SHAPE: Survey of Health and Pesticide Exposure
The Telephone Survey

(funding provided by DEFRA under the title: "Survey Of Health Complaints Among Sheep-Dippers", Project Number VM0299)

Scientific Report

Tony Fletcher, Rachel MacLehose
Public and Environmental Health Research Unit, (formerly Environmental Epidemiology Unit), London School of Hygiene and Tropical Medicine

Fintan Hurley, John Cherrie & Hilary Cowie
Institute of Occupational Medicine, Edinburgh

Goran Jamal & Peter Julu
Department of Neurology, Central Middlesex Hospital, Imperial College of Science Technology and Medicine

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Executive Summary

A number of organisations in the UK have been providing support to sheep farmers and others who have experienced ill-health, attributed by them in many cases to exposure to organophosphate (OP) formulations. Four of these organisations agreed to cooperate in the present study, which aimed to describe the health and exposure of support group members. The study consisted of a structured assessment of the health and exposure of those who took part; the information was gathered principally by means of telephone interviews. A sub sample was examined clinically with a range of neurological tests; methods and results from the clinical study will be reported in a further report.

The support groups were able to contact 907 of the total of 1844 individuals for whom they had sufficient and current contact details. Following screening out of those without potential OP exposure, 524 eligible participants were invited for telephone interview, of whom 471 were interviewed. Analyses focused on 367 individuals after excluding those with reported diagnoses (such as diabetes) or use of medications with potential neurological side-effects.

A quantitative cumulative OP exposure score was calculated, by linking estimates of OP concentrations in various occupations and tasks obtained by modelling and expert judgement, with individuals' corresponding frequency and/or duration of exposure, using information obtained from the telephone surveys. The 367 individuals showed a wide range of estimated cumulative OP exposures. For sheep dippers and handlers the estimated cumulative exposure was broadly comparable to that found in an earlier cross sectional survey of active sheep farmers; i.e. on average, the sheep dippers and handlers studied from the four support groups had not experienced unusually high lifetime exposures to OPs in the course of their work.

The study participants had been self-selected as people with chronic illness which they attributed to OP exposures. Results from the telephone survey confirmed that the health of those studied was generally poor, with 75% reporting their overall health as only fair or poor. A wide range of symptoms was reported, including 81% of participants reporting concentration/memory difficulties, and 74% fatigue. For only a small proportion (18%) could we identify other reported medical history or medication which might prompt these or other symptoms of neurological damage. After excluding this 18%, symptoms consistent with neurological damage remained especially prevalent.

Four out of five of those interviewed reported having had an acute OP exposure episode; on average these had on poorer health than the others. This is consistent with the view that people who experience an acute response to OP exposures may also suffer long-term neurological health effects. From our survey it appears that most of the reported illness is therefore among those with at one time or another rather high OP exposures, though their lifetime cumulative exposures were not unusually high compared with other exposed workers. It is plausible that the ill-health of many of these is related to, or made worse by, their OP exposure history. However, methods of self-selection into the support groups and therefore into the study could generate similar findings even if exposure to OPs had not caused the neurological damage found. We have no way of distinguishing reliably, from within this study, whether or to what extent OPs caused or contributed to the symptoms of neurological damage reported by the study participants.

A significant minority, about one in five, had reported that they had not experienced an acute response but nevertheless included many with neuropathy signs and symptoms. We are cautious in drawing conclusions from these patterns but it may be that some of these are a long term effect of OPs on health, and we conclude that these results support the need for further research addressing this specific question.

ACKNOWLEDGEMENTS

We gratefully acknowledge all those who participated, the four support groups, the Study Advisory Group, several colleagues or former colleagues who assisted us, in particular Ben Armstrong and Paul Wilkinson at LSHTM and Mairi Graham, Brian Miller, Adele Pilkington and Colin Soutar at IOM, and DEFRA who funded the study. Responsibility for the study and conclusions is of course ours alone.

1. INTRODUCTION

1.1 Background

These brief remarks are included here to set in context the survey, but this is not a synthesis of the relevant literature. A report on the toxicity of organophosphates (OPs), by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (an Advisory Committee of the Department of Health and the Devolved Administrations), considered the potential long term health effects of OPs (Committee on Toxicity, 1999). The Committee concluded that "neurological abnormalities can occur as a long-term complication of acute OP poisoning", but that the evidence related to chronic low-level exposure to OPs, i.e. exposures insufficient to cause acute overt toxicity, "is less convincing" of long-term adverse health effects.

Anecdotal evidence collected by support groups suggested that there were many cases of serious long term illness among people with a history of OP exposure, including both those with, and some without, episodes of acute overt toxicity; illness that generally the individuals concerned attributed to their exposures to OPs.

Yet cross-sectional studies of people occupationally exposed to OPs in sheep-dipping reported only apparently relatively modest adverse health effects. One study reported rather subtle associations with OP exposure using neuropsychological, neurobehavioural and neuromuscular testing (Stephens et al, 1995). Another study reported higher rates of symptoms (sensory more than motor) in OP exposed sheep dippers compared to non-exposed workers (Pilkington et al, 1999).

One aspect that might contribute to these differences between the experience of the support groups and cross-sectional studies of current workers could be selective drop out of those who are ill, leading to a relatively healthy population of workers available for study in cross-sectional studies. Thus a study which would include assessing the health of those who may have retired early due to ill-health was desirable. Given that the support groups had assembled apparently large numbers of people with sickness potentially OP-related, it was proposed to conduct a systematic study of those groups, to describe their health and their exposures to OPs. This conforms with another recommendation of the COT report, that more information was required 'on the presentation, prior exposure to OPs, severity and subsequent clinical course of people in the UK with chronic illnesses that they attribute to OPs' (Committee on Toxicity, 1999). DEFRA supported the proposal and commissioned the study.

1.2 The sufferers groups and data maintained

The study team worked with four groups that supported individuals who had been exposed to organophosphate chemicals. Individuals on the databases of these groups had contacted the organisations for information and advice; there has been no systematic collection of data by these groups on exposed individuals. The support groups who took part in the study are:

- Action on Pesticide Exposure (PEX)

The PEX project is based at the Pesticide Action Network UK (PAN-UK). In 1998 PAN-UK incorporated the database from the Pesticide Exposure Group of Sufferers (PEGS) into the PEX database. Individuals in this combined database had been exposed to any of a greater range of pesticides compared to the members of the other support groups, which focused more specifically

on exposure to OPs.

- Northern Ireland Organophosphorus Sufferers Association (NIOPSA)

This group was founded in 1997 and had approximately 90 individuals on their database, the majority of whom had been exposed to organophosphates through sheep dip.

- Organophosphate Information Network (OPIN)

OPIN grew from an environmental group and since 1992 has focussed its activities on the health effects following occupational exposure to organophosphates. The majority of individuals on the OPIN database had been exposed to OPs through sheep dipping activities.

- Organophosphate Users Support Group (OPUS)

OPUS was established in 1999 and aims to provide support to individuals living in the border region of England and Wales and who have suffered from exposures to pesticides. Many of these individuals were exposed to sheep dip and other agricultural chemicals. Approximately 200 individuals were on the OPUS database at the time of recruitment to the SHAPE survey.

1.3 Aims and objectives of study; envisaged strengths and limitations

1.3.1 Aims and objectives

The broad aim of the present study, as described in the proposal, was "to collect systematic information on [the members of the support groups in order] to provide a descriptive overview….. a picture of the total size and characteristics of this substantial population".
It was not proposed to collect information on any comparison or control groups.

The five specific objectives of the study were:

i. To provide a descriptive overview of the study population in terms of both health status and exposure history, based on information collected systematically by telephone interview and questionnaire.

ii. For a sub-sample of the population, to provide an overview of their health status by detailed clinical and neurological assessment**.**

iii. For a sub-sample of the population, to validate self-reported health status in relation to their clinical assessments.

iv. To describe the information supplied to, and the information and advice received from the HSE, VMD and the health service.

v. To provide an overview of the reported ill health in this population in relation to reported exposure to pesticides and veterinary medicines and other potential risk factors.

The specific objectives addressed in this report are objectives (i), (iv) and (v), above. Methods and results from the clinical assessments (objective (ii)), and their relevance to the study as a whole (objective (iii), also objective (v)) will be reported separately. (As part of quality control, an audit of the clinical study data was instituted. That audit is not yet complete.)

1.3.2 Envisaged strengths and limitations

It was recognised from outset that the study population is self-selected, probably in respect of both ill-health and exposure (generally people joined the support groups because they thought their health had been affected by exposure to OPs). In terms of design the study is in effect an extended case series, but with the added complication that the cases believe that exposure to OPs caused or contributed to their ill-health.

Thus, while the study had unique potential to describe systematically the health and other characteristics of people throughout the UK who considered they had been damaged by exposure to OPs, the self-selection of the study group *jointly* on health and exposure also imposed limitations on what could be achieved. These strengths and limitations were understood from the outset. We consider it useful to recall them here, where aims and objectives are stated, because those aims and objectives are necessarily different from conventional epidemiological studies that gather information on both health and exposures, but with different subject selection criteria. Thus, for example, the proposal states:

> "Given detailed information on all these cases providing a consistent description of their health status and patterns of past exposure to OPs and details of other potential causes, then it will be possible to summarise the consistency of symptoms and reported diagnoses within this population, and in comparison with the literature."

On the other hand, it was also acknowledged explicitly that this study is limited in the conclusions that it can draw ; for example:

> "It will not be possible to estimate the rates or risk (as for example a relative risk) for any conditions in this population relative to OP sheep dip exposure because the selection operating between the total population of sheep farmers and those who end up in the databases is not known. Neither can we attribute individual causality on the basis of self-reported exposure and ill-health. We can however describe the patterns of illness in these people and assess the number that report ill-health that *might be attributed to OP use in sheep dip, either acutely or chronically*. That effectively means those who are left after identifying those whose condition would appear unlikely or less likely to be attributable to OPs…"

Nor was it possible to identify a suitable control group for comparison with the support group members to assess exposure-response (E-R) relationships in a way that avoids confounding with methods of study selection, and so overcome this limitation.

1.4 Summary plan of work and associated plan of this report

1.4.1 Plan of work

The project started in January 2001. Background work was initially scheduled for a 3-month period with the interviews due to start in Month 4 (April). However, the Foot and Mouth outbreak started in late February 2001 and, given the initial scale of the outbreak, it was felt to be inappropriate to start contacting individuals to participate in the project. At this stage we were unaware how many of the potential participants in the study were still actively involved in farming or were currently involved in farming related businesses.

Interviews were rescheduled to start in mid August, with individuals being contacted from mid July onwards. The intermediate period was used to further refine the questionnaires.

Contact with potential participants started in mid July and continued until early November 2001. To comply with the Data Protection Act, initial contact was made by the support groups themselves. Programming of the telephone interview schedule and piloting the schedule occurred in late July through to mid August. Following the pilot study further refinements were made to the questionnaire and CATI (Computer Assisted Telephone Interview) programming. The main stage of the telephone interviews took place between October 1st and mid December 2001.

In mid November 2001 written questionnaires were sent out to individuals who had either requested a written version, or to individuals who could not be contacted. The majority of these were returned by mid January. Data entry for the written questionnaires started in early March and was completed by mid April.

Reports of the telephone interviews were created and mailed to all participants in early February 2002. Any amendments received were entered and the final dataset cleaned.

Individuals were selected for the clinical study in March and the clinical tests started in April and continued to the end of May 2002. Analysis of the written and telephone interviews took place from May onwards. The project was suspended between September 2002 and April 2003. Final analysis and writing up took place subsequently. This has included peer review of earlier drafts of the final report. .

1.4.2 Plan of report

To address the above objectives the study team used the following analytical approaches. We have collected systematically information on current health status and past exposure history, focussing in particular reports of neurological and neuropathological symptoms which would be expected to be more sensitive indicators of possible OP effects.

We were in the first instance interested in the prevalences of these symptoms, and whether the prevalences were higher than those reported in other, comparable surveys.

While we need to set them in the context of concerns about the selection of this study group, the analysis has focused largely on describing a number of internal patterns of symptom reporting in these data. Several approaches have been taken. First an overview of the patterns of numbers of symptoms reported, secondly analyses of internal predictors for symptom reporting (both personal characteristics and OP exposure related), thirdly measures of correlations between symptom reporting.

- The patterns of numbers of symptoms reported can provide some indication of the coherence of the reported symptoms, including the extent to which the population may include some individuals with propensities to report positively on a wide range of conditions.

- To explore explanations for differences in symptom reporting between individuals in the study population, regression analyses were performed. For a symptom list of particular interest, we first assessed how the reporting was dependent on a number of demographic characteristics (age, sex, educational level, reported alcohol and smoking). Then with adjustment for potential confounders, the relation between reported acute OP episodes and symptom reporting was assessed – bearing in mind the *caveats* described earlier, that selection may have distorted true underlying relationships in the exposed population as a whole. Within the subgroup of people who had worked in sheep dipping, the association

with a quantitative score of cumulative OP exposure score was assessed, again adjusted for potential confounding.

- The method of multiple correlation analysis was used to explore if there was evidence of clustering together of particular groups of symptoms.

By agreement with DEFRA, this report concentrates on the methods and results from the questionnaire study of health and exposures. We focus in particular on results from the telephone interviews, where the data are strongest. Simple descriptions are provided of results from the more limited written questionnaire data. Methods and results from the clinical examinations will be included at a later date. That will enable more incisive assessment of the patterns of ill-health in the population studied; discussion at this stage is necessarily limited.

2 RECRUITMENT FOR TELEPHONE INTERVIEWS

2.1 Eligibility criteria:

Participants were eligible if they met the following criteria:

- Aged over 18 years
- Exposed to organophosphates (either through sheep dipping or other activity) AND had been exposed on more than a single one-off occasion.
- Gave their consent to participate in the project.

2.2 Recruitment to the questionnaire phase of the study

Recruitment to the study was done in close collaboration with the 4 support groups (SGs) involved in the project: OPIN, PEX, NIOPSA and OPUS. Members of each group have self-referred themselves to these organisations and no comprehensive data collection on all affected individuals has been attempted by these groups.

The organisations, with the exception of OPUS, used the same procedure to recruit people to the study. Members of OPIN, PEX and NIOPSA were contacted by letters from the support groups asking if they wished to be involved in the study. This was then followed up by a short telephone call by the SG. If the individual agreed to participate details were forwarded to the London School of Hygiene and Tropical Medicine (LSHTM), where the lead researchers were based. Contact with the individual was made by the LSHTM to assess eligibility and to gain consent. Eligible participants were then sent a checklist for completion prior to the telephone interview. Members of OPUS were initially contacted by letter and the replies were sent to the LSHTM. Recruitment then continued in the same manner as the other SGs.

Some individuals requested that they not be interviewed by telephone, but to be sent a written version of the questionnaire instead or receive a personal visit. One individual received a personal visit and 108 requested (via the support groups) that they would like to receive a written questionnaire. Questionnaires were also sent to individuals who could not be contacted by the support groups.

2.3 National Centre for Social Research (NCSR)

Details for all eligible and consenting individuals were sent to the NCSR. Individuals' full names, addresses, telephone numbers, ID numbers, available times and any other relevant information were sent to the NCSR. Trained interviewers carried out the interviews by appointment. The interviews were conducted using CATI (computer assisted telephone interview) methods. Participants were told that they could split the interviews into one or more sessions if required - if this occurred another appointment was scheduled.

Participants were sent a transcript of their answers once all the interviews had been completed and were given a month to review them and to return them with corrections if necessary. Recruitment by the support groups started in July 2001 and the telephone interviews were completed by mid December.

2.4 Questionnaires

The questionnaire could be split into two distinct sections - health and exposure. The health questionnaire covered a number of different aspects: general health, past medical history, symptom checklists, questions about acute events, reporting illness to the authorities and the health of children in the family. Different sources were used for each of these sections. The IOM exposure questionnaire, i.e. as developed for and used by Pilkington et al. (1999), was used as a base for much of the exposure questionnaire.

The questionnaire was piloted in July 2001 and subsequently underwent substantial revisions, taking account of suggestions from the Study Advisory Group. The Study Advisory Group was comprised of members of the research group, representatives from the Support Groups, DEFRA and additional experts. The full membership is given in Appendix C. Checklists were supplied to participants in the telephone interview in advance of their telephone interview - these provided guidance to the interviewee as to the structure of the interview, and importantly allowed for participants to think about dates relevant to their symptoms and conditions and job history, in advance of the interview.

2.5 Data analysis: health

The telephone interviews were conducted using Computer Assisted Telephone Interview (CATI) technology. Data were automatically entered into the widely-used statistical survey analysis package SPSS during the course of the interview. Answers to open ended questions were stored in Microsoft Excel spreadsheets. Responses to the written questionnaire were double entered into SPSS and any discrepancies were assessed by a third individual.

Health data were analysed using SPSS (Version 11.01) to produce a wide range of descriptive tables. Further data descriptions and statistical regression analyses were carried out using the Genstat statistical language/ package (Genstat Committee). Logistic regression methods were used to analyse individuals' responses (yes, no) to 32 questions about specific symptoms or conditions. In addition, the symptoms were grouped into broad categories, e.g. five sensory symptoms, eight motor symptoms, giving 13 neuropathy symptoms in total. The number of positive responses in each group was also analysed using logistic regression methods; i.e. assuming a binomial distribution, a logit link function, and 'n' possible occurrences.

Explanatory variables included in these regression analyses (as well as a fitted constant) were:

- ***Gender***: fitted to estimate the log odds for women relative to men; results are presented as estimated odds ratios (ORs).
- ***Age***: expressed as a continuous variable – detailed data descriptions, by age category, showed that the effect of age could be captured sufficiently well by means of a linear trend. Results in some tables are re-expressed to show the effect (OR) of a 20-year age difference.
- ***Ever experienced an acute response to OP exposure?*** Analyses estimated the log odds for reporting 'yes' compared with 'no'. (This variable was called 'opimeff', short for 'OPs, immediate effect')
- ***Smoking status*** at time of survey, coded as lifelong non-smoker, ex-smoker or current smoker;
- ***Age at which the subject finished his/her full-time education***; coded in three categories as (i) 16 years or less; (ii) 17 or 18 years; and (iii) more than 18 years
- ***Typical past use of alcohol*** coded as none, low, medium and high. Where subjects reported that their tolerance to alcohol had changed, we analysed typical usage *before* any associated

change in alcohol usage, because the analyses were designed to explore the effect of alcohol use on presence/ absence of reported symptoms, rather than *vice versa*.

The purpose of these analyses was threefold:

i. To understand better the illnesses reported by study subjects, by describing the reported symptoms in relation to these various actual or potential explanatory variables;
ii. In particular, to estimate the effect on symptoms reporting of ever having experienced and acute response to OP exposure, adjusting as necessary for other, possibly confounding, risk factors; and
iii. To develop a sparse but reliable model of other explanatory variables (including past acute response to OPs) against which to examine possible associations with cumulative exposure to OPs from sheep dipping and from other activities – methods for those exposures and analyses are described in Chapter 3, following.

3 METHODS: EXPOSURE ASSESSMENT

3.1 Data collection and processing

Data used in assessing individual exposures were collected as part of the telephone questionnaire. A full occupational history was recorded for each individual. Additional questions on sheep dip exposure were based on those used in a previous study of sheep dipping (Pilkington *et al* 1999). These were augmented with questions on other routes of OP exposure (warble fly on cattle, application of insecticides to arable crops, treatment of stored grain or grain storage buildings, treatment of orchards and other work using insecticides). Where exposure to sheep dip was reported, supplementary questions were asked on the use of protective clothing and on the cleaning out of the dip bath after dipping. Questions concerned with the use of insecticides within the home were also included, for example use of insecticides in the garden, head lice treatment, timber treatment, pet treatment. In addition, for each job notified in the occupational history, subjects were asked if the job involved working with any vibrating equipment, lead or solvents. As with the health part of the questionnaire, input from the advisory group and its members was an important step in refining the questionnaire.

3.2 Exposure to OP pesticides and derivation of exposure metrics

The main route of exposure to organophosphate pesticides is via the dermal route. Assessment of cumulative exposure to pesticides should therefore be based on the underlying biological processes that are involved with dermal uptake into the body. The main dermal uptake process is diffusion of chemicals in the skin contamination layer through the stratum corneum towards the peripheral blood supply. Cherrie and Robertson (1995) proposed an exposure metric based on this approach, 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_{sk}). The exposure metric (E_{sk}) is obtained by multiplying these terms together:

Equation 1: $E_{sk} = C_{sk}.t.S_{sk}$

Information from the exposure questionnaire was used to provide an estimate of exposure using the metric shown above. The more general form of the equation to derive the exposure estimates for organophosphate pesticides in sheep dipping is shown below.

Equation 2: $E_{sk} = E_{sk,dip} + E_{sk,conc} + E_{sk,splash} + E_{sk,handling} + E_{sk,fall} + E_{sk,clean}$

This equation comprises six additive terms, representing exposure to dilute dip, concentrated dip on the hands, concentrated dip splashed onto the body, dip residue while handling sheep post dipping, falling into the dip and cleaning the dip bath after the work is complete. Each of these additive terms was calculated taking into account issues such as the fraction of the skin area that could potentially be contaminated during the task, the proportion of time protective equipment was reported to be used, the proportion of the relevant body area covered with clothing or gloves as a fraction of the whole of that body part, and the effectiveness of the clothing or gloves at reducing exposure.

Metrics to estimate exposure to other sources of organophosphates covered in the questionnaire were also developed. These were:

- Treatment of cattle for warble fly
- Treatment of arable crops

- Treatment of stored grain
- Treatment of orchards
- Other work with organophosphate pesticides
- Use of insecticides within the garden
- Other uses of pesticides at home

The exposure to these pesticides was estimated in a similar way to that for sheep dip, although because less detailed information was collected in the questionnaire about these activities the exposure reconstruction was necessarily simpler. Exposure metrics for handling solvents, lead, using hand-arm and whole-body vibrating tools were also derived. Again as less detailed information was collected in the questionnaire about these activities the exposure reconstruction was also necessarily simpler.

Finally, for the sheep dipping tasks, total lifetime days dipping was calculated as well as indicators for never / ever handled concentrate, never / ever splashed with concentrate, never / ever fell into dip bath and never / ever fell into dip. "Never / ever" exposed to concentrate was also calculated for sheep dipping, other work related OPs and OPs used in the home.

These methods are described in more detail in Appendices D-E.

3.3 Comparison with exposure metrics used in previous IOM study

Using formulae from the 1999 IOM report on OP exposure in sheep dipping (Pilkington *et al*, 1999) we derived exposures and exposure times for sheep dipping which were comparable to those included in the previous report. These figures apply only to time since 1970 (i.e. they assumed no exposure began before 1971), whereas our other exposure estimates include time earlier than this. While the information was collected to be as comparable as possible, it was collected in a different manner and there was not opportunity in this study (as in the earlier study) for validation of current exposure indices.

4. RESULTS: TELEPHONE SURVEY DATA

4.1 Identification and inclusion of subjects

4.1.1 Recruitment to the study

A total of 1844 individuals were registered with the 4 groups. Contact was made with 64% of individuals on the OPIN database, 40% of the PEX database and 70% of those on the NIOPSA databases. The primary reason for non-contact was the lack of a telephone number or telephone numbers being ex-directory. Individuals for whom telephone contact could not be made were sent written questionnaires. 200 letters were sent out by OPUS, but only 38 were returned to the LSHTM, giving a response rate of 19%. 129 individuals were registered with at least 2 support groups.

4.1.2 Contact by the LSHTM

A total of 692 names were sent to the LSHTM for telephone contact by the support groups. Once duplicate names had been identified a total of 595 individuals remained for telephone contact by the LSHTM and a further 87 requested written questionnaires. Contact was successfully made with 98% of the 595 individuals. 14% (81) of the individuals contacted were found to be ineligible and a further 2% (10) who were eligible refused to give their consent. 10 of the 595 individuals contacted requested a written questionnaire or personal interview(1) rather than having a telephone interview.

4.1.3 Recruitment from the written questionnaires

Questionnaires were sent to those individuals who could not be contacted by the telephone by the support groups and to those who were contacted by telephone either by the support groups or by the LSHTM and specifically requested a written version. Of the 720 questionnaires sent out, 254 (35.3%) were returned, of these, just over half (140) were returned blank or incomplete, giving a 'completed response rate' of just 19.4%. 114 questionnaires were returned completed. As the response rate for this group is so low compared to the excellent response rate achieved in the telephone study (98%) it was agreed by the Study Advisory Group that the written responses would not be incorporated into the overall analysis as it would be difficult to draw conclusions about these respondents. Descriptive results of the health data from the written questionnaires is shown in Appendix G.

4.1.4 Telephone interviews by National Centre for Social Research (NCSR)

Details of 494 eligible individuals were sent to the National Centre for Social Research (NCSR) for telephone interview. 25 of these individuals took part in the pilot study. Of the remaining 469 individuals, 447 were successfully contacted and interviewed (95.5%). Of those that were not interviewed 9 refused and 3 were too ill to participate and 1 withdrew from the study. The remaining 8 were sent written questionnaires. 1 duplicate name was inadvertently sent to the NCSR and 1 participant withdrew after the interviews were completed, leaving a final dataset of 446 individuals. Table 1 summarises the recruitment process and numbers.

Table 1. Summary of recruitment

	TOTAL	
	n	%
Total on Support Group (SG) databases	1844	
Total numbers of individuals contacted by SGs	907	49.2
Total number of individuals NOT contacted	882	47.8
Total sent to LSHTM for study	729	39.5
Total on LSHTM database (after duplicates removed)	692	
Requested written prior to LSHTM contact	87	
Eligible for telephone contact by LSHTM	605	
Contacted by LSHTM (% of eligible)	595	98.4
Eligible	524	86.6
Eligible but no consent given	10	1.7
Ineligible	81	13.4
Requested written questionnaire /personal visit	10	1.7
Not contacted by LSHTM	11	1.8
Sent to NCSR for telephone interview	494	81.7
NCSR telephone interviews	494	
Successful (pilot)	25	5.1
Successful (main)	446	90.3
Incompletes	22	4.7
* Duplicate name found between pilot and main phase, so final figure for contact by NCSR was 493		
Written Questionnaires		
Total number questionnaires sent out	720	
Number questionnaires returned	254	35.2
Total number of questionnaires completed	114	15.8

4.1.5 Exclusions of individuals from telephone analysis

For the results presented here some additional exclusion criteria were applied before the main analysis was conducted. First, although 471 interviews were completed, 25 of these were done during the pilot phase and some questions were refined or added after review of the pilot experience, thus the data were not exactly equivalent for the individuals in the pilot and main phases. For the detailed tabulations which follow we restricted the population to those 446 in the main interview phase. Secondly, we excluded those with reported medical conditions or pharmaceutical use with the potential for neurological side effects. These are listed in detail in Table 2. In total 79 individuals had one or more reason for being excluded on these grounds, leaving 367 for the analysis. For the analysis relating to acute/non acute exposure, the analysis was restricted to 355, as data on acute experiences was missing for 12 individuals. Typically, data descriptions have been based on this set of 367. For some descriptive analyses focusing on symptoms of damage to the autonomic system, further exclusions (mainly for reasons of reported hypertension) were made, leaving 290 for analysis. Regression analyses were based on 351 of the 367 subjects because of missing data for age (one person), acute response or not to OP exposure (12

people) and missing data on alcohol use (three people) – see Section 2.5 for details of the methods used and variables included.

Table 2. Exclusion criteria

	N
Successful interviews (main)	**446**
Conditions indicating exclusion	
Parkinsons	7
Diabetes	14
Rheumatoid arthritis	29
Excessively high arches of the feet	17
Stroke	2
Raynauds syndrome	1
Frontal lobe syndrome	3
Medications indicating exclusion	
B12, Neocitimin	9
Methotrexate	2
Gabapentin	2
Drugs for infections:	1
CNS drugs: Nitrous oxide, Thalidomide, Phenytoin	2
Cancer treatment drugs/Drugs of abuse / Heart condition drugs	0
Individuals meeting exclusion criteria	**79**
TOTAL FOR ANALYSIS	**367**
Additional exclusions for autonomic analysis	
High blood pressure	104
Ulcerative colitis	1
Menieries disease	2
Hypothalmic disturbance	1
TOTAL FOR ANALYSIS (autonomic)	**290**

4.2 Characteristics of study population

4.2.1 General characteristics

Of the 367 individuals from the telephone study included in the final data descriptions, there were 276 (75%) men and 91 women in the study. The average age of the group was 53.2 years (range 19-83y), with 85% of the study population aged between 40 and 69 years. The age distribution of men and of women was very similar, with the average age of the males (range 19-81y) and females (range 27-83y) being identical, at 53.2 years, the overall average.

Overall, 66% of males and 48% of females had finished their education by age 16. 56% of the respondents were either employed (13%) or self-employed (43%). 24% reported that they were unable to work due to long term or short term ill health. 13% were retired and the remainder was engaged in other activities such as looking after the home or family.

15% of all respondents reported themselves as being current smokers, with slightly more men (17%) reporting current smoking compared to women (9.9%), and 39% had smoked in the past,

giving just under half of the study population as lifelong non-smokers. These levels of current smoking are lower than figures for England collected by the Health Survey for England.

4.2.2 Health status

Participants in the study were asked to assess their current health status and asked to scale their health on a 5-point scale. Two had missing data; 32 (8.7%) reported 'excellent' or 'very good'; 59 (16.1%) reported 'good'; 139 (37.9%) reported 'fair' and 135 (36.8%) reported that their health was 'poor'.

4.2.3 Limited activity

As a measure of current health status respondents were asked about their activities over the previous 4 weeks. Most (290: 79%) reported limitation in work or activity over the previous 4 weeks, with very similar numbers (283: 77%) reporting they had accomplished less than they would have liked due to physical (ill-)health over the same period.

As would be expected, there was a clear trend with individuals' self reported health status. Of those reporting that their health status was fair, 77% reported that they were limited in their work or activity over the past 4 weeks. This rose to 98% for those with self reported 'poor' health status. Even amongst those who reported their health to be excellent or very good, a high proportion, 40.6%, reported limitations on their activities. A similar pattern was seen for questions about accomplishing less due to physical health and limitations on climbing stairs (Table 3. Self reported health status and limitations on activity in the last 4 weeks

As well as showing high levels of self-reported ill-health in the study population, these results also show some basic coherence in individuals' response to the telephone questionnaire.

Table 3. Self reported health status and limitations on activity in the last 4 weeks

Health status	Limited in work or activity over previous 4 weeks			Accomplished less than liked due to physical health over last 4 weeks			Are there days when your health makes it difficult to climb several flights of stairs		
	Yes	%	Total	Yes	%	Total	Yes	%	Total
Excellent/ Very good	13	40.6	32	10	31.2	32	6	18.8	32
Good	35	59.3	59	39	66.1	59	20	33.9	59
Fair	107	77.0	139	106	76.3	139	94	67.6	139
Poor	133	98.5	135	127	94.1	135	122	90.4	135
Missing	2	100.0	2	1	50.0	2	0	0.0	2
Total	290	79.0	367	283	77.1	367	242	65.9	367

4.3 Acute effects, symptoms and past medical conditions

Respondents were asked whether or not they had suffered any immediate health effects following exposure to organophosphates. 79% (291 individuals) of the total study population responded positively. 12 individuals did not report whether or not they had had an acute episode or not, so the data refer to 355 individuals.

4.3.1 Distribution by age and sex

Table 4. Age and sex distribution of those experiencing acute and non acute events

	Acute event						Non acute event						Total	
	Male		Female		Total		Male		Female		Total			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
18-29	4	*1.8*	0	*0*	4	*1.4*	2	*4*	1	*7.1*	3	*4.7*	7	*2.0*
30-39	18	*8.3*	6	*8.1*	24	*8.2*	4	*8*	1	*7.1*	5	*7.8*	29	*8.2*
40-49	46	*21.2*	22	*29.7*	68	*23.4*	14	*28*	2	*14.3*	16	*25.0*	84	*23.7*
50-59	87	*40.1*	28	*37.8*	115	*39.5*	15	*30*	6	*42.9*	21	*32.8*	136	*38.3*
60-69	53	*24.4*	15	*20.3*	68	*23.4*	11	*22*	4	*28.6*	15	*23.4*	83	*23.4*
70-79	7	*3.2*	2	*2.7*	9	*3.1*	4	*8*	0	*0*	4	*6.3*	13	*3.7*
80-95	1	*0.5*	1	*1.4*	2	*0.7*	0	*0*	0	*0*	0	*0.0*	2	*0.6*
Missing	1	*0.5*	0	*0*	1	*0.3*	0	*0*	0	*0*	0	*0.0*	1	*0.3*
Total	217	*100.0*	74	*100.0*	291	*100.0*	50	*100.0*	14	*100.0*	64	*100.0*	355	*100.0*
Mean age	53.6		53.2		53.5		52.5		52.1		52.4		53.2	

The distribution by age and sex was similar for those reporting or not reporting an acute episode is given in Table 4. Men comprised 75% of the group of those who reported having had at least one acute response to OPs, and 78% of the non-acute group. The mean age of the acute group (53.5 years) was also very similar to that of the non acute group (52.4 years). Detailed examination of the age distribution in Table 4 indicates that those who had experienced an acute response were somewhat more tightly clustered around the middle of the distribution, the 50-59 age group.

The broad conclusion is that the two groups were very similar in terms of age and gender. An implication is that neither age nor gender is an important confounder when the 'acute' and 'non-acute' groups are compared in terms of their reporting of symptoms, past medical conditions and other events; i.e. tables unadjusted for age and gender are not misleading when comparing the 'acute' and 'non-acute' groups.

We have, in what follows, made extensive use of this simplification when presenting summary data, while nevertheless formally adjusting for age and gender when carrying out regression analyses of symptoms, subsequently.

4.3.2 Relationship between self-reported health status and past acute response to OPs

Table 5. Self reported health status by acute exposure status

Self reported health status	Acute		Non acute		Missing	
	n	%	n	%	n	%
Excellent/Very good	19	*6.5*	12	*18.8*	1	*8.3*
Good	50	*17.2*	9	*14.1*	0	*0.0*
Fair	106	*36.4*	27	*42.2*	6	*50.0*
Poor	115	*39.5*	15	*23.4*	5	*41.7*
Missing	1	*0.3*	1	*1.5*	0	*0.0*
Total	291	*100.0*	64	*100.0*	12	*100.0*

Table 5 shows that a higher proportion of those who had had an acute episode reported their health to be either fair or poor than those who had not had an acute episode (75% vs 65%). Correspondingly, individuals in the acute group were also less likely to report their health as 'good', 'very good' or 'excellent'; for example, 6.5% of those who had experienced an acute response reported their health to be either excellent or very good, compared with 18.8% of the non acute group.

4.3.3 Most reported symptoms and conditions

Table 6. Reported symptoms by sex, ranked.

	Males		Females		ALL	
Reported Symptoms	yes %	Rank	yes %	Rank	yes %	Rank
Difficulty remembering or concentrating	81.90	1	80.20	1	81.47	1
Fatigue	74.60	2	72.50	2	74.11	2
Joint stiffness or pain	68.50	5	71.40	3	69.21	3
Irritability/outbursts of anger	70.30	3	64.80	8	68.94	4
Trouble finding words	68.50	6	69.20	4	68.66	5
Feeling depressed/low	68.50	4	62.60	13	67.03	6
NBT* Hands.	59.40	9	69.20	5	61.85	7
Night sweating	60.50	8	63.70	11	61.31	8
Feeling anxious	62.00	7	58.20	18	61.04	9
Difficulty in falling or staying asleep	57.20	11	67.00	6	59.67	10
Gastric conditions	57.60	10	64.80	9	59.40	11
MW** Legs or hips	55.80	14	64.80	10	58.04	12
Fatigue, lasting 24 h after exertion	55.80	13	62.60	14	57.49	13
MW Upper arms or shoulders	54.30	16	60.40	16	55.86	14
Muscle twitches	54.70	15	57.10	19	55.31	15
MW Hands	50.70	19	63.70	12	53.95	16
Muscle cramps	51.40	18	56.00	21	52.59	17
Feeling that your personality has changed	56.90	12	39.60	36	52.59	18
Itchy skin or rashes	42.80	24	67.00	7	48.77	19
Problems with sight	45.30	21	57.10	20	48.23	20
Dizziness	45.70	20	51.60	26	47.14	21
Difficulty with writing	44.60	22	53.80	24	46.87	22
NBT Feet	43.50	23	56.00	22	46.59	23
Trembling or shaking	41.70	26	56.00	23	45.23	24
Episodes of feeling disorientated	42.00	25	49.50	27	43.87	25
Loss of interest in sex	36.60	33	62.60	15	43.05	26
Unintended weight loss or gain	36.20	34	53.80	25	40.60	27
Nightmares/vivid dreams	40.20	28	41.80	32	40.60	28
Shortness of breath at rest	40.60	27	39.60	37	40.33	29
Pains in hands	38.40	30	38.50	38	38.42	30
Chest pain	39.50	29	35.20	44	38.42	31
Sinus congestion	37.00	32	41.80	33	38.15	32
Dry mouth	37.00	31	40.70	34	37.87	33
Alcohol intolerance	54.00	17	59.30	17	36.56	34
Diarrhoea	35.90	35	37.40	42	36.24	35
Problems with hearing	35.50	36	37.40	43	35.97	36
Pains in feet	33.00	37	45.10	29	35.97	37
Sore throat	31.90	39	47.30	28	35.69	38

NBT Elsewhere	31.20	41	44.00	30	34.33	39
Coming down with infections more easily	30.80	42	44.00	31	34.06	40
Hay fever or allergies	31.90	38	38.50	39	33.51	41
Feeling feverish	30.40	44	38.50	40	32.43	42
Wheezing	30.80	43	30.80	47	30.79	43
MW Toes or feet	27.20	45	40.70	35	30.52	44
Impulsive suicidal thoughts	31.20	40	22.00	49	28.88	45
Vertigo	25.00	46	34.10	46	27.25	46
Dental problems	23.90	47	35.20	45	26.70	47
Constipation	18.80	49	38.50	41	23.71	48
Incontinence	17.40	50	28.60	48	20.16	49
Wasting of muscles	20.30	48	16.50	50	19.35	50

* NBT: Numbness, Burning or Tingling ** MW: Muscle Weakness

Table 7. Overall reporting of past medical conditions.

Past Medical History	No	Yes	Yes %	Total
Angina	342	25	6.81	367
Arthritis (NOT rheumatoid)	287	80	21.80	367
Asthma	297	70	19.07	367
Brucellosis	359	8	2.18	367
Cancer	349	18	4.90	367
Chronic Fatigue Syndrome or ME	218	149	40.60	367
Dementia	361	6	1.63	367
Depression	181	186	50.68	367
Eczema	307	60	16.35	367
Epilepsy	357	10	2.72	367
Fibromyalgia	342	25	6.81	367
Head injury with loss of consciousness	332	35	9.54	367
Heart arrhythmia	286	81	22.07	367
Heart attack (including myocardial infarction and coronary thrombosis)	360	7	1.91	367
Heart murmur	345	22	5.99	367
Hepatitis	354	13	3.54	367
High blood pressure/hypertension	291	76	20.71	367
Irritable bowel syndrome	259	108	29.43	367
Meningitis	360	7	1.91	367
Migraine headaches	264	103	28.07	367
Multiple Sclerosis	353	14	3.81	367
Osteoporosis	354	13	3.54	367
Persistent headaches	217	150	40.87	367
Restless leg syndrome	251	116	31.61	367
Schizophrenia	366	1	0.27	367
Shingles	307	60	16.35	367
Thyroid problems	341	26	7.08	367
Tuberculosis	361	6	1.63	367
Other conditions	286	81	22.07	367
Surgical history	215	152	41.42	367

Table 6 shows the frequency of reporting of symptoms, by gender. Table 7 shows the reporting of past medical conditions. The two tables show unusually high levels of illness reported by those included in the telephone questionnaire.

Within this framework, those who had experienced an acute episode reported a higher proportion of positive responses to questions about past medical history and about individual symptoms. Table 8 shows the reporting and ranking of all the symptoms by acute exposure status; the table includes the 10 aspects of past medical history, and the 10 individual symptoms, most frequently reported among the 291 individuals who said they had experienced an acute response. The rankings in Table 8 also show that much the same set of conditions (whether past history or individual symptoms) were reported most frequently by the 64 who did not report an acute response; for example, the most frequently reported symptom in both groups was difficulty remembering or concentrating.

However, there are clear differences between the two groups in the percentages reporting symptoms and past conditions; again for example, 84% of the acute group reported this symptom compared to only 67% of the non acute group. A similar pattern was also seen in the reporting of past medical history, those in the acute group reporting a higher proportion of conditions. The most notable difference between the groups was with depression, with over 54.6% of the acute groups reporting a diagnosis as compared to only 29.7% of the non acute group.

Table 8 Reporting of past medical history and overall symptoms by exposure to an acute episode

	Acute exposure n=291			No acute n=64		
	n	%	Rank	n	%	rank
Past Medical History						
Depression	159	54.6	1	19	29.7	3
Persistent headaches	122	41.9	2	22	34.4	2
Chronic Fatigue Syndrome or ME	117	40.2	3	23	35.9	1
Restless leg syndrome	96	33.0	4	15	23.4	4=
Irritable bowel syndrome	86	29.6	5=	15	23.4	4=
Migraine headaches	86	29.6	5=	12	18.8	7=
Heart arrhythmia	67	23.0	7	12	18.8	7=
High blood pressure/hypertension	64	22.0	8	10	15.6	10
Arthritis (NOT rheumatoid)	63	21.7	9	14	21.9	6
Asthma	62	21.3	10	5	7.8	12=
Reported Symptoms						
Difficulty remembering or concentrating	245	84.2	1	43	67.2	1
Fatigue	221	76.0	2	41	64.1	2
Irritability/outbursts of anger	211	72.5	3	32	50.0	7=
Joint stiffness or pain	206	70.8	4=	37	57.8	3
Trouble finding words	206	70.8	4=	36	56.3	4
Feeling depressed/low	205	70.5	6	31	48.4	9=
NBT Hands.	192	66.0	7	29	45.3	13=
Night sweating	184	63.2	8	31	48.4	9=
Alcohol intolerance	165*	62.9	9	30**	51.7	6
Feeling anxious	181	62.2	10	32	50.0	7=

* denominator is 262, ** denominator is 58

The 32 reported symptoms were classified into broad groups, to facilitate analysis and the identification of patterns. The groupings, the numbers of associated symptoms, and the average number of symptoms reported are shown in Table 9, separately for those who did, and who did not, report an acute episode; those in italics are sub-groups of the three major headings of neuropathy, neurobehavioural and autonomic symptoms. Table 9 appears to include 34 symptoms because 'trembling and shaking' was included both as a motor and as an anxiety symptom, and similarly 'dry mouth' was included both as an anxiety and as an autonomic symptom. Details of the groupings used are given in Table 10. Symptoms selected for more detailed analyses.

Table 9. Summary scores (mean number of symptoms) by symptom group (sub-groups in italics) and by ever reported an acute response to OPs, or not

	Total no. of symptoms	Acute	Non acute	Total
	n	291	64	355
Neuropathy	13	6.2	4.3	5.87
Sensory	*5*	*2.3*	*1.5*	*2.16*
Motor	*8*	*3.8*	*2.8*	*3.71*
Neurobehavioural	15	8.2	5.9	7.88
Anxiety	*6*	*3.0*	*2.2*	*2.89*
Orientation	*2*	*1.3*	*1.0*	*1.25*
Language	*2*	*1.2*	*0.9*	*1.15*
Depression	*5*	*2.7*	*1.9*	*2.58*
Autonomic	6	2.3	1.7	2.17

Again, these summary data show that people who reported having had an acute response to OPs reported more symptoms than those who did not, a result that applied to every category of symptoms examined. For symptoms, the size and statistical significance of these differences, between those who reported and acute response to OPs and those who did not, are examined further below, adjusting for age and gender differences – both the number of symptoms in a group, and occurrence or not of symptoms individually, were analysed. Key results are described in the main text; detailed results are given in Appendices H & I.

Table 10. Symptoms selected for more detailed analyses.

Grouping	Symptom
Neuropathy Sensory	pain in hands pain in feet NBT feet Numbness, burning, Tingling NBT hands NBT elsewhere
Neuropathy motor symptoms (also anxiety)	muscle weakness feet muscle weakness hand muscle weakness arms muscle weakness legs muscle cramps muscle twitches trembling or shaking muscle wastage
Neurobehavioural Anxiety	Dizziness difficulty in staying/falling asleep feeling anxious chest pain
Neurobehavioural Orientation	episodes of feeling disorientated Difficulty remembering or concentrating
Neurobehavioural Language	Trouble finding words Difficulty with writing
Neurobehavioural Depression	feeling depressed or low Suicidal thoughts outbursts of anger/irritability unintended weight loss or gain feeling personality has changed
Autonomic (also anxiety)	constipation diarrhoea dry mouth gastric conditions incontinence problems with sight

4.4 Comparison with other studies-non specific symptoms

The questionnaires used in the SHAPE study used 2 of the Gulf War studies (Fukuda, 1998) (Unwin, 1999 as sources of questions. Of the 82 symptoms and conditions that the SHAPE study asked about, 27 of these overlapped with the Unwin study and 25 with the Fukuda study. Both of these studies looked at non-specific symptoms.

Of the symptoms that overlapped with the Unwin study, within the top 5 reported symptoms 3 were also in the top 5 of the Gulf war cohort (fatigue, joint stiffness or pain and irritability/anger) and 7 overlapped with the top 10. (Table 11)

Within the 23 overlapping symptoms with the Fukuda study, 3 symptoms were common to both the SHAPE and Fukuda Veterans cohort top 5 symptoms (joint stiffness or pain, irritability and difficulty remembering or concentrating). Within the top 10 symptoms in the Fukuda study, 5 symptoms overlapped. These are shown in Table 12.

Table 11. Ranking of symptoms. SHAPE and Gulf War (Unwin) study

Reported Symptoms	GW Gulf (3284)		GW Bosnia (1815)		GW Era (2408)		SHAPE ALL (367)	
	%	rank	%	rank	%	rank	%	rank
Irritability/outbursts of anger	55.20	1	33.60	1	25.80	3	68.94	4
Fatigue	50.70	2	26.30	3	27.70	2	74.11	2
Difficulty in falling or staying asleep	48.00	3	30.70	2	28.40	1	59.67	10
Joint stiffness or pain	40.00	4	21.80	4	23.50	4	69.21	3
Difficulty remembering or concentrating	39.70	5	17.20	6	15.10	6	81.47	1
Chest pain	25.30	6	13.20	9	11.80	10	38.42	31
NBT Hands.	24.70	7	8.70	15	11.10	11	61.85	7
Night sweating	24.60	8	12.80	10	9.90	12	61.31	8
Sore throat	22.30	9	15.20	7	13.30	7	35.69	38
Nightmares/vivid dreams	21.70	10	13.80	8	9.10	15	40.60	28
Hay fever or allergies	21.60	11	18.70	5	15.80	5	33.51	41
Wheezing	20.60	12	10.10	13	9.50	13	30.79	43
Diarrhoea	20.10	13	11.40	12	12.10	8	36.24	35
Sinus congestion	19.90	14	11.70	11	12.00	9	38.15	32
Dry mouth	17.60	15	9.40	14	6.80	18	37.87	33
NBT Feet	17.10	16	5.50	21	7.00	17	46.59	23
Dizziness	17.00	17	7.20	16	7.60	16	47.14	21
Loss of interest in sex	17.00	18	7.10	17	5.40	20	43.05	26
Shortness of breath at rest	15.50	19	6.40	18	5.60	19	40.33	29
Alcohol intolerance	12.30	20	5.40	22	4.20	22	36.56	34
Trembling or shaking	12.20	21	5.70	20	3.90	23	45.23	24
Problems with hearing	11.80	22	5.90	19	9.40	14	35.97	36
Episodes of feeling disorientated	10.60	23	3.40	25	3.70	24	43.87	25
Constipation	9.90	24	4.90	23	4.70	21	23.71	48
Feeling feverish	8.90	25	3.70	24	3.00	26	32.43	42
Gastric conditions	8.20	26	3.30	26	3.50	25	59.40	11
Problems with sight	5.50	27	2.60	27	2.30	27	48.23	20

Table 12. Ranking of symptoms. SHAPE and Gulf War (Fukuda) study

Reported Symptoms	Fukuda-veterans		Fukuda non deployed		ALL (367)	
	%	rank	%	Rank	%	Rank
Sinus congestion	52.00	1	39.00	1	38.15	32
Fatigue	43.00	2	17.00	3	74.11	2
Difficulty remembering or concentrating	34.00	3	9.00	9=	81.47	1
Joint stiffness or pain	30.00	4	11.00	6	69.21	3
Difficulty in falling or staying asleep	28.00	5	13.00	5	59.67	10
Gastric conditions	27.00	6	15.00	4	59.40	11
Trouble finding words	26.00	7	9.00	9=	68.66	5
Irritability/outbursts of anger	25.00	8	9.00	9=	68.94	4
Itchy skin or rashes	23.00	9	7.00	12=	48.77	19
Hay fever or allergies	19.00	10	19.00	2	33.51	41
Feeling depressed/low	18.00	11	10.00	7=	67.03	6
Diarrhoea	18.00	12	4.00	17=	36.24	35
Feeling anxious	17.00	13	7.00	12=	61.04	9
Sore throat	17.00	14	10.00	7=	35.69	38
Shortness of breath at rest	16.00	15	6.00	15=	40.33	29
Chest pain	15.00	16	7.00	12=	38.42	31
Loss of interest in sex	14.00	17	6.00	15=	43.05	26
Dizziness	14.00	18	4.00	17=	47.14	21
Fatigue, lasting 24 h after exertion	13.00	19	2.00	21=	57.49	13
Night sweating	13.00	20	4.00	17=	61.31	8
Episodes of feeling disorientated	7.00	21	1.00	23	43.87	25
Wheezing	6.00	22	3.00	20	30.79	43
Feeling feverish	5.00	23	2.00	21=	32.43	42

Individuals in the acute group were also less likely to report good health. 6.5% of the acute group reported their health to be either excellent or very good as compared to 18.8% of the non acute group. 79.5% of the acute group reported fair or poor health compared to 65.6% of the non acute group.

These symptoms are compared to those reported in the HSE study that examined symptom reporting following occupational exposure to organophosphate pesticides in sheep dip. (Jackson, 2001). Exposed individuals were sheep farmers and controls were quarry workers. The HSE study examined 73 different symptoms grouped into 6 categories. The SHAPE study used 19 different symptoms-of these, 16 overlapped with the HSE study. Some of the symptoms were recorded with different definitions-these are also shown in Table 13 Only 2 symptoms (headaches and tiredness) from the HSE exposed group appear in the top 5 in the SHAPE study. Within the SHAPE top 10 symptoms, there are 5 common symptoms with the HSE exposed and 6 with the HSE controls.

Table 13. Acute symptoms reported in SHAPE study and HSE comparisons.

	ALL (291)		HSE-exposed 119		HSE-controls 118		HSE definitions
	%	rank	%	rank	%	rank	
Headache	79.04	1	39.09	3	22.43	6	
Tiredness	76.63	2	42.20	2	38.32	4	lethargy
Aching muscles	70.10	3	8.26	11	50.00	1	general ache
Weakness	69.07	4	0.00	16	13.89	9	general weakness
Chest tightness	55.67	5	7.34	12	8.33	13	chest pain
Nausea	45.36	6	7.27	13	7.41	14	feelings of nausea
Muscle cramp	45.02	7	48.18	1	9.43	11	general cramp
Apathy	43.64	8	n/a		n/a		
Runny nose	42.96	9	36.36	4	37.96	5	
Watery eyes	42.61	10	10.00	9	19.44	8	
Sore throat	42.27	11	23.15	6	22.22	7	
Blurred vision	41.24	12	14.55	8	9.26	12	
Temperature/high fever	36.08	13	9.17	10	1.85	16	fever
Loss of appetite	35.05	14	6.42	14	10.19	10	
Other	29.21	15	n/a		n/a		
Cough with phlegm or sputum	28.87	16	25.00	5	42.06	2	productive cough
Dry cough	26.12	17	22.94	7	42.06	3	cough
Vomiting	16.15	18	1.83	15	4.63	15	
Difficulty in passing urine	13.75	19	n/a		n/a		
Mean number of symptoms reported	8.39						

4.5 Multivariate analysis of symptom patterns (i.e. clustering or co-occurrence of symptoms)

We investigated patterns of symptom occurrence (e.g.: Do persons reporting muscle weakness in feet also report pain in feet? Do persons reporting autonomic symptoms also report neuro-pathological symptoms?), in the hopes of shedding light on the source of these symptoms.

4.5.1 Statistical methods

There are two technical issues that obliged us to use some rather technical procedures for this:

1. Where health is measured on numerical scales, a natural measure of association between two of them is the correlation coefficient. In our case each symptom was simply reported as present or absent – a dichotomous scale. Although correlations can be calculated for such variables, they are problematic, and there is no measure of association of equivalent currency for them.
2. The large number of symptoms (32) makes the total number of pair-wise associations between them large (496), too many for elaborate or even quite simple description and analysis of each. Methods for reducing dimension of large numbers of associations are well-developed when they are of numerical variables (eg principle component analysis), if sometimes hard to interpret. For dichotomous variables analogous methods are newer and interpretation is not so straightforward but offer an alternative to ad-hoc selection of specific associations to investigate.

We approached these dual problems by undertaking a multiple correspondence analysis (MCA) and reviewing multiple pair-wise associations between symptom. We approached these dual problems by undertaking a multiple correspondence analysis (MCA) and reviewing multiple pair-wise associations between symptom. MCA (also called homogeneity analysis) is an analogous procedure to principle component analysis more suitable for dichotomous variables. MCA describes the principle components of co-variability (co-occurrence) of symptoms in just a few "dimensions", which can be thought of a scores made up of weighted counts of the symptoms (some weights may be negative). We used the SPSS procedure "HOMALS" to do this to the list of 32 symptoms.

4.5.2 Results

The explanatory power of each dimension is reflected in the magnitude of the eigenvalues for each dimension. The MCA analysis identified a first and easily strongest dimension (eigenvalue 0.27) as a score placing positive weights on all symptoms. Indeed, though the weights differed somewhat between symptoms, the score was very highly correlated (r=0.99) with the simple count of occurrences of all 34 symptoms. Table XX summarises the Discrimination Measures for each symptom in relation to each dimension. Underscored values indicate that the contribution to (weight for) the score for the report of that symptom was negative . It can be seen that for dimension 1 all parameters are positively weighted. This dimension can be seen as describing a pattern whereby persons in the study tended to report more than one symptom. In other words, if someone reported one symptom, it increased likelihood that they reported another.

This pattern of clustering of symptoms in general in some respondents was also identified in various other ways. The logistic regression analyses of symptom scores (see elsewhere in this report) showed variation between persons above that expected at random (by the binomial distribution). Further, each symptom was strongly and significantly associated (by logistic regression) with each other symptom and the sum of all other symptoms.

Beyond this general tendency to report either many or few symptoms, in the subsequent dimensions are there particular patterns of symptoms that tended to be reported together? We found suggestive evidence for this. The second strongest dimension (eigenvalue 0.07) gave positive weights to several neuropathological/sensory symptoms and negative weights to neuro-behavioural symptoms (especially of anxiety and depression),. This may be interpreted as suggesting that after allowing for general tendency to report symptoms, there was some tendency to report symptoms in one or other of these groups, but not both.

The third strongest dimension identified by MCA (eigenvalue 0.05) had moderate but consistently-weighted for the autonomic symptoms, suggesting some tendency for persons to report these several of these symptoms from this group if they reported any, after allowing for other factors. (That these weights are negative rather than positive is arbitrary – the sign of scores is immaterial.)

As an alternative approach to investigating these patterns in the second and third dimension, we calculated odds ratios for reporting one symptom given that the other was reported, after adjusting in logistic regression for the total number of other symptoms reported, and these tended to support the interpretation above of the correspondence analysis: (a) There was a preponderance of odds ratios below one for association between neuro-behavioural and neuropathological symptoms, corresponding to the opposite weights in the second dimension identified in the correspondence analysis. (b) Theere was a broad pattern of higher ORs within the neuro-behavioural, neuropathological, and autonomic symptom groups, representing associations between symptoms on the same group and confirming a general tendency to report multiple symptoms from the same

group more commonly than reporting those from different groups, as suggested in the second and third dimensions of the correspondence analysis.

We emphasize that the evidence for specific patterns of symptom co-occurrence could only be seen once the general pattern for one symptom report to make another more likely was discounted. We repeated these analyses limiting the sample to those persons who had had an acute episode, and to sheep-dippers. These showed broadly the same pattern, in particular as regards the strong first dimension.

Table 14. Discrimination measures by symptom and dimension in Multiple Correspondence Analysis of symptom reports (n=355)

		Dimension		
Grouping	Symptom	1	2	3
Neuropathy Sensory	pain in hands	.411	.101	.028
	pain in feet	.388	.156	.054
	NBT feet	.336	.128	.012
	Numbness, burning, Tingling NBT hands	.296	.031	.000
	NBT elsewhere	.181	.065	.022
Neuropathy motor symptoms	muscle weakness feet	.333	.181	.101
	muscle weakness hand	.430	.080	.001
	muscle weakness arms	.338	.023	.000
	muscle weakness legs	.358	.089	.002
	muscle cramps	.370	.030	.009
	muscle twitches	.306	.009	.009
(also anxiety)	trembling or shaking	.284	.000	.032
	muscle wastage	.137	.067	.002
Neurobehavioural Anxiety	Dizziness	.201	.048	.059
	difficulty in staying/falling asleep	.203	.019	.029
	feeling anxious	.215	.176	.056
	chest pain	.232	.017	.014
Neurobehavioural Orientation	episodes of feeling disorientated	.285	.090	.001
	Difficulty remembering or concentrating	.253	.107	.010
Neurobehavioural Language	Trouble finding words	.277	.077	.001
	Difficulty with writing	.389	.001	.001
Neurobehavioural Depression	feeling depressed or low	.196	.246	.104
	Suicidal thoughts	.108	.243	.084
	outbursts of anger/irritability	.242	.157	.056
	unintended weight loss or gain	.218	.000	.053
	feeling personality has changed	.294	.160	.153

Autonomic	constipation	.155	.025	.078
	diarrhoea	.206	.020	.192
(also anxiety)	dry mouth	.229	.001	.039
	gastric conditions	.335	.022	.139
	incontinence	.135	.007	.053
	problems with sight	.237	.002	.049

4.6 Immediate health effects following exposure

Respondents were asked to identify from the checklist any acute symptoms that they may have suffered. They were also asked about when the symptoms set in, how long they took to recover from them, and the number of times they have experienced these acute effects. Most (90%) had experienced an acute response on more than one occasion; 63% reported past acute response on more than 10 occasions.

Table 15. Immediate health effects following exposure

	Once- 10 acute exposures			11-50+ acute exposures		
	n	%	rank	n	%	rank
Headache	72	75.0	1	152	81.3	1
Tiredness	69	71.9	3	150	80.2	2
Aching muscles	70	72.9	2	129	69.0	3
Weakness	68	70.8	4	128	68.4	4
Chest tightness	46	47.9	6	112	59.9	5
Sore throat	32	33.3	13	89	47.6	6
Watery eyes	33	34.4	12	87	46.5	7
Nausea	41	42.7	9	86	46.0	8
Apathy	41	42.7	8	84	44.9	9
Runny nose	37	38.5	10	83	44.4	10
Muscle cramp	47	49.0	5	81	43.3	11
Blurred vision	42	43.8	7	75	40.1	12
Temperature/high fever	32	33.3	14	71	38.0	13
Loss of appetite	34	35.4	11	66	35.3	14
Cough with phlegm or sputum	20	20.8	16	60	32.1	15
Dry cough	16	16.7	18	58	31.0	16
Other	28	29.2	15	54	28.9	17
Vomiting	16	16.7	17	28	15.0	18
Difficulty in passing urine	13	13.5	19	25	13.4	19
Total in group	96			187		

Information on exposure frequency was missing for 8 individuals.

Table 15 shows the symptoms reported by those who experienced up to 10 acute events and for those with 11-50+ acute events. These two groups experienced the same top 4 events: headache, tiredness and aching muscles and weakness. On average (arithmetic mean over the 291 subjects who reported past acute effects) 8.39 acute symptoms were reported. In over 70% of cases acute symptoms set in on the same day of exposure, in 13% they appeared the following day. 24%

overall reported a recovery period of greater than 2 weeks and 15.8% reported that they did not ever recover.

4.7 Neuropathy symptoms

As noted in Table 9, 13 of the self-reported symptom questions were grouped as neuropathy symptoms. These were further subdivided into two categories: motor and sensory. Data descriptions of the motor symptoms included an attempt to express severity. No measure of severity of symptoms was incorporated into the sensory scores, nor into the statistical regression analysis (unless number of symptoms in a group is viewed as a measure of severity).

4.7.1 Sensory symptoms

The five symptoms that were classified as sensory were:

- Pains in hands
- Pains in feet
- Numbness, burning or tingling (NBT) in hands
- NBT feet
- NBT elsewhere

Overall 24% of respondents did not report any sensory symptoms, but there was a marked difference between the acute and non acute groups with 44% of the non acute group reporting no symptoms versus only 20% of the acute group Table 9 earlier, summarised the number of reported sensory symptoms. Overall a mean of 2.17 symptoms were reported. Those who had experienced an acute episode reported a greater number of sensory symptoms (mean of 2.31 symptoms) compared to those without an acute episode (mean 1.5 symptoms). 17% of the acute group had experienced all 5 of the sensory symptoms compared to 9% of the non acute group.

Regression analyses showed no effect of age (Table 16). There was a clear gender difference, with women more likely than men to report sensory symptoms (odds ratio (OR) 1.5, $p<0.05$). Adjusting for gender and age, the odds of reporting any sensory symptom was almost twice as high among those who reported having had an acute response, a difference that was highly significant statistically (OR 1.95, $p<0.01$). Further analyses showed no clear or suggestive effect of smoking status, age at ending education, or typical past use of alcohol on the number of sensory symptoms reported. Details are given in Appendix H.

Table 16. Summary results from logistic regression analyses of number of sensory symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	1.50	1.02-2.22	2.04	<0.05
Age (per 20 years *younger*)	1.04	0.76-1.43	-0.25	NS
Ever acute response to OPs (Y v N)	1.95	1.22-3.10	2.79	<0.01

Table 17. Summary of symptom-specific results, based on logistic regression analyses of symptom occurrence on gender, age and acute response or not

Symptom	Gender: F v M		Acute: Y v N	
	OR	p-value	OR	p-value
Hand pain	(1.0)	NS	2.3	<0.05
Foot pain	1.6	<0.01	(1.6)	NS
NBT hands	1.6	<0.1	2.3	<0.01
NBT feet	1.7	<0.05	2.2	<0.05
NBT elsewhere	1.9	<0.05	1.8	<0.1

Analysis of the sensory symptoms individually showed broadly similar results, with some detailed differences (Table 17). There were no clear or suggestive gender differences for hand pain, and the estimated effect for NBT hands was statistically significant at the 10%, but not at the 5%, levels. The association with ever having had an acute response was most marked – highest OR, and strongest statistical significance – for hand pain, NBT hands, and NBT feet. There was no evidence that smoking, education or alcohol consumption was additionally relevant to the reporting of individual sensory symptoms.

4.7.2 Motor symptoms

Total number of motor symptoms

The mean motor symptom scores (i.e. mean number of motor symptoms reported by individuals summed across all four of the above sub-groups) were summarised earlier in Table 9. On average those who had reported an acute exposure reported 3.9 motor symptoms, from a maximum of eight, compared with an average of 2.8 among those who had not suffered an acute response.

Logistic regression analyses again showed no effect of age (Table 18) – the very weak estimate of higher prevalences at lower ages was far from significant statistically. There was again evidence of a gender difference, with (as for sensory symptoms) women more likely than men to report motor symptoms. However, the estimated odds ratio was somewhat lower (OR 1.36) than for sensory symptoms and the finding was statistically significant at the 10% level (i.e. $p<0.1$) rather than the 5%. Adjusting for gender and age, those who reported having had an acute response were again more likely to report any of the motor symptoms, and although the estimated relative risk was somewhat lower than for sensory symptoms, at 1.73 rather than 1.95, the effect was again highly significant statistically ($p<0.01$).

Table 18. Summary results from logistic regression analyses of number of motor symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	1.36	0.97-1.91	1.80	<0.1
Age (per 20 years *younger*)	1.16	0.88-1.53	-1.08	NS
Ever acute response to OPs (Y v N)	1.73	1.17-2.57	2.75	<0.01

Further analyses again showed no clear or suggestive effect of age at ending education, or of past intensity of alcohol consumption. There was however some evidence that (adjusting for age, gender and acute response or not) current smokers reported more motor symptoms than non-smokers or ex-

smokers. For example, the contrast between current and non-smokers suggested an OR of 1.55 ($p<0.1$). Further details are given in Appendix H.

Sub-groups of motor symptoms

The eight motor symptoms were divided into four groups of two symptoms each according to severity. The groupings, which were intended to express increasing severity, are as follows:

- Motor 1:
  - Muscle weakness (MW) toes or feet
  - MW hands
- Motor 2:
  - MW upper arms or shoulders
  - MW legs or hips

- Motor 3
  - Muscle cramps
  - Muscle twitches
- Motor 4
  - Trembling or shaking
  - Muscle wastage

Table 19 shows the reporting of the eight motor symptoms by these groupings and also by acute episode status. Overall, it might be expected that the % of people reporting *some* symptoms would decrease (or, equivalently, the number reporting *no* symptoms would increase) with increasing symptom severity; and in particular, that the number reporting *both* symptoms in a group would decrease with increasing severity. Results (Table 19) showed some evidence in support of this view, for Motor Groups 2, 3 and 4; for example fewer individuals reported both symptoms in 'Motor 4' – the highest severity category. However 157 subjects (44%) reported no muscle weakness in the extremities (toes or feet, or hands) (Motor 1), contrary this trend.

What is clear from Table 19, however, is that for motor symptoms as well as for sensory symptoms earlier, those who reported having had an acute effect of OPs also reported more symptoms. Specifically, in each of the four groups, the proportion reporting no symptoms was lower, and the reporting both symptoms was higher, in the 'acute' group compared with the 'non-acute' group.

Table 19. Reporting of motor symptoms, by whether or not subject reported having experienced and acute response to OP exposure

		Acute		Non acute		Total	
	No. symptoms	n	%	n	%	n	%
Motor 1	0	116	39.9	41	64.1	157	44.2
	1	89	30.6	9	14.1	98	27.6
	2	86	29.6	14	21.9	100	28.2
Motor 2	0	84	28.9	30	46.9	114	32.1
	1	70	24.0	9	14.1	79	22.2
	2	137	47.1	25	39.1	162	45.6
Motor 3	0	84	28.9	24	37.5	108	30.4
	1	94	32.3	22	34.4	116	32.7
	2	113	38.8	18	28.1	131	36.9
Motor 4	0	127	43.6	45	70.3	172	48.4
	1	128	44.0	14	21.9	142	40.0
	2	36	12.4	5	7.8	41	11.6
	Total**	291	100.0	64	100.0	355*	100.0

* Numbers do not add up to 367 as 12 individuals did not report whether they had had an acute episode or not
** This row total column (numbers and percentages) applies to *each* of the four symptom groups, Motor 1 – Motor 4.

Results from analyses of the motor symptoms individually are summarised in Table 20; as before, more details are given in Appendix H & I. Results are reported for differences associated with gender and with ever having had an acute response, from logistic regression models also incorporating age.

Table 20 shows that while there was some general consistency in pattern, there were also important differences between the symptoms individually.

- Results for the two Motor 1 symptoms were the most clearly similar to those for sensory symptoms earlier.
- Results for 'trembling and shaking' (Motor 4) also clearly showed a gender difference, and the difference associated with ever having had an acute response was very marked. In addition, there was a suggestive difference associated with age with the coefficient suggesting higher risks of reporting the symptom at younger ages (OR 1.4 for each 20 years *younger*, $p<0.1$). In all, results for 'trembling and shaking' – which also is an anxiety symptom – seem different from the other 12 neuropathy symptoms, and especially the more severe of the motor symptoms.
- Gender differences in the other five motor symptoms declined in size and statistical significance with increasing severity of symptoms.
- The estimated effect of past acute response was generally positive but was very far from statistical significance for muscle twitches and muscle cramps.

Table 20. Summary of symptom-specific results, based on logistic regression analyses of symptom occurrence on gender, age and acute response or not

Symptom		Gender: F v M		Acute: Y v N	
		OR	p-value	OR	p-value
Motor 1	MW hands	1.8	<0.05	2.3	<0.01
	MW toes or feet	1.9	<0.05	(1.7)	NS
Motor 2	MW upper arms/ shoulders	(1.3)	NS	(1.5)	NS
	MW legs or hips	(1.5)	NS	1.8	<0.05
Motor 3	Muscle cramps	(1.2)	NS	1.7	<0.1
	Muscle twitches	(1.1)	NS	(1.4)	NS
Motor 4	Muscle wastage	(0.8)	NS	(1.3)	NS
	Trembling or shaking	1.7	<0.05	3.5	<0.001

Regarding effects not shown in Table 20,

- An effect of age was also found for muscle twitches (OR 1.5 for each 20 years *younger*; $p<0.1$) but not for any other symptom.
- Adjusting for age, gender and past acute response, higher prevalences in smokers compared to non-smokers were fund for MW toes and feet (OR 2.3, $p<0.05$) and for 'trembling or shaking' (OR 2.1, $P<0.05$). There was some suggestion of a smoking effect linked with MW legs or hips and MW cramps, but the pattern was unclear.
- Statistically significant differences between alcohol categories in the reporting of MW cramps ($p<0.01$) were not easily interpretable – adjusting for other factors, highest prevalences were found among those with low alcohol consumption; then among those with 'none' or 'medium'; and lowest prevalences among those with 'high' past alcohol consumption.

4.7.3 Neuropathy symptoms overall

Total number of symptoms

The overall neuropathy scores are summarised in Table 9, that is, the total number of neuropathy symptoms reported by individuals, broken down by motor and sensory scores. The mean neuropathy score reported was 5.87 symptoms (maximum of 13); those with an acute episode reported the highest mean score of 6.17.

Regression analysis of number of positive responses from all 13 symptoms together showed:

- evidence of more symptoms reported by women than men (OR 1.5, $p<0.05$)
- no clear or suggestive evidence that numbers of symptoms varied with age
- strong evidence that, having adjusted for gender, those with past acute response to OPs reported more neuropathy symptoms than those without (OR 1.8, $t = 3.12$, $p<0.001$)
- no evidence of a general effect of alcohol or age at ending education
- suggestive evidence that, compared with non- and ex-smokers, current smokers reported more symptoms, the detailed analysis indicating that this applied to selected symptoms only.

Changes in neuropathy symptoms

Respondents were asked whether they were still suffering from the symptoms classified as neuropathy; data are available for 10 of the 13 symptoms. The least improvement was seen in terms of muscle strength in legs and hips and toes and feet, followed by pain in hands and feet. The reduction of muscle twitching showed the most improvement.

4.8 Neurobehavioural symptoms

4.8.1 Neurobehavioural symptoms overall; key sub-groups

In all, 15 of the symptoms questions from the telephone survey referred to neurobehavioural symptoms. These were grouped into four neurobehavioural groups:

- anxiety
- orientation
- language
- depression.

Analysis was done on each of these groups separately – numbers of symptoms in the sub-group, and individual symptoms within each group – and on neurobehavioral symptoms overall. Simple descriptive results for the groups are summarised in Table 9, above. Those with an acute event reported the greatest number of symptoms (mean=8.19); and indeed, in all categories, those who had reported an acute effect of OPs also reported more neurobehavioural symptoms. Overall 97% of all respondents reported at least one symptom from at least one group.

Table 21. Summary results from logistic regression analyses of number of 15 neurobehavioural symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	1.00	0.79-1.35	0.26	NS
Age (per 20 years *younger*)	1.40	1.12-1.74	-3.01	<0.01
Ever acute response to OPs (Y v N)	1.89	1.39-2.57	4.08	<0.001

Summary results from regression analyses of the total number of neurobehavioural symptoms are given in Table 21. In contrast to the neuropathy symptoms, there was no evidence of a gender difference overall. There was, however, a clear relationship with age, with higher prevalences in younger people. The OR was estimated as 1.4 per 20 years *younger* (equivalently, 0.72 per 20 years *older*), a result that was highly significant statistically ($p<0.01$). In addition, and adjusting for age (and gender), the reporting of neurobehavioural symptoms was again higher in people who reported an acute response to OPs, compared with those who didn't (OR 1.9, $t = 4.1$, $p<0.001$), a result that was very highly significant statistically.

Adjusting for age, gender and acute response (or not), there was no evidence that neurobehavioural symptoms overall were associated with age at leaving education, or past intensity of alcohol use. However there was some evidence that current smokers reported more neurobehavioural symptoms than ex-smokers or life-long non-smokers, with the OR for current smokers relative to non-smokers estimated as 1.6 ($p<0.1$). As before, further details are given in Appendix H.

4.8.2 Anxiety

Six symptoms were considered for anxiety; dizziness, dry mouth, trembling or shaking, difficulty in falling or staying asleep, feeling anxious and chest pain. 10% of the total respondents did not report a single symptom associated with anxiety. Amongst those who had reported an acute episode only 7% reported no symptoms compared to 20% of those without an acute event.

Regression analyses of number of positive responses from the six anxiety symptoms in relation to gender, age and ever acute response (Table 22) showed very similar results to those from neurobehavioural symptoms overall (Table 21). Further analyses also showed very similar results for education, alcohol and smoking, with the contrast between current and non-smokers estimated as an OR of 1.5, almost significant at the 5% level.

Table 22. Summary results from logistic regression analyses of number of six anxiety symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	1.15	0.85-1.56	0.90	NS
Age (per 20 years *younger*)	1.31	1.02-1.68	-2.12	<0.05
Ever acute response to OPs (Y v N)	1.81	1.27-2.58	3.27	<0.01

As expected, analyses of the six symptoms individually showed some differences in results for age, ever acute response and smoking (Table 23), and for gender and other factors (not shown in Table 23).

- The effect of age was rarely shown clearly, and never at the $p<0.05$ level, in analyses of the anxiety symptoms individually. However, the estimated direction of effect always suggested higher prevalences in younger people, leading to a statistically significant ($p<0.05$) finding for total number of positives out of the six symptoms, as noted earlier.
- The evidence that people with past acute response to OPs reported more anxiety symptoms came most clearly for 'trembling or shaking', then for chest pain and anxiety.
- There was evidence of an effect of gender on 'trembling or shaking' (OR for women relative to men 1.7, $p<0.05$, as discussed earlier – Table 20) and on difficulty sleeping (OR 1.6, $p<0.1$). However, other symptoms showed no evidence of a gender effect.

Table 23. Summary of symptom-specific results for anxiety symptoms, based on logistic regression analyses of symptom occurrence on gender, age, acute response or not, and smoking habit

Symptom	Age: per 20y younger		Acute response: Y v N		Smoking: Current v Non	
	OR	p-value	OR	p-value	OR	p-value
Anxiety	(1.4)	NS	1.8	<0.05	(1.1)	NS
Dizziness	1.5	<0.1	(1.5)	NS	(0.9)	NS
Dry mouth	(1.1)	NS	(1.6)	NS	2.0	<0.05
Trembling or shaking	(1.4)	<0.1	3.5	<0.001	2.1	<0.05
Difficulty sleeping	(1.3)	NS	(1.3)	NS	(1.5)	NS

Chest pain	(1.3)	NS	2.3	<0.05	2.1	<0.05

- An effect of smoking (higher prevalences in current compared with non-smokers) was shown for the physical symptoms of dry mouth, trembling or shaking and chest pain.
- There were some suggestions that past consumption of alcohol was associated with the reporting of anxiety, dry mouth and chest pain, but there was no consistent pattern to these results.

4.8.3 Language

Two symptoms were associated with a language disorder: trouble finding words and difficulty with writing. Once again the highest proportion of individuals reporting symptoms associated with language problems was found amongst those reporting a previous history of an acute event.

Regression analyses of number of language symptoms showed no evidence of an effect of age or of a gender difference. (Table 24) They did however confirm that the relative risk of reporting a language symptom was higher in those who had reported an acute response (OR 2, $p<0.05$, and almost significant at the 1% level). There was no evidence of an effect of smoking or education; and some evidence that those with low alcohol consumption reported more language problems than other people. Similar results were found for the two language symptoms individually.

Table 24. Summary results from logistic regression analyses of number of two language symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	1.21	0.75-1.94	0.78	NS
Age (per 20 years *younger*)	1.24	0.85-1.81	-1.09	NS
Ever acute response to OPs (Y v N)	1.99	1.18-3.37	2.57	<0.05

4.8.4 Orientation/memory

Orientation and memory also considered two symptoms: episodes of feeling disoriented and difficulty remembering or concentrating. Those with an acute episode reported a mean of 1.3 symptoms compared with 1.0 reported by those without an acute event (Table 9). Regression analyses of the symptoms individually showed that the effect, while present for both symptoms, was associated more with memory and concentration than disorientation, though the latter was almost significant at the 5% level.(Table 25) Both symptoms showed a similar effect of age; there was evidence that a higher proportion of current smokers reported feeling disoriented.

Table 25. Summary of symptom-specific results for orientation/ memory, based on logistic regression analyses of symptom occurrence on gender, age, acute response or not, and smoking habit

Symptom	Age: per 20y younger		Acute response: Y v N		Smoking: Current v Non	
	OR	p-value	OR	p-value	OR	p-value
Feeling disoriented	1.5	<0.05	1.8	<0.1	2.0	<0.05
Difficulty remembering	1.6	<0.1	2.9	<0.001	(0.9)	NS

or concentrating						

4.8.5 Depression

Five symptoms were associated with depression; feeling depressed or low, impulsive suicidal thoughts, outbursts of anger, unintended weight loss or gain and feeling that your personality has changed. Overall, 15% reported none of these symptoms and 12% reported all five. The highest reporting of depressive symptoms was amongst those reporting an acute event.

Table 26. Summary results from logistic regression analyses of number of five depression symptoms on gender, age and acute response or not

Factor	OR	CI	t-value	p-value
Gender (F v M)	0.85	0.60-1.20	-0.92	NS
Age (per 20 years *younger*)	1.59	1.19-2.11	-3.18	p<0.01
Ever acute response to OPs (Y v N)	1.98	1.33-2.95	3.35	p<0.001

Regression analyses of number of positive responses from the five depression symptoms in relation to gender, age and ever acute response (Table 26) again showed a statistically significant effect of age, with younger people reporting more depression symptoms than older ones; and a highly statistically significant effect of past acute response to OPs (OR 2, p<0.001). There was no clear or sustained difference associated with gender – symptom-specific results, discussed below, showed that this was the result of contrasting patterns in the five symptoms individually. Once again, there was some evidence that current smokers reported more depression symptoms than non-smokers (OR 1.5, P<0.1). There was no evidence that age at leaving education, or past alcohol consumption, was associated with the reporting of symptoms of depression.

Once again, analysis of individual symptoms showed some consistency and some differences (Table 27).

- The relationship with age was found clearly and consistently, a little weaker for feeling depressed or low.
- Higher reporting among those who had a past acute response to OPs was also found consistently, except for impulsive suicidal thought.
- In fact, apart for age, impulsive suicidal thoughts were associated with (i) *gender*, with the OR for women being *lower* than for men (OR 0.6, p<0.1) and (ii) use of alcohol, with the OR for each of the three categories of use (low, medium and high) being higher than for non-users – for example, the contrast between those with medium past alcohol consumption and non-drinkers showed an OR of 2.7 (p<0.05). None of the other four symptoms was associated with alcohol use.
- Other effects of gender were for (i) personality changes, with women again reporting *less* than men (OR 0.5, p<0.01) and (ii) unintended weight change, with women reporting *more* than men (OR2.1, p<0.01). These contrasting effects of gender cancelled one another out when all five symptoms were analysed together – see Table 8e, above.
- Higher symptoms reporting for smokers compared with non-smokers was found for feeling depressed or low, personality changes and unintended weight gain – i.e. for the more chronic conditions, compared with irritability/ outbursts of anger or impulsive suicidal thoughts, where there was no clear effect of smoking.
- Finally, there was higher reporting of unintended weight change among people who stayed on longest in education (i.e. left at age >18). Compared with those who left earliest, the OR

was 2.4 (p<0.01). With many comparisons and possible relationships being examined, some statistically significant results will appear by chance. It is unclear if this is one.

Table 27. Summary of symptom-specific results for symptoms of depression, based on logistic regression analyses of symptom occurrence on gender, age, acute response or not, and smoking habit

Symptom	Age: per 20y younger		Acute response: Y v N		Smoking: Current v Non	
	OR	p-value	OR	p-value	OR	p-value
Feeling depressed/ low	1.4	<0.1	2.8	<0.001	2.1	<0.1
Impulsive suicidal thoughts	1.9	<0.01	(1.2)	NS	(1.2)	NS
Outbursts of anger	1.6	<0.05	2.7	<0.001	(1.1)	NS
Unintended weight change	1.7	<0.05	2.2	<0.05	2.1	<0.05
Personality changes	1.8	<0.01	2.0	<0.05	1.9	<0.1

4.9 Autonomic symptoms

Exclusions:. After the additional exclusions were made (Table 2), 290 remained in the dataset. Table 28 gives the age and sex breakdown of the remaining individuals. The age and sex remains similar to that in the main analysis of 367.

Table 28 Description of individuals in the autonomic analysis

	18-29		30-39		40-49		50-59		60-69		70-79		Total	
	n	%	n	%	n	%	n	%	N	%	n	%	n	%
Male	6	2.0	18	6.2	55	19.0	84	29.0	47	16.2	8	2.8	220	75.5
Female	1	0.3	7	2.4	20	6.9	25	8.7	15	5.2	3	1.0	71	24.5
Total	7	2.4	25	8.6	75	25.9	109	37.6	62	21.4	11	3.8	290	100.0

Age for 1 male is missing

Six symptoms were considered for the autonomic analysis: constipation, diarrhoea, dry mouth, gastric conditions, incontinence and problems with sight. Overall, the mean number of symptoms reported was 2.17. Those with an acute episode had a mean of 2.3 symptoms and the non acute group had a mean of 1.68 symptoms. The non acute group had twice as many individuals not reporting any autonomic symptoms as compared to the acute group. (Table 9)

Regression analyses were based on the same 351 subjects as for the other symptoms. This is a disparate group of symptoms and so the main results given refer to the symptoms individually – see Table 29.

Table 29. Summary of symptom-specific results for symptoms of autonomic analyses, based on logistic regression analyses of symptom occurrence on gender, age, and acute response or not

Symptom	Gender: F v M		Age: per 20y younger		Acute response: Y v N	
	OR	p-value	OR	p-value	OR	p-value
Constipation	2.5	<0.001	1.8	<0.05	(0.8)	NS
Diarrhoea	(1.2)	NS	(1.4)	<0.05	1.9	<0.05
Dry mouth*	(1.1)	NS	(1.1)	NS	(1.6)	NS
Gastric symptoms	(1.3)	NS	1.7	<0.05	2.2	<0.01
Incontinence	2.1	<0.05	0.5	<0.05	4.3	<0.01
Problems with sight	1.6	<0.1	(1.0)	NS	(1.4)	NS

* Also included earlier, as a symptom of anxiety – Table 23.

- Relatively more women, and younger people, reported constipation, but people who had experienced an acute response did not. There was some evidence that smokers and ex-smokers reported more than non-smokers; the OR for smokers relative to non-smokers was 2 ($p<0.1$). There was also a clear trend of less constipation with higher alcohol consumption: the OR for high consumption relative to none was 0.4 ($p<0.1$, almost significant at the 5% level).
- Diarrhoea was reported relatively more often by younger people – the OR was small – and by people who had reported an acute response (OR 1.9 and almost significant statistically at the 5% level). People with medium or high alcohol consumption also reported this symptom *less* often (OR 0.4 for high vs none, $p<0.05$).
- None of the three main variables – gender, age or past acute exposure – was clearly associated with dry mouth but, as noted earlier, current smokers were twice as likely to report dry mouth relative to non-smokers (OR 2, $p<0.05$).
- For gastric symptoms there was a mild effect of age and a stronger relationship with having reported an acute response. There were no clear additional gender differences, and no relationship with smoking, alcohol or education.
- Incontinence was reported relatively more often by women and by *older* people. The association with past acute response was especially marked. Current smokers reported the problem more often than non-smokers (OR 2, $p<0.1$). There was no relationship with alcohol or education.
- Neither age nor past acute response was associated with sight problems; the odds ratio for women compared to men was not small (1.6) but only weakly significant statistically. Similarly, there was some evidence ($p<0.1$) that current smokers reported more problems than non-smokers (OR 1.8).

4.10 Chemical sensitivity

68 % of respondents reported that they were sensitive to everyday chemicals. Almost twice as many of those with an acute episode compared to those without one reported chemical sensitivity (74% vs 41%). Of those reporting sensitivity, those with an acute episode reported a higher frequency of suffering than those without.

4.11 Attribution of ill health and medical treatment

If respondents had suffered an acute event or long term illness, further questions were asked about their health, exposure that they attributed to their ill health, clinical management and reporting of their exposures to the authorities. Data are available for 343 individuals.

4.11.1 Attribution of ill health

Table 30 shows different activities to which participants attribute their illness. (Respondents were able to give multiple answers.) The responses were coded by the interviewer. Activities relating to sheep dipping and handling dipped sheep accounted for the highest proportion of responses (44%) followed by the handling of cattle and other activities. Other activities included greenhouse work, exposure to recently treated livestock at markets, living in proximity to farms and retail work. There were no marked differences in attribution between the acute and non acute groups.

Table 30 Activities attributed to ill health

Activity	Acute		Non acute		All	
	n	%	n	%	n	%
Sheep dipping	193	31.4	27	30.0	220	31.2
Handling dipped sheep	82	13.4	11	12.2	93	13.2
Handling cattle	68	11.1	10	11.1	78	11.1
Other	64	10.4	11	12.2	75	10.6
Handling fleeces	62	10.1	10	11.1	72	10.2
Applying insecticides to crops	32	5.2	5	5.6	37	5.3
Over spraying/drift	32	5.2	5	5.6	37	5.3
Pet treatment	22	3.6	3	3.3	25	3.6

Handling/treating grain	19	3.1	4	4.4	23	3.3
Wood treatment	17	2.8	1	1.1	18	2.6
Solvents	10	1.6	1	1.1	11	1.6
Aerial spray	9	1.5	1	1.1	10	1.4
Orchard work	4	0.6	1	1.1	5	0.7
Total no. of responses	614	100.0	90	100.0	704	100.0
TOTAL	291		64		367	

% is percentage of total responses. Total is total number of individuals in each category.

4.11.2 Clinical treatment

The majority of respondents (78.2%) had sought treatment from their GP for their ill health that they thought was due to organophosphates. 34% had also sought medical treatment from another source, such as an accident and emergency department. 13.4% thought that someone contacted the National Poisons Information Service about their case. 27.8% reported that they had been admitted to hospital due to work with organophosphate compounds. (Data were missing for 35 individuals)

49% of individuals were referred on for further treatment. The majority of these individuals were referred to a hospital consultant (41.4%), 9.8% were admitted as hospital inpatients and 3% were referred to a National Poisons Unit clinic. 3% were referred to an Accident and Emergency Department.

151 individuals were referred to a hospital consultant. The majority of these saw a neurologist, followed by a psychiatrist and cardiologist. 63 individuals were referred to more than one consultant.

Of the 13 individuals referred to the NPIS, 6 reported that they attended the Medical Toxicology Clinic at Guy's and St. Thomas' Hospital in London, 4 attended the other regional centres and further data was missing for the remaining 3 individuals. Half of those were not given any diagnosis, 3 were given a diagnosis (2 OP related), one was awaiting results and data is not available for the 10th individual.

4.11.3 Satisfaction with medical care

Respondents who reported that they had either suffered an acute response to OPs or believed that they suffered a long term OP induced illness were asked to rate the medical care and treatment that they received. Overall 66.1% reported that they were either somewhat or very dissatisfied with the treatment that they had received.

Looking at self reported health status against satisfaction with medical care reveals as expected that those who report themselves as sicker are less satisfied with their medical care against those who are healthier. It is interesting to note that even amongst those who consider themselves to be in good health, over 30% are dissatisfied with their medical treatment. (Table 31).

Table 31. Current health status and satisfaction with medical care

	Self reported health status									
	Excellent/Very good		Good		Fair		Poor		Total	
Satisfaction with	n	%	n	%	n	%	n	%	n	%

medical treatment										
Very satisfied	6	31.6	9	20.0	17	14.7	11	9.3	43	14.4
Somewhat satisfied	4	21.0	11	24.4	19	16.4	22	18.6	56	18.8
Somewhat dissatisfied	2	10.5	10	22.2	31	26.7	24	20.3	67	22.5
Very dissatisfied	6	31.6	15	33.3	48	41.4	58	49.2	127	42.6
Total	19	100	45	100	116	100	118	100	298*	100

- data on treatment satisfaction missing for 76 and on health status for 2

4.11.4 Reporting to the authorities

182 reports were made to the HSE, VMD and PSD regarding organophosphate exposure. The majority of these were made to the HSE (24%), with 21% being made to the VMD and the remaining 8% to the PSD. Only in a third of cases did the respondents report that they had received an official report back from these agencies. (33% from the VMD, 36% from the HSE and 33% from the PSD).

5. EXPOSURE ASSESSMENT RESULTS

5.1. Involvement in tasks with potential exposures

Table 32 shows the distribution of the study group according to whether they reported any exposures to sheep dip, other OPs, solvents, lead or vibration. Results are shown separately for men and women, and for those excluded from the health analysis due to their medical conditions.

Table 32 Distribution of the study group by type of exposure, sex and medical exclusions.

	Included				Excluded			
	Men		Women		Men		Women	
Sheep dipping	203	*74*	44	*48*	42	*71*	8	*40*
Handling recently dipped	175	*63*	42	*46*	39	*66*	5	*25*
Treating cattle	150	*54*	26	*29*	38	*64*	6	*30*
Applying insecticide	93	*34*	1	*1*	18	*31*	3	*15*
Treating grain	72	*26*	11	*12*	22	*37*	1	*5*
Work in orchards	28	*10*	12	*13*	6	*10*	3	*15*
Other pesticide work	82	*30*	29	*32*	22	*37*	9	*45*
Using garden insecticides	183	*67*	55	*62*	38	*66*	11	*55*
Using home pesticides	79	*29*	19	*21*	27	*46*	5	*25*
Using solvents (not sheep dip)	48	*17*	11	*12*	12	*20*	3	*15*
Using lead	28	*10*	1	*1*	4	*7*	1	*5*
Using WBV machinery	94	*34*	8	*9*	24	*41*	0	*0*
Using HAV machinery	93	*34*	10	*11*	21	*36*	2	*10*

Each cell contains number *and percentage* of subjects exposed

In general more men than women were involved in tasks with potential exposures. Almost three-quarters of men had taken part in sheep dipping compared to less than half of the women.

5.2 Further information on sheep-dipping jobs (included data set only)

5.2.1 Number of sheep dipping jobs

In total, the included subjects reported 334 jobs involving sheep dip (281 held by men and 53 by women). Four subjects reported having one sheep dip job which they stated to be job number 11. Only 10 jobs were recorded on the questionnaire and no information is available for these four jobs. Information was therefore analysed for 330 sheep dip jobs.

Of the 330 jobs, 46 (14%) were carried out by a contractor. No further data were recorded for these jobs.

5.2.2 Time spent sheep dipping

Days dipped per year ranged from 1 to 180 across jobs, with an average of 8.4 days. Over 60% of jobs lasted less than 5 days per year, with almost half of these lasting 2 days. Only 10 (4%) jobs were reported as lasting 50 days or more, with 10 (4%) between 20 and 50 days and 25 (9%) between 10 and 20 days. Two-thirds of jobs (186) were carried out only in the compulsory dipping periods.

Hours per day spent dipping sheep ranged from 1 to 17, with the majority of jobs (143; 51%) lasting 6 to 8 hours. Nine jobs were reported as lasting more than 10 hours, while 97 jobs (35%) lasted 5

hours or less. Average flock size ranged from 30 to 7000 sheep. There was a positive association between flock size and hours per day spent dipping, and between flock size and number of days dipping per year.

5.2.3 Implements used for sheep dipping

The most commonly used implement for submerging the sheep was wooden. (Table 33)

Table 33. Implements used for dipping sheep.

What implement did you use most often?	No of jobs	*% of jobs*
Wooden implement	121	*54*
Metal implement	64	*29*
Hands	20	*9*
Feet	11	*5*
Other	8	*4*

Each cell contains number and *percentage of column total*
Note: 60 jobs had missing data for this question.

5.2.4 Protective clothing

For around 60% of the jobs recorded, waterproof trousers and/or waterproof footwear were worn. In 26 jobs (8%) no protective clothing was worn. (Table 34)

Table 34. Protective clothing worn whilst dipping sheep.

What protective clothing did you wear?	No of jobs	*% of jobs*
Waterproof trousers	192	*58*
Waterproof footwear	209	*63*
Waterproof overalls	45	*14*
Waterproof jacket	110	*33*
Waterproof gloves	90	*27*
Protective visor	24	*7*
Protective hat	14	*4*
Bib	23	*7*
None	26	*8*

When protective clothing was worn it tended to be worn always or usually. A few subjects who reported wearing specific types of protective clothing, subsequently said that the frequency with which they wore it was ‘never’. (Table 35)

Table 35. Frequency of use of protective clothing

	How much of the time did you wear……?							
	Always		Usually		Sometimes		Never	
Waterproof trousers	148	*77*	19	*10*	25	*13*	0	*0*
Waterproof footwear	193	*92*	7	*3*	8	*4*	1	*0*
Waterproof overalls	30	*67*	6	*13*	7	*16*	2	*4*
Waterproof jacket	63	*57*	23	*21*	23	*21*	1	*1*
Waterproof gloves	57	*63*	14	*16*	18	*20*	1	*1*
Protective visor	14	*58*	5	*21*	5	*21*	0	*0*
Protective hat	8	*57*	6	*43*	0	*0*	0	*0*
Bib	17	*74*	3	*13*	2	*9*	1	*4*

Table includes only those who reported wearing each type of protective clothing
Each cell contains number of jobs *and percentage of row total*

5.2.5 OPs on the skin

For almost one third of all jobs (93 jobs, 33%) individuals reported being always soaked to the skin with dip wash on any part of their body. For 41 jobs (14%), individuals reported usually being soaked to the skin and for 102 jobs (36%) individuals reported being sometimes soaked to the skin by dip wash. For six jobs this information was not available and for the remaining 42 jobs individuals reported never being soaked to the skin.

The most common sites for soaking to the skin were the hands, arms and face. Individuals reporting being soaked on the feet were proportionally more likely to report always being soaked to the skin. (Table 36)

Table 36. Frequency of soaking to the skin.

	Frequency of soaking to the skin			
Site of soaking	Always	Sometimes	Usually	Total
Hands	57	21	56	134
Arms	63	27	49	139
Feet	22	3	7	32
Legs	49	19	30	98
Face	59	22	55	136
Head/Neck	23	5	14	42
Torso	43	18	17	78

Each cell contains number of jobs

5.2.6 Work with concentrate and the dip bath

In 108 of the 290 (38%) sheep dipping jobs carried out by the respondent, it was reported that the respondent always poured out the concentrate or added it to the bath. In 22 jobs (8%) this was done usually, in 76 jobs (27%) sometimes and in 74 jobs (26%) it was never done. Of the 206 jobs where some concentrate handling took place, in 100 (49%) gloves were always worn, in 13 (6%) gloves were usually worn, in 33 (16%) gloves were sometimes worn and in 60 (29%) gloves were never worn.

The most commonly used dipping bath was a straight swim. (Table 37)

Table 37. Type of dipping bath used

What type of dipping bath did you use most often?	No of jobs	*% of jobs*
Straight swim	229	*81*
Circular	27	*10*
Mobile/portable	17	*6*
Other	11	*4*

Each cell contains number and *percentage of column total*

In seventy per cent of jobs (199 jobs) the respondent reported ever cleaning out the bath after dipping was complete. The number of times the bath was cleaned in any one job ranged from 1 to 20. The dip bath was usually emptied using pails (100 jobs; 50%) followed by slurry tanker (39 jobs; 20%) and other methods (60 jobs; 30%).

In around half of all jobs, concentrate was never splashed or spilled (150 jobs; 53%). Splashes or spills occurred once a year in 58 jobs (20%), 2-3 times per year in 42 jobs (15%) and three or more times a year in 21 jobs (7%).

5.3 Exposure to sheep dip

The average exposure level to sheep dip was 63.9 across the study group of 446 subjects. This exposure level was slightly lower among the 79 subjects excluded for medical reasons (mean = 41) than among the 367 included subjects (mean = 69). The difference was statistically significant at the 10% level. Sheep dip exposures for women were significantly lower than for men (means 24 and 77 respectively, p = 0.003). The subject with the highest exposure to sheep dip reported dipping sheep for 9 hours a day for 100 days a year for 27 years.

For the 200 subjects who handled concentrate during sheep dipping, on average, around 56% of their total exposure to sheep dip came from exposure to dilute dip while dipping sheep, followed by around 20% of total exposure from pouring concentrate, 9% from concentrate spills or splashes, 7% from handling sheep after dipping and 7% from cleaning the dip bath. For the 51 subjects who did not handle concentrate, on average around 59% of their total exposure came from exposure to dilute dip while dipping sheep, 25% from handling sheep after dipping, 10% from falling into the dip bath and 5% from cleaning the dip bath.

5.4 Regression analyses of symptoms on sheep dip and other OP exposure

Overall, 209 subjects (47%) were exposed to both sheep dip and other OPs, 168 to sheep dip only, 42 to other OPs only while 27 subjects had no or negligible exposure to sheep dip and other OPs. There was no evidence of any significant association between the two variables.

Methods

Further regression analyses were carried out to examine whether or not, adjusted for other factors, there was evidence that exposure to OPs during dipping was associated with reporting of symptoms as part of the telephone questionnaire survey. The focus on OP exposure during sheep dipping reflected that this had been estimated more reliably than other OP exposures, which in turn reflected how the project had begun. However the analyses also considered the role of other OP exposure, subdivided into four categories – none, low, medium and high.

One aim of the earlier regression analyses (Chapter 4) had been to identify what other risk factors should be included when modelling a possible relationship with exposure. Results had shown that, typically, reporting of symptoms was associated with age or gender, though rarely with both simultaneously. In addition, there was consistent evidence that, adjusted for age and gender, people who had reported an acute response to OPs also reported more symptoms. There was weaker evidence that being a current smoker, rather than a lifelong non-smoker, was additionally related to symptoms reporting.

Further regression analyses used the same methods as before (Section 2.5), with individual symptoms being analysed using logistic regression and related methods being used for the number of positive symptoms in a group. In considering the role of exposure we set up the analyses as follows:

a. Analyses were restricted to people who had dipped sheep, i.e. to 202 subjects from among the 355 on whom earlier regression analyses had been based. This is because our main interest was in sheep dippers and their exposure to sheep dip OPs. (Note: One of the 202 was excluded because of missing data on age.)
b. All analyses adjusted for gender, age and smoking habit, whether individually these were statistically significant or not. No adjustment was made for education or alcohol use, and so there were no further exclusions because of missing data on alcohol use.
c. OP exposure during sheep dipping was included as a continuous variable. Other OP exposure was categorised into none (33 subjects, 16%), low (56: 28%); medium (70: 35%) and high (43: 21%).
d. Dip exposure and Other OP exposure were jointly included in the regression model, as well as gender, age, and smoking habit, and their estimated coefficients and associated significance levels examined.
e. Experience of past acute response to OPs was then added to the model, so that the apparent effect of dip exposure and other OP exposure could be examined with adjustment for past acute response, as well as without.
f. In separate series of analyses dip exposure was included (i) on the ordinary scale and (ii) on the log scale, the earlier data descriptions having shown that a small number of subjects with very high estimated dip exposures might exert a strong influence on the results.

In total, these analyses included, as before, 32 individual symptoms and nine groups or sub-groups of symptoms.

Results

Consistently across endpoints, these analyses showed the following.

i. ***There was no evidence, in any of the analyses, that dip exposure was positively associated with symptoms.*** Indeed – see further, below – such evidence as there was of a relationship suggested that that higher symptoms reporting was associated with lower estimated cumulative exposures to sheep dip OPs. As discussed later, this finding needs to be considered in the context of the self-selection of the study population.
ii. ***Dip exposure on the ordinary or log scale:*** In otherwise similar models, i.e. with the same outcome variable and the same non-exposure explanatory variables, the analyses of dip exposure on the ordinary and on the log scales gave identical or almost identical results, in terms of statistical significance.
iii. ***Adjustment for past acute response to OPs:*** In otherwise similar models, the estimated size and statistical significance of the dip exposure coefficient was *larger* when past acute response was *not* included as an explanatory compared with when it was. For purposes of illustration we will therefore focus on results *without* adjusting for past acute response.

Initial screening focussed on the compound endpoint variables of the number of positive responses in the same sub-groups of symptoms variables as were analysed in Chapter 5. Table 38 shows, for selected endpoints, (i) the odds ratio per 100 units of dip exposure in regression models which simultaneously adjusted for gender, age, smoking habit and other OP exposures; (ii) statistical significance of sheep dip in a model *without* other OP exposures; and (iii) the statistical significance of other OP exposures as a group of four variables (based on χ^2 with 3 degrees of freedom), in a model with age, gender, smoking habit and sheep dip OPs.

Table 38. Summary statistics from regression analyses of number of positive responses in various symptom groups. All results adjusted for gender, age and smoking habit. Odds ratios (OR) for sheep dip adjusted also for other OP exposure. p-value for other OP exposure adjusted also for sheep dip OP.

Symptom Group (and nr. of symptoms)	Sheep dip OP		Other OP
	OR	p-value	p-value
Neuropathy (13)	0.99	0.66	0.89
Sensory (5)	0.99	0.82	0.86
Motor (8)	0.98	0.61	0.80
Neurobehavioural (15)	0.96	0.14	0.39
Anxiety (6)	0.95	0.13	0.60
Orientation (2)	0.93	0.11	0.22
Language (2)	0.94	0.21	0.16
Depression (5)	0.98	0.68	0.69
Autonomic (6)	0.99	0.81	0.22

None of the effects shown in Table 12a was statistically significant at the 10% level.

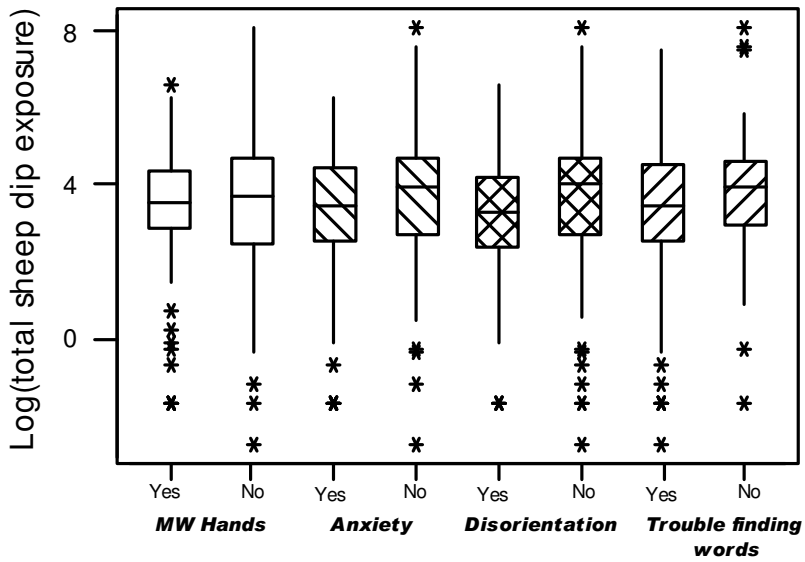
- There was no evidence that estimated exposures to OPs (either sheep dip or other OPs) were associated with the reporting of neuropathy symptoms overall or by sub-group (sensory or motor).
- Examination of symptom-specific results for neuropathy symptoms showed a *negative* coefficient for *muscle weakness in the hands* (estimated OR 0.86 per 100 units; $p<0.1$, adjusted for age, gender, smoking habit and other OP exposure). Unadjusted for other OP exposure, this negative association was statistically significant at the 5% level. None of the other neuropathy symptoms suggested a relationship with either sheep dip or other OP estimated exposures.
- None of the six autonomic symptoms was associated with sheep dip exposure. There were indications of an association of some autonomic symptoms (dry mouth, constipation, gastric symptoms, incontinence) with other OP exposures, but again, detailed examination of coefficients (zero exposure contrasted with low, medium or high) did not show credible relationships. In particular, the adjusted odds ratio in the high-exposed group was less than 1, suggesting lower reporting compared with the zero exposed category.
- There were no clear or strongly suggestive associations between either sheep dip OPs or other OPs and any of the five symptoms of depression.
- Table 12a does however suggest that there may be something happening with other neurobehavioural symptoms – the p-values shown, while not statistically significant at conventional levels, are suggestively low.

- Among the six anxiety symptoms, the strongest association was with *anxiety* itself as a lone symptom; again, the evidence was for a negative association. Statistical significance was strong ($p<0.01$) without inclusion of other OP exposures, less so ($p<0.05$) after their inclusion. The odds ratio (adjusting for age, gender, smoking and other OP exposures) was estimated at 0.8 per 100 units sheep dip OPs. As noted above, there was some evidence that other OP exposures were associated with dry mouth, but the symptom was relatively *less* frequent in the high exposure category. Trembling or shaking, dizziness, difficulty sleeping, or chest pain were not associated with either exposure variable.
- *Disorientation* was also negatively associated with sheep dip exposure. Again, statistical significance was more clear ($p<0.05$) before adjustment for other OP exposures. After adjustment, the estimated OR (0.82 per 100 units exposure) was just short of significance at the 5% level. A suggestive effect of other OP exposures arose from *higher* symptoms occurrence in the *low* exposure category. There was no association between either of the two exposure variables and problems with memory and concentration.
- There was some evidence of a negative association between both sheep dip and other OP exposures with *trouble finding words* but not with difficulty with writing.

In summary, for most variables there was no evidence of an association with sheep dip OP exposure. Such evidence as there was pointed to a negative association, i.e. higher symptom reporting among those whose estimated exposures were lower. This negative association showed through clearly for MW hands, for anxiety, for disorientation and, less clearly, for trouble finding words. The estimated odds ratio per 100 units sheep dip exposure was generally low, compared to the odds ratios estimated for gender, age (per 20 years) and, especially, effects of past acute response to OPs.

In order to see whether the negative association of sheep dip exposure with these symptoms was being driven by a few outlying points, or was reflecting the distribution as a whole, we did some additional data descriptions. Results (Figure 1) showed that the association was driven by the distribution as a whole, and not by outliers specifically. For ease of representation, sheep dip exposure in Figure 1 is on the log scale. However (i) statistical significance was similar, whether exposure was on the log scale or the ordinary scale; (ii) the boxes in the middle of the plots contain the middle 50% of the distribution and that refers to the same individuals, whether exposure is

Boxplots of selected symptoms by log of total exposure to sheep dip



represented on ordinary or the log scale.
Figure 1: Boxplots of selected symptoms by log of cumulative exposure to sheep dip OPs. Symptoms selected are those which showed a statistically ignificant negative association with sheep dip OPs.

The many analyses carried out also looked for evidence of interactions between sheep dip exposures and, variously, age, gender, past acute response and smoking habit. Some of these analyses showed statistically significant or suggestive results. However, as noted above, the results about sheep dip exposure overall were generally negative, in both senses – not much evidence of association and, where there was evidence, the association was negative. Also, as noted earlier, when many comparisons are made, some of these will be statistically significant even by chance. For these reasons we have not attempted to interpret these interaction terms, even when statistically significant. However details of these and indeed all the above analyses are given in Appendices H & I .

5.5 Exposure to other OPs

Total exposure to other OPs was calculated by adding together exposures from warble fly treatment of cattle, application of pesticide to arable crops, treatment of stored grain or orchards, working with other pesticides and using insecticides in the garden or at home.

One subject had a very high exposure to other OPs (exposure level 86854 compared to the next highest value of 46952). This exposure was almost entirely due to work with other pesticides which was reported as being carried out 365 times a year for 7 hours at a time over a period of 19 years. This subject has been excluded from the data descriptions below.

Average exposure to other OPs was 1070, ranging from 0 to 46952. Levels for women (mean 574) were significantly lower than for men (mean 1235), a difference which was statistically significant at the 5% level. There was no difference in average exposure level between the included and excluded subjects. On average 37% of total exposure to other OPs arose from exposure at home, and 32% from exposure from handling cattle after warble fly treatment. On average, 13% of exposure came from working with other pesticides.

5.6 Handling of concentrate

As part of the characterisation of exposure to OPs, the frequency and duration of jobs which entailed the handling of concentrate were calculated. It was thought that peak exposures were most likely to occur in jobs where concentrate handling took place. Three variables designating concentrate handling events were calculated –

- Concentrate handling in sheep dip jobs: positive if the subject poured out concentrate or added it to the bath, or if the subject splashed or spilled concentrate on himself
- Other occupational concentrate handling: positive if the subject diluted pesticide for warble fly treatment, applied pesticide to arable crops using an aerial spray, diluted pesticides for spraying on arable crops, diluted pesticides for treating orchards or diluted pesticides during other pesticide work
- Non-occupational concentrate handling: positive if the subject diluted pesticides or insecticides for garden or home tasks (e.g. garden insecticides, headlice treatment etc)

Overall 147 (33%) of the study group had never handled concentrate. Two hundred subjects handled concentrate in sheep dipping jobs, 144 subjects in other occupations and 75 subjects had non-occupational concentrate exposure. There was some overlap between these three groups of subjects.

5.7 Exposure to solvents, lead and vibration

Sixty-two subjects reported being exposed to solvents, 41 men and 10 women from the included data set and 9 men and 2 women from the medically excluded data set. Exposure ranged from 0 to 518400 units – with a mean value of 10,341. The one individual with exposure level of 518400 had worked for 36 years, 8 hours a day with daily exposure to over 2 litres of solvent in a small poorly ventilated room. Excluding this individual, the next highest exposure level was 27648. The following data descriptions for solvent exposure exclude this one outlying value.

Excluding the outlier, the average exposure to solvents was 2013 (range 0 to 27648). There was no significant difference in exposures between the included and excluded subjects (means 2082 and 1695 respectively). Solvent exposure levels were lower among the 12 women (mean level 697) than among the men (mean level 2335). This difference was close to statistical significance at the 5% level (p=0.06).

Only 30 subjects had any exposure to lead – 25 included men, 4 excluded men and one woman, who was from the excluded group. The mean exposure level for lead was 803 (range 0 to 7245). There was no significant difference in lead exposure levels between the included and excluded subjects although the mean level for the excluded subjects was lower (327) than the mean level for the included subjects (898).

One hundred and twenty-three subjects were exposed to hand-arm vibration, 91 men and 10 women from the included data set and 20 men and 2 women from the excluded group. Mean exposure level for hand-arm vibration was 1116 (range 0 to 13500). There was no significant difference in exposure level between the included and excluded group, while women had on average lower exposures than men (mean levels 479 and 1185 respectively).

One hundred and twenty-one subjects had exposure to whole body vibration (83 of whom had also had exposure to hand-arm vibration) – 90 men and 8 women from the included group and 23 men from the excluded group. Mean exposure level was 3933 (range 0 to 21900). There was no significant difference between exposure levels for the included and excluded groups. However, the few women with whole body vibration exposure had much lower exposure levels than the men (mean levels 1409 and 4112 respectively), a difference which was statistically significant (p = 0.002).

The majority of study subjects (258; 58%) were not exposed to solvents, lead or vibration and a further 82 subjects (18%) were exposed to one substance only. Of the remaining 106 subjects – 75 were exposed to two substances, 17 to three substances and 11 to all four substances. The most common combination of substances was hand-arm and whole body vibration.

5.8 Comparison of exposures with previous IOM study group

The exposure metric used to calculate exposure to OPs in the previous IOM study was different to that used in the current study. It was of interest to investigate whether the exposure levels among subjects in the current study were similar to those experienced by subjects in the IOM study.

Exposure indices comparable to those used in the IOM study were therefore calculated for the current study population. Four indices were calculated: total days spent dipping, task-based splash exposure, concentrate handling events and exposure index = 3.6*concentrate handling events + 0.2*splash exposure.

Table 39 compares the exposures of the SHAPE study participants and the IOM study group. The IOM study group comprises 612 sheep-dipping farmers and the SHAPE study group comprises the 251 participants who had been exposed to sheep dip. The IOM data are taken from Table 7.5 of the Phase 2 report (Pilkington *et al*, 1999).

Table 39 Comparison of exposures in present study (SHAPE) and IOM study

	Days dipping		Splash exposure		Concentrate		Exposure index	
Statistic	IOM	SHAPE	IOM	SHAPE	IOM	SHAPE	IOM	SHAPE
minimum	1	0	0	0	0	0	0	0
25th %ile	28	24	1080	825	9	0	350	226
median	54	56	2440	1951	185	30	1250	671
75th %ile	102	134	5000	4880	484	135	2700	1416
maximum	1350	5467	75770	198653	9348	4800	48810	39731
mean	91	160	4480	6200	418	172	2400	1857
s.d.	127	460	7260	17839	816	486	4280	4769

For the total number of days dipping, the distribution of exposures is similar in the two study groups, with very similar values for the minimum and median, and the 25th and 75th percentiles. The maximum days dipping is much higher for the SHAPE data set indicating that this study group has more extreme high values and these are reflected in the higher arithmetic mean value and the larger standard deviation. The distribution of the splash exposure scores shows a similar pattern. Exposure from concentrate handling is lower among the SHAPE study group for all summary distribution measures. These lower concentrate exposures are also reflected in the lower total exposure index which is directly calculated from the concentrate exposures and, with much lower weighting, the splash exposure scores. The mean age for the SHAPE study group was 53.2 years so they were older than the IOM group who had a mean of 45.1 years. Thus in spite of a longer potential for exposure the SHAPE population was not substantially more exposed than the IOM study population.

6. DISCUSSION

6.1 Advantages and disadvantages of studying a case series self-selected on possible cause of illness

This study was and is a unique opportunity to understand the health and exposures to OPs of a very special group of people, the members of four support groups of individuals who believe that their health has been damaged by exposure to organophosphates during sheep dipping or other activities. These are people who come from all regions of the UK. As results from the present study have shown, they include women as well as men (though a substantial majority are men) and they cover a very diverse range of ages (though all but 15% of those who took part in the telephone study were aged 40-69).

Above all, it was expected that the support group would include many people who are seriously ill. In that way, the study group was expected to include people who are too old, or too ill, to have been included in a study (such as that by Pilkington et al, 1999) of people who were exposed but still working in occupations with risks of further exposure to OPs. The intention underlying the study was that useful insights would follow from a better understanding of the health and exposures of people who did not need to be young and fit enough to continue at work.

However, as noted earlier (Section 1.3), while the strengths of the study derive from this unique opportunity, there are limitations which also derive from the distinctive selection processes that led people to make contact with the support groups. Recruitment was from groups of people who had come together on the basis that their health had been adversely affected by past exposure to OPs. This is different from the conventional design of epidemiological studies, which usually involves a selection of subjects which may be based on *either* exposure (e.g. a cross-sectional or longitudinal study based on occupation) *or* ill-health (e.g. a case-control study), but not on both. Selection which simultaneously involves both exposure and (ill-)health, as in the present study, introduces severe complications to the interpretation of results. This is especially so in interpreting relationships as causal or not.

As noted earlier, we were aware of these difficulties at the outset, and indeed highlighted them in our proposal. Nevertheless we, the sponsors (DEFRA), the participating organisations, and the individuals who took part, all considered that the benefits of the study outweighed these limitations. Specifically, there was a clear and strong interest in understanding better the health and exposure characteristics of the people who had, to a greater or lesser degree, aligned themselves with one of the several OP support groups. However, because of the self-selection of people in those groups, the study we proposed was focused on *describing* the characteristics of the participants, rather than on investigating exposure-response relationships as would be done in a conventional epidemiological study.

These distinctive aspects of how the study group was selected provided a framework for the plan of work throughout the study, as they do again now in this discussion of results.

We do not see this as any kind of fundamental flaw of the study design. Rather, it is an intrinsic characteristic of the groups being studied which has made it possible to study issues which have not been studied previously, but has also limited or prevented study of other important questions – issues that would normally be addressed in other studies that appear superficially similar to the present one (in that they involve data both on health and on exposures), but which are not subject to

the complex self-selection that underlies why people participated in the support groups and so in the present study.

What would be a fundamental flaw would be to seek to use the study and its results to provide answers to questions which it is not capable of answering.

6.2 Participation rates and exclusions

There was strong support for the study from the support groups and their members. In part, this reflected relationships in place before the study started. Also, visits were made by the lead researchers (TF and RM) to the groups. Representatives of the groups participated in the study advisory group, and so also in the choice of questions to be asked in the questionnaire study. More generally, it reflected a wish by the support groups to further an understanding of the role of OPs in relation to health generally, and an understanding of the health difficulties of their members in particular, and a great amount of work by the support groups centrally to promote the study and to help ensure high participation rates.

This support showed in the strong participation rates at all stages of recruitment to the study. For example, of the 524 eligible for telephone survey, all but 10 (1.7%) gave their consent to the study; and of the 494 sent to NCSR for telephone interviewing, all but 22 (4.7%) completed the relevant interview (i.e. either pilot study or main study) successfully. (There were some subsequent exclusions for missing data on particular items.) This shows a very strong commitment to the study, both at organisational and individual level.

The main study results were based on analyses of variously 351 to 367 individuals, much fewer than might at first sight have seemed to be available. Results in Section 4.1 earlier showed that the main reason for exclusions is that the support groups had inadequate information by which to contact many of the people for whom they had some record; also, there were duplicates across the various groups. That lack of contact information does not reflect a lack of organisation among the support groups. Rather, it reflects that individuals contacted the groups for many purposes; many chose not to follow up an initial enquiry. In addition, the groups have accumulated contacts over a number of years and some earlier contact information became out of date now. The more reliable contact information was available for those who wanted to participate more fully in the groups; it is these that can most properly be called ‘members’; and it is on these that the present study is based – a core set of 692 individuals in total.

Section 4.1 shows in particular the very high participation rates among those eligible for telephone interview, and who did not opt for the alternative of a written questionnaire. The detailed analyses reported here have focussed on this subset. Partly this was because the numbers were much greater – after exclusions, more than four times as many provided completed telephone questionnaires compared with completed written questionnaires. It was also because the very high participation rates in the telephone survey ensured that the data gathered there could be considered representative of those eligible, and fit enough to take part in such a survey. Completed written questionnaires, on the other hand, came by diverse routes, many of which implied major non-response, with the additional layer of self-selection issues that is always likely to accompany major non-response. (It would not be surprising, for example, if those who were sufficiently motivated to complete a written questionnaire were people who were on average relatively ill.) For both these reasons, we focussed on those who took part by telephone. However, limited results are also presented for those who completed a written questionnaire.

6.3 Health and exposures of those studied; comparisons with other groups

Health

A naïve interpretation of the health results from the telephone survey suggests very high rates of self-reported ill-health among the participants, thereby confirming what was to be expected: the members of these groups undoubtedly consider themselves to be ill, a view that is borne out by their answers to a great number of questions about past symptoms and medical conditions.

There are two ways in which this naïve interpretation was checked; both ways supported it. The most direct way was to compare prevalence of self-reported illness in the present study with prevalences reported in other studies of people in the UK and elsewhere using similarly worded questions. Such comparisons are necessarily limited in validity, because of differences between studies in terms of detailed study methods and relevant characteristics of the subjects. Nevertheless (see Section 4) the evidence of higher rates of symptoms in the present study group is so striking that it cannot plausibly be explained by minor methodological differences. Indeed, the methodological differences may operate *against* higher reporting in the present study. For example, the comparison groups in Section 4 were on average younger than those in the present study; and the detailed results of the present study – see Section 4, and also the later discussion – showed higher rates in younger people, implying that the differences between studies would have been greater if comparisons were restricted to younger people only.

The less direct way of checking the naïve interpretation was to examine internal consistency in the patterns of symptoms reported in the present study. Again, the detailed analyses reported earlier, and discussed more fully below, showed important evidence of coherence, in terms of how different sets of symptoms varied in relation to one another and in relation to age, gender and other factors.

Both approaches therefore support the first main conclusion: there were very high levels of reported ill-health in those who took part in the telephone survey, and the systematic pattern of detailed results from the questionnaire study do not support a view that these high rates were the result of random over-reporting. If they had been, the results would not have had the coherence which we found.

High rates of illness are, of course, what we expected; but it is helpful to have expectations confirmed on such a core issue.

The more limited data from the written questionnaires also showed high rates of self-reported ill-health. Partly, this may reflect additional selection effects, as noted above, though the prevalences are quite similar to the telephone interview derived data.

The study was designed to include a third means of checking the reliability and validity of the self-reported questionnaire results: by comparison with results from detailed clinical examination, for a subset of participants. (For health, it is desirable to have corroboration, on at least a sample basis, from more objective measurements.) This will be addressed in a separate report detailing the results of the clinical examinations.

Exposures

On the other hand, results showed that exposures to sheep dip OPs were not unusually high. The comparison was based on results from the study by Pilkington et al (1999) of health and long-term exposures in currently working farmers and farm workers who dipped sheep. There are the usual difficulties of precise comparisons across different studies but, taking the result at face value, it was somewhat surprising, in that we expected that the exposures of those in the present study might be untypically high.

It seems that the support group members are a group with high rates of neurological illness (both neuropathy and neurobehavioural), not unusually high exposures, and (after exclusions for medication and other known or strongly suspected causes of neurological disease) no identifiable plausible alternative explanations for their neurological ill-health. This suggests strong selection effects, giving either (i) a highly susceptible subgroup of responders to OPs or (ii) a collection of people, with past exposure to OPs, who have developed neurological illness for unknown and unidentified reasons; or, of course, some mixture of these.

Formal control groups

Because of these several ways of taking 'cross-bearings' on the study results, we had decided from the outset *not* to include formally within the study a comparison or control group of subjects not drawn from the support groups. Our purpose was to describe the characteristics of 'cases', of a possibly wide range of severity, who had self-selected on the basis of exposure to OPs as the likely cause of their ill-health. There is no doubt that differences with other groups could be assessed with greater confidence if others had been included (on a sample basis of sufficient size) formally within the present study. But the specific selection considerations of the present group would always be a key issue in interpreting any differences found. In particular, we did not find it possible to identify a suitable control group for comparison with the support group members that would allow us to assess exposure-response (E-R) relationships in a way that avoids confounding with methods of study selection, and so overcome this limitation.

To re-iterate, and perhaps say it another way – the spirit of the present study is one of an extended and large-scale case series investigation, with cases self-selected according to possible cause of their difficulties, rather than one of formal comparisons with external groups. We did, however, carry out formal regression analyses as well as detailed data descriptions, to understand the coherence of the data. We discuss some of these results now.

6.4 Pattern of symptoms

Although people have reported a wide range of numbers of symptoms, with some individuals reporting very few symptoms through to positive replies by others on almost all of them, statistical analysis of the data revealed some interesting patterns. From the analyses of 32 symptoms of, respectively, neuropathological, neurobehavioural and autonomic problems, we have found strong correlation across all of them: positive reporting of one symptom makes positive reporting of another symptom more likely. After taking this correlative tendency into account, other patterns emerged. Within each symptom cluster there is further correlation: multiple reporting of neuropathological symptoms (and the other groups) are correlated, beyond the overall covariance between symptoms. In particular two dimensions emerge, one reflecting either neuropathological or neurobehavioural symptoms (but not both), one involving autonomic symptoms.

These analyses suggest some pattern to the symptom reporting which was supported by the regression analyses discussed below where, for example, gender differences were found more for neuropathological than neurobehavioural symptoms, and conversely for age-related differences.

6.5 Effect of memory

Nearly 80% of subjects reported difficulty in remembering and concentrating. This raises questions about the reliability of data provided in a study which depends on recall of events, especially exposures. However, difficulty in remembering and concentrating is likely to refer to short-term memory. It does not necessarily follow that recall of past events is particularly unclear, especially if

these are events which are in some sense memorable, e.g. an acute response to past OP exposure. Also, subjects had time to prepare for the interviews and this will have assisted in recall of information relevant to the study.

6.6 The role of non-exposure characteristics in symptom reporting

The data descriptions and the regression analyses were designed to understand relationships with various non-exposure characteristics, and in particular, to see if apparent higher rates of symptoms among those who reported having experienced an acute response to OPs (possibly on several occasions) were instead due to other, confounding, factors. We consider, in turn, the principal non-exposure explanatory variables.

Gender
For many symptoms, there was evidence of a gender difference, with women reporting more symptoms than men. Prevalences across symptoms averaged approximately 20% higher for women, though this overall number aggregates across symptoms with quite different gender patterns. Higher rates among women were found for sensory symptoms generally, for milder motor symptoms, and for some autonomic symptoms. The effect was less clear for neurobehavioural symptoms; it was found, for example, for orientation/ memory but not for language and for few of the symptoms of anxiety or depression. For only two symptoms were men's reporting prevalence much (~30%) higher than women's: 'feeling that your personality has changed', and 'impulsive suicidal thoughts', both of which are symptoms of depression.

We think that these differences are likely to reflect differences in study selection and in reporting rather than fundamental biological differences in response to OPs or other risk factors.

Age
Relationships were found principally for neurobehavioural rather than physical (neuropathy) symptoms, and relative reporting was higher in *younger* people. One possible explanation is that younger people may have different baseline expectations than older people, in that older people expect greater infirmity as a 'natural' consequence of ageing. If so, that might apply to neurobehaviour rather than to neuropathy, because neuropathy is relatively rare, and there is not a clear expectation that this is an inevitable consequence of older age, so people will report it at any age.

It may be relevant that incontinence showed an expected increase with older age – contrary to other symptoms. This (and the higher reporting of impulsive suicidal thoughts among men, earlier) further supports the validity of the responses, i.e. that people were not simply 'talking up' their difficulties to show that they were ill.

Effect of past acute response
For almost all symptoms, the data descriptions and more detailed analyses showed that those who reported a past acute response reported higher levels of other symptoms. This was confirmed following formal adjustment for age and gender, though the data descriptions showed that the age and gender distributions of the two groups were very similar, implying no serious confounding.

The naïve interpretation is that these results are consistent with the view that an acute response may lead to long-term chronic damage.

We have considered whether there is a plausible alternative explanation, influenced by selection. It may be that those who have been exposed, and have developed illness, are more likely to attribute

their illness to OPs if they have had an acute response. However, that would suggest that the 'illness threshold' for people who had an acute response was *lower* than for those who didn't. (That would also imply that the proportion 291/355 = 82% who reported having had an acute response may be biased upwards, through relative under-representation of those who didn't have or recall such a response).) However, this speculation is *not* supported by the fact that those who had reported an acute response had *more* symptoms than those who didn't.

There may however be a reporting bias – it may be that having had an acute response in some sense legitimises people's sense of being unwell, and so it is not impossible that it may lead to higher reporting of symptoms. This is speculative – we have no data with which to asses it.

Effect of current smokers compared with lifelong non-smokers
Effects were found, or suggested, for many symptoms. The direction of causality is unclear; i.e. we do not know if these ways of characterising ill-health are yet another adverse consequence of smoking; or, if having these conditions and health difficulties leads people to take up smoking, as a 'pseudo-relief'. The former seems more likely than the latter.

Alcohol use
There are similar difficulties of interpretation. However, evidence for an association with alcohol consumption was very limited.

Age at leaving full-time education
There was very little evidence of a relationship with this indicator of SES.

6.8 (Lack of) positive association between exposure sheep dip and other OPs, and reporting of symptoms

The issue of what can be reliably derived in terms of exposure-response relationships from a study with selection effects such as this is so important that we re-visit it here.

Estimated cumulative past exposure to OPs
Given that subjects had self-selected both on exposure and on health, several members of the study team, and of the Study Advisory Group, were doubtful about whether or not meaningful results could be obtained from conventional modelling of exposure-response (E-R) relationships. The proposal was very cautious about whether such analyses would be done, and indeed some of the team remained reluctant to go down that road, because of the likelihood that results could be misinterpreted. To summarise the issue: conventional epidemiological methods may be suitable for identifying an E-R relationship if (i) there is selection on the exposure dimension, but is independent of health status; or, conversely, (ii) if there is selection on health, but independent of exposure. Either of these approaches has the potential to make available for analysis a dataset which is a 'fair' sample of the underlying population.

In the present study, however, selection is presumed to be based on individuals' assessments of (i) health; (ii) exposure; and (iii) some beliefs about the relationship between them. It is likely that these will lead to a preferential inclusion of people with poor health *and* quite high exposures, and to the virtual exclusion of people in good health and low exposures. Apart from weakening study power, by limiting the effective exposure range of the study, this almost certainly will lead to biased estimates of relationships. Specifically, there may well in reality be an E-R relationship which is not observable in a study of the present design.

In discussion within the team, prior to embarking on such an analysis, we considered that (i) if there appeared to be a real (positive) relationship, it was unlikely that this would have been generated artificially by the selection process but (ii) a real relationship could quite easily be unobservable within these data.

Spurred by various factors, including referees' comments on an earlier draft, we did examine possible relationships, using logistic regression methods. Unsurprisingly, most of the symptoms examined showed no evidence of a relationship. Somewhat to our surprise, some symptoms (muscle weakness of the hands; anxiety; disorientation; and, possibly, difficulties with words) were *negatively* associated with estimated cumulative sheep dip exposure.

Clearly, we do not interpret these findings as evidence that exposure to sheep dip OPs is protective against neurological disease. Rather, they confirm the somewhat obvious fact that the study population is the result of an unusual selection process, and that counter-intuitive results may therefore occur.

These results are not necessarily meaningless, in the context of the overall selection process. We could speculate, for example, that people who make contact with the support groups but with only a low degree of exposure are more likely to be those low-exposed people who were also especially anxious about their health. We have no way from within the study of assessing this possibility.

Other OP exposure
Broadly similar considerations apply to other OP exposures, except that data for these exposures, and the reconstruction of past exposures, were less detailed than for sheep dip OPs. This weakens the likelihood of detecting relationships, whether positive or negative.

Interactions between sheep dip and other possible risk factors
In some instances, there appeared to be evidence of an interaction between cumulative exposure to sheep dip OPs and other risk factors – age, gender, etc. As noted in the text, the results about sheep dip exposure overall were generally negative, in both senses – not much evidence of association and, where there was evidence, the association was inverse. Also, when many comparisons are made, some of these reach statistically significance even by chance. For these reasons we have not attempted to interpret these interaction terms, even when statistically significant.

6.9 Concluding remarks

Recruited through 4 support organisations, 471 individuals with OP exposures and in many cases health problems they attribute to OPs, were systematically interviewed. Their health profile was poor, with high prevalences of symptoms compared to population surveys addressing similar symptom categories. For only a small proportion (18%) could we identify other reported medical history or medication which might prompt such symptoms. After excluding them, symptoms consistent with neurological damage were especially prevalent. While they had all reported some OP exposure – in most cases occupational exposures related to dipping sheep – the extent of exposure was estimated as no more than typical for sheep farmers.

Four out of five of those interviewed reported having had an acute OP exposure episode. This group was on average sicker than the others. This is consistent with the view that people who experience an acute response to OP exposures may also suffer long-term neurological health effects. From our survey it appears that most of the reported illness is therefore among those with at one time or another rather high OP exposures, i.e. exposures sufficient to generate an acute response.

We conclude that symptoms of chronic ill-health reported by these individuals are plausibly related to, or made worse by, their OP exposure history.

A significant minority, about one in five, had reported that they had not experienced an acute response but nevertheless included many with neuropathy signs and symptoms. We are cautious in drawing conclusions from these patterns but it may be that some of these are a long term effect of OPs on health, and we conclude that these results support the need for further research addressing this specific question.

7 REFERENCES

Cherrie JW, Robertson A (1995). Biologically relevant assessment of dermal exposure. Annals of Occupational Hygiene; 39:387-392.

Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (1999) Organophosphates. UK Department of Health

Fukuda K, Nisenbaum R, Stewart G et al. Chronic multisymptom illness affecting Air Force Veterans of the Gulf War. JAMA. 1998. 280(11): 981-8.

Genstat Committee (ed. Payne, RW). Genstat, Sixth Edition. Oxford: VSN International.

Jackson CA & Spurgeon A. Symptom Reporting following occupational exposure to organophosphate pesticides in sheep dip. HMSO: HSE books. 2001.

Pilkington A, Buchanan D, Jamal GA, Kidd M, Sewell C, Donnan P, Hansen S, Tannahill SN, Robertson A, Hurely JF, Soutar CA. (1999) Epidemiological study of the relationship between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers. Phase 1 Cross-sectional exposure-response study of sheep dippers. IOM Technical report TM/99/02b

Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, Harrington, JM. (1995) Neuropsychological effects of long-term exposure to organophosphates in sheep dip. Lancet, 345, 1135-1388.

Unwin C, Blatchley N, Coker W et al. Health of UK servicemen who served in Persian Gulf War. Lancet. 16;353(9148):169-78.