (17%)	1506 (15%)
Occupational exposure to pesticides (ever)					
Sheep dip	0 (0%)	1912 (100%)	0 (0%)	0 (0%)	1912 (19%)
Other insecticides	0 (0%)	1030 (54%)	832 (100%)	0 (0%)	1862 (19%)
Herbicides	0 (0%)	1505 (79%)	714 (86%)	393 (40%)	2612 (27%)
Fungicides	0 (0%)	865 (45%)	640 (77%)	159 (16%)	6017 (17%)
Wood preservatives	0 (0%)	893 (47%)	344 (42%)	738 (75%)	1975 (20%)

*Percentages do not total to 100 because data were missing for some men.

Table 3 Clustering of neurological symptoms according to previous work with pesticides

Number of symptoms reported*	Never worked with pesticides			Ever worked with sheep dip			Ever worked with insecticides, never with sheep dip			Ever worked with other pesticides, never with sheep dip or insecticides			All subjects		
	O†	E‡	O/E§	O†	E‡	O/E§	O†	E‡	O/E§	O†	E‡	O/E§	O†	E‡	O/E§
0	4671	4044.2	1.2	1327	1071.6	1.2	601	493.1	1.2	712	587.8	1.2	7311	6185.8	1.2
1	893	1752.7	0.5	347	666.5	0.5	135	273.8	0.5	165	324.9	0.5	1540	3036.6	0.5
2	302	287.1	1.1	128	155.4	0.8	45	58.5	0.8	55	69.3	0.8	530	565.4	0.9
3	132	23.8	5.5	53	18.2	2.9	31	6.3	4.9	35	7.6	4.6	251	53.3	4.7
4	67	1.1	} 98.2	27	1.2	} 47.5	9	0.4	} 52.6	12	0.5	} 47.9	115	2.8	} 73.6
5	28	0.0		21	0.0		9	0.0		8	0.0		66	0.1	
6	10	0.0		8	0.0		2	0.0		1	0.0		21	0.0	
7	6	0.0		2	0.0		0	0.0		2	0.0		10	0.0	

*From the seven symptoms listed in table 1.
†Observed number of subjects.
‡Expected number of subjects if prevalence of each symptom were statistically independent (see text).
§Based on expected numbers rounded to two decimal places.

concerned, and multiple neurological symptoms being most frequent among those who had used the pesticides most frequently (see supplementary table C, supplementary tables are available at http://oem.bmj.com/supplemental). For example, after adjustment for age, area and somatising tendency, reporting of ⩾3 neurological symptoms was 2.5 (95% CI 1.1 to 6.0) times more common in men who had used other pesticides on ⩾50 days, and 7.7 (95% CI 1.5 to 38.2) times more common among those who said that they had experienced fever or chills within 48 h of using such a pesticide.

Table 6 gives age-standardised prevalence rates for consulting a GP because of four categories of health problem that have been proposed to occur as a long-term consequence of exposure to organophosphates. For each health problem, the lifetime prevalence of consultation was marginally higher among men who worked with sheep dip than in those who had never worked with pesticides. For three of the problems, it also tended to be higher than in those who had worked with other pesticides. However, consultations because of thoughts about self-harm or suicide were marginally more common among men who had worked with other pesticides but not sheep dip.

To explore possible confounding by acute effects of recent exposure to pesticides, we repeated the analyses for tables 3–5 after the exclusion of 2320 men who might have worked with pesticides in the past year (ie, those whose last reported use of pesticides was at the same age or 1 year less than the age at which they answered the questionnaire; see supplementary table D, supplementary tables are available at http://oem.bmj.com/supplemental). Rates of symptoms tended to be somewhat higher than in the full study sample for all three categories of past work with pesticides, and associations between symptoms and past exposure to pesticides were, if anything, stronger.

DISCUSSION

In this cross-sectional survey, the neurological symptoms that we assessed tended to cluster within individuals and were more common in past users of sheep dip than in men who had never worked with pesticides. However, the clustering was not specific to those who had worked with sheep dip, and the symptoms also occurred with increased frequency in occupational users of other pesticides. Report of multiple neurological symptoms was strongly associated with somatising tendency, and was more frequent in past users of sheep dip, but men who had worked only with other pesticides (including those who had never used insecticides occupationally) also had an increased prevalence. Moreover, in past users of sheep dip, there was no relation to handling the concentrate, which is a known determinant of higher exposure.[8] Neurological symptoms tended to be more common in men who had used sheep dip most often, and in those who reported acute symptoms within 48 h of using sheep dip. However, a similar pattern was seen for pesticides other than sheep dip or insecticides. Nor was the association between past use of pesticides and consulting a GP because of neuropsychiatric symptoms specific to sheep dip.

The response rate in the study was substantially lower than we have achieved in earlier postal surveys of the general population.[9–11] An important difference was that previously we have obtained the names and addresses of subjects from their GPs, and sent them a personalised invitation to participate with a covering letter of support from their own doctor. However, the ethics committee that considered the current survey concluded that this method was unacceptable (as subjects had not given permission for the release of their names and addresses to researchers), and insisted that the mailing should be carried out on our behalf by an organisation that already held the necessary contact details. General practices were unable to take on the required administrative work, especially the chasing of non-responders, and we were therefore obliged to fall back on a non-personalised letter sent via local health agencies. In a parallel exercise (unpublished), we sent the same questionnaire to a sample of men living adjacent to our study areas via their own GP. Only a single mailing was possible, but the response to this (33%) was markedly higher than to the first mailing in the main survey (23%), suggesting that the mode of approach had an important impact on the response rate.

The low response to the questionnaire (31%) may have led to over-representation of individuals with symptoms in the study sample, or perhaps to selective exclusion of subjects with particularly severe and disabling illness. However, it seems less likely that it would importantly have biased associations of neuropsychiatric symptoms with occupational exposure to different categories of pesticide, or with the other risk factors examined. In support of this, when analyses were repeated separately for the 7172 men who responded without a reminder and the 2672 late responders, patterns of association were broadly similar.

Similarly, although some subjects may have failed to recall all past exposures to pesticides, this is unlikely to have been differential in relation to different categories of pesticide. Ideally, we would have obtained information relating to individual pesticides, but we thought it unlikely that subjects would recall lifetime exposures to specific agents with sufficient completeness and accuracy. Many pesticide products have been used in British agriculture over the past 40 years, and their names are not always easily memorable. Moreover, two products with similar names may differ importantly in their

Table 4 Association of neurological and psychiatric symptoms with occupational exposure to pesticides and somatising tendency

Risk Factor	All subjects	⩾3 Neurological symptoms*			⩾4 Neurological symptoms*			Anxiety*†			Depression*†		
	n	n	PR (95% CI)‡	PR (95% CI)§	n	PR (95% CI)‡	PR (95% CI)§	n	PR (95% CI)‡	PR (95% CI)§	n	PR (95% CI)‡	PR (95% CI)§
Occupational exposure to pesticides													
Never worked with pesticides	6109	243	1.0	1.0	111	1.0	1.0	1170	1.0	1.0	701	1.0	1.0
Ever worked with sheep dip	1913	111	1.5 (1.2 to 1.9)	1.3 (1.0 to 1.6)	58	1.7 (1.2 to 2.4)	1.4 (1.0 to 2.0)	424	1.1 (1.0 to 1.2)	1.0 (0.9 to 1.2)	259	1.2 (1.0 to 1.4)	1.1 (0.9 to 1.3)
Ever worked with insecticides, never with sheep dip	832	51	1.5 (1.1 to 2.0)	1.4 (1.0 to 1.8)	20	1.3 (0.8 to 2.1)	1.2 (0.7 to 1.9)	174	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.1)	95	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)
Ever worked with other pesticides, never with sheep dip or insecticides	990	58	1.5 (1.1 to 2.0)	1.3 (1.0 to 1.7)	23	1.3 (0.8 to 2.1)	1.1 (0.7 to 1.7)	216	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.2)	106	0.9 (0.8 to 1.1)	0.9 (0.7 to 1.0)
Somatising tendency score¶													
0	5263	87	1.0	1.0	38	1.0	1.0	572	1.0	1.0	310	1.0	1.0
0.1–0.5	2705	91	2.0 (1.5 to 2.7)	2.0 (1.5 to 2.7)	22	1.1 (0.7 to 1.9)	1.1 (0.7 to 1.9)	591	2.0 (1.8 to 2.3)	2.0 (1.8 to 2.3)	303	1.9 (1.6 to 2.2)	1.9 (1.6 to 2.2)
0.6–1.0	1214	136	6.8 (5.2 to 8.9)	6.7 (5.1 to 8.8)	60	6.9 (4.6 to 10.3)	6.8 (4.5 to 10.2)	471	3.6 (3.2 to 4.1)	3.6 (3.2 to 4.1)	290	4.1 (3.5 to 4.8)	4.1 (3.5 to 4.8)
>1.0	581	145	15.3 (11.7 to 20.0)	15.0 (11.4 to 19.5)	89	21.5 (14.7 to 31.6)	21.1 (14.4 to 30.9)	341	5.6 (4.9 to 6.4)	5.6 (4.9 to 6.4)	254	7.4 (6.3 to 8.7)	7.4 (6.3 to 8.7)

PR, prevalence ratio.
*For each outcome, the comparator for risk estimates was all subjects who did not have the outcome.
†Possible or probable.
‡Adjusted for age (in eight bands) and area.
§Adjusted for age and area, and also mutually adjusted.
¶81 of the 9844 subjects were excluded because somatising tendency score was missing.

Table 5 Associations with neurological and psychiatric symptoms in past users of sheep dip

Risk Factor	All past users of sheep dip	⩾3 Neurological symptoms*			⩾4 Neurological symptoms*			Anxiety*			Depression*		
	n¶	n	PR (95% CI)†	PR (95% CI)‡	n	PR (95% CI)†	PR (95% CI)‡	n	PR (95% CI)†	PR (95% CI)‡	n	PR (95% CI)†	PR (95% CI)‡
Lifetime use of sheep dip (days)													
<10	416	17	1.0	1.0	9	1.0	1.0	90	1.0	1.0	48	1.0	1.0
10–49	700	35	1.3 (0.7 to 2.4)	1.3 (0.7 to 2.4)	17	1.3 (0.6 to 2.8)	1.3 (0.6 to 2.9)	150	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.3)	84	1.1 (0.7 to 1.5)	1.1 (0.8 to 1.5)
50+	693	54	2.1 (1.2 to 3.6)	1.6 (0.9 to 2.8)	28	2.1 (1.0 to 4.6)	1.4 (0.6 to 3.0)	160	1.2 (0.9 to 1.5)	1.0 (0.8 to 1.4)	110	1.4 (1.0 to 2.0)	1.2 (0.9 to 1.8)
Handled sheep dip concentrate													
No	544	31	1.0	1.0	14	1.0	1.0	129	1.0	1.0	78	1.0	1.0
Yes	1369	80	1.1 (0.7 to 1.6)	1.0 (0.6 to 1.5)	44	1.3 (0.7 to 2.4)	1.1 (0.6 to 2.1)	295	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)	181	0.9 (0.7 to 1.2)	0.9 (0.7 to 1.2)
Ever experienced symptoms within 48 h of work with sheep dip													
Never	1355	58	1.0	1.0	26	1.0	1.0	258	1.0	1.0	155	1.0	1.0
Fever or chills§	101	14	3.9 (2.1 to 7.1)	2.1 (1.1 to 3.9)	7	4.9 (2.0 to 11.6)	1.9 (0.8 to 5.0)	33	1.7 (1.2 to 2.5)	1.1 (0.8 to 1.6)	26	2.3 (1.5 to 3.5)	1.5 (1.0 to 2.3)
⩾4 symptoms§	156	31	5.1 (3.2 to 7.9)	2.4 (1.5 to 3.9)	17	6.8 (3.6 to 12.8)	2.7 (1.4 to 5.5)	58	2.0 (1.5 to 2.6)	1.2 (0.9 to 1.6)	47	2.6 (1.9 to 3.7)	1.6 (1.1 to 2.2)

*For each outcome, the comparator for risk estimates was all men who did not have the outcome.
†Adjusted for age (in eight bands) and area.
‡Adjusted for age, area and somatising tendency (classified as in table 4).
§These risk factors overlapped. Each was analysed separately relative to never having experienced acute symptoms.
¶Information on risk factors was missing for some subjects.

Table 6 Lifetime prevalence of consultation with general practitioner (GP) because of neuropsychiatric symptoms according to earlier work with pesticides

Reason for consulting GP	Never worked with pesticides		Ever worked with sheep dip		Ever worked with insecticides, never with sheep dip		Ever worked with other pesticides, never with sheep dip or insecticides	
	n	Prevalence (%)*	n	Prevalence (%)*	n	Prevalence (%)*	n	Prevalence (%)*
Change in personality (eg, a tendency to depression or irritability)	501	8.2	168	9.0	60	7.2	84	8.4
Difficulty speaking (eg, in finding the right words or getting words out)	128	2.0	40	2.3	17	2.1	19	1.9
Difficulty with handwriting	98	1.5	32	1.9	10	1.3	14	1.5
Thoughts about self-harm or committing suicide	149	2.5	55	2.9	28	3.3	37	3.9

*Prevalence rates directly standardised to the age distribution of the total study sample.

active ingredients. This lack of specificity in our data may have led to dilution of associations when analyses were based on broader classes of pesticide. However, it should not have caused spurious associations. Misclassification of exposure to sheep dip seems less likely. Dipping sheep is a relatively memorable experience, distinct from other farming activities, and not easily confused.

A further methodological issue relates to the discrimination between acute and chronic effects of pesticide exposure. To explore possible confounding by the acute effects of recent exposure to pesticides, we repeated analyses after exclusion of men who might have worked with pesticides in the year before completing the questionnaire. This gave somewhat stronger associations between symptoms and past exposure to pesticides, with rather higher rates of symptoms for all three categories of pesticide use. It is possible that some men had given up work with pesticides as a consequence of neurological illness, leading to a lower frequency of symptoms in recent users.

It has been proposed that low-level exposure to organophosphates can lead to a syndrome, COPIND, comprising various specified neuropsychiatric symptoms, often with a history of acute sensitivity to organophosphates. Thus, in a survey of 175 farmers from southwest England there was a marked excess of these symptoms in those who reported exposure to organophosphates.[4] However, the number of farmers unexposed to organophosphates was small, and it was not established that the clustering of COPIND symptoms was unique to those with organophosphate exposure.

Our results support the hypothesis that COPIND symptoms cluster within individuals, but indicate that the clustering is not specific to people with exposure to organophosphates. It was apparent in men who had worked with sheep dip and other insecticides, and also in those who had worked only with other pesticides, or had not worked with pesticides at all (table 3). Although report of multiple neurological symptoms was more common in men who gave a history of acute symptoms following work with sheep dip, a similar association with earlier acute symptoms was also observed in men who had worked only with pesticides other than sheep dip or insecticides.

We did, however, find an excess of neurological symptoms in men who had worked with sheep dip and other insecticides as compared with non-users of pesticides (table 1). This is consistent with the results reported by Davies *et al*,[4] and also with those from several other investigations,[12–16] including the Agricultural Health Study in the US.[17]

The question then arises as to whether this consistent excess of neurological symptoms is attributable to toxicity, or occurs through non-toxic, psychological mechanisms. To look for evidence of toxicity, some investigators have carried out neurophysiological testing in workers with past exposure to organophosphates and unexposed controls.[1 8] However, the results have been inconsistent.

Some features of our own findings would accord with a toxic pathogenesis for the observed increase in neurological symptoms. In particular, the risk of symptoms increased with the total number of days on which sheep dip had been used.

On the other hand, several other aspects would favour a non-toxic mechanism. No elevation of risk was found in relation to handling of sheep dip concentrate, despite this being an important determinant of higher exposure,[8] and an activity that should not be too difficult to recall. Moreover, the association with neurological symptoms was not specific to sheep dip and insecticides. All of the symptoms studied also occurred excessively in men who had worked with other pesticides but never with sheep dip or insecticides. Interestingly, in the US Agricultural Health Study, which also found a higher prevalence of neurological symptoms in workers handling pesticides, the increase was more specific to insecticides, although it applied to organochlorines as well as organophosphates and carbamates (many of which are also cholinesterase inhibitors).[17] The absence of an association with pesticides other than insecticides in the US study could be explained if a neurotoxic herbicide or fungicide had been used on a large scale in the UK but not in the USA. However, of the herbicides and fungicides that have been used most widely in the UK over the past 40 years (phenoxy herbicides, ALS and ACCase inhibitors, paraquat, glyphosate, glufosinate ammonium, benzimidazoles, dithiocarbamates, triazoles and strobilurins), few exhibit prominent neurotoxicity. Another possibility is that in the UK there has been greater public concern about the adverse effects of pesticides in general, and a cultural difference in health beliefs and expectations has predisposed to a different pattern of psychologically mediated symptoms.[18]

Also suggestive of a psychological component to the reported neurological symptoms is their strong association with somatising tendency (table 4). An association between somatising tendency and depression is not surprising. Somatic illnesses can

Main messages

- Neurological symptoms were more common in past users of sheep dip, and also in men who had worked with other pesticides.
- Neurological symptoms clustered strongly within individuals, but the clustering was not specific to those who had worked with sheep dip or insecticides.
- Past use of pesticides was not associated with current anxiety or depression.

Policy implications

Chronic illness as a result of work with sheep dip may in some cases arise through psychological rather than toxic mechanisms, and may not always be preventable by controls on exposure.

often be depressing, especially if severe, while in the reverse direction, low mood may lead to a heightened awareness of somatic symptoms. Notably, however, the associations with neurological symptoms were even stronger, with prevalence ratios in excess of 15 for the highest scores of somatising tendency. It could be that organophosphates or other toxins cause chronic neurological illness, and also multiple non-neurological symptoms, although this would not be anticipated from their known toxicology. Perhaps a more plausible explanation is that people who are generally prone to dwell on somatic complaints are more likely to be aware of, and to report, neurological symptoms when questioned. This may apply particularly when they have been exposed to a perceived environmental hazard, and increased rates of non-specific symptoms have been described in relation to various potentially hazardous exposures, without any clear evidence of underlying pathology.[18 19] In a recent community-based prospective study in New Zealand, the number of symptoms reported at baseline significantly predicted the number of symptoms reported after a subsequent aerial pesticide spraying campaign, and also the number of symptoms that individuals attributed to the pesticide.[20]

In conclusion, our results indicate that neurological symptoms are more common in men who have worked with sheep dip, but that the association is not specific to sheep dip or insecticides. We cannot exclude a toxic cause for the increased prevalence of symptoms, but several features of our observations suggest that in many cases they are mediated by psychological mechanisms.

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