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Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers. Phase 2. Cross-sectional exposure response study of sheep-dippers

Pilkington A, Buchanan D, Jamal GA, Kidd M, Sewell, C, Donnan P, Hansen S, Tannahill SN, Robertson A, Hurley JF, Soutar CA

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INSTITUTE OF OCCUPATIONAL MEDICINE

Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers

Phase 2

Cross-Sectional Exposure-Response Study of Sheep Dippers

by

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Epidemiological study of the relationships between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy, and neuropsychological abnormalities in sheep farmers and dippers

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SUMMARY

Overview of the aims

In 1994, the then Minister of Agriculture, Fisheries and Food announced that the Government had accepted advice from the Medical and Scientific Panel of the Veterinary Products Committee that there should be further research into the effects on health of organophosphate (OP) sheep dips. Subsequently, the Health and Safety Executive (HSE), the Department of Health and the Ministry of Agriculture, Fisheries and Food (MAFF) jointly commissioned a major epidemiological study into the effects of long-term exposure to OP sheep dips. This study was carried out between November 1995 and April 1999 by the Institute of Occupational Medicine in Edinburgh, in collaboration with the Institute of Neurological Sciences in Glasgow. The conduct and results of the research are being reported in three companion volumes, of which this report is the second.

The broad aim of the study as a whole was to investigate whether cumulative exposure to sheep dip OPs is related to clinically detectable measures of neuropathy. The specific objective of Phase 2 was by means of a cross-sectional field study of sheep farmers and dippers to study the relations between cumulative exposure to OPs, and clinically relevant indices of peripheral neuropathy. Phase 1 of the study developed the exposure model applied in Phase 2, and Phase 3 studied the clinical features of a sub-group of subjects from Phase 2.

Study design

The study consisted of a cross-sectional comparison of exposure to sheep dip OPs and chronic peripheral neuropathy throughout the UK. For practical reasons it was decided to base the study on two areas of the UK where there is a relatively high density of sheep farming. The inclusion of two areas was designed to give some indication of consistency across location, and consequently of ability to generalise the results, without overly complicating the conduct of the study. The areas chosen in England were Hereford and Worcester, and the Borders, Lothians and Ayrshire in Scotland.

Two groups of low-exposed workers from the same broad geographical areas were included to augment the numbers of low-exposed sheep dippers: the first a group of pig and chicken farmers and farm workers, the second a group of other unrelated workers. It was planned to survey 600 sheep dippers and 200 low-exposed workers.

Suitable farms were identified from a sampling frame, and contact was made with the farm owner to help recruit all potentially exposed persons employed at the farm. The sampling frame for recruitment of farms into the study was constructed from databases of annual census data for farms. The databases are maintained by the Ministry of Agriculture, Fisheries and Food (MAFF) for farms in England and Wales and by the Scottish Office for farms in Scotland.

We opted for a design based on clustering of farms within parishes, but with a restricted number of farms selected from any one parish. Of the farms sampled 56% were Scottish farms and 44% English farms.

Census data is also kept by MAFF and the Scottish Office on pig farms, in a similar manner to that kept for sheep farmers. MAFF also sought and obtained approval from the Office for National Statistics and the Scottish Office for the release of pig farm census data for the same geographical areas covered by the sheep farm data.

Chicken farmers were recruited in Scotland on the basis of local knowledge of the location of farms, and the IOM having performed previous occupational health and hygiene work at some of these locations. The ceramics workers were recruited with the assistance of the British Ceramics Confederation. A number of member ceramics companies in the same broad geographical areas as the farms were approached concerning their willingness to participate in the survey. Two companies were selected and visited, one in south east Scotland and the other in the English Midlands

Exposure history questionnaire

Retrospective exposure information was obtained for the period of common usage of OPs (1970 onwards), using a questionnaire developed during the first phase of the study. Phase 1 of the study involved careful observations of task and working practice in relation to uptake of OPs as assessed by urinary OP metabolites. The exposure history questionnaire was developed on the basis of relatively stable and easily identifiable features of the sheep dipping roles, i.e. features which were related to uptake as shown in Phase 1 of the study, and were also considered amenable to recall at survey in Phase 2. The main features included were flock size; concentrate handling; and principal task/job. Information was also gathered on the use of gloves and other personal protective equipment (PPE), although Phase 1 had shown little benefit from their use, possibly because the gloves and PPE were usually in poor condition.

The questionnaire was administered by trained clerks. A pilot study established that the recall of farmers and farm workers was better when questioned by job rather than by pre-determined time periods and this underpinned the questionnaire design. Aspects of the work histories were later summarised into various surrogate indices of cumulative exposure such as total number of dipping days, total number of concentrate handling events, exposure to dilute dip (in the form of splash score) and a combined index based on the Phase 1 uptake model. Based on the Phase 1 findings, the use of gloves or PPE was not formally included in these indices.

Neuropathy symptoms and sensory tests

Neurological assessments were conducted using a symptoms questionnaire in conjunction with a series of quantitative sensory tests (QST) based on the Mayo Clinic Methodology (Dyck *et al*, 1980). For this study, the design of the questionnaire was modified, as the original was designed for clinical use, while in this case the questionnaire was to be administered to farm workers in the field by a trained technician. Also, the full battery of neurophysiological tests, particularly the EMG and nerve conduction studies, was not appropriate for a field study carried out by a non-specialist. However, two automated tests for thermal sensation (hot and cold) and another for vibration sensation were suitable for application by a trained technician using portable equipment. All three tests had demonstrated high sensitivity and specificity in a laboratory setting with controlled ambient temperature.

The Mayo Clinic methodology however supports the use of sensory testing and questionnaire as a diagnostic screening test for neuropathy, and an integral part of the overall study design included a clinical follow up a subgroup of field participants with a complete battery of test in the third phase of the survey. It is therefore considered that the choice of tests used was fit for the intended purpose.

Reproducibility of field medical measurements

The study was designed from the outset to include a detailed clinical examination of selected subjects who had earlier participated in the field survey. Phase 3 was included in order to assess the reliability of case identification, to characterise the nature and severity of any abnormalities, and to include a neuropsychological assessment of subjects attended. Subjects selected for Phase 3 were a sample of Phase 2 subjects stratified on the basis of the likelihood of neuropathy using field measurements. Further details are contained within the Phase 3 report (Pilkington et al, 1999c).

In an agreed change to the original protocol, the analysis of case identification in the field relative to the clinic was carried out prior to the exposure-response analysis of the field survey data in Phase 2. This was done due to the unexpectedly high number scoring positive for abnormal sensory thresholds in relation to clinical reference values among both ceramics workers and farmers.

For the modified version of the Mayo Clinic neuropathy scoring system that had originally been proposed as a method of scoring likelihood of neuropathy status in the field, reproducibility between field and clinic was found not to be sufficiently better than chance to warrant use as the principal response variable in exposure-response analyses. When the specific component scores that were combined in the scoring system were analysed separately, it revealed that it was the scoring of the sensory test thresholds relative to a clinical reference values that were least reproducible. This lent weight to earlier suspicions that the high proportion of ceramics workers in the control group who had scored 'abnormal' for cold and vibration thresholds, in particular, could not be plausible.

Since, the use of the clinical reference values to detect abnormality in the sensory test thresholds measured in the field could not be justified, it was decided that the symptoms score and the three sensory test thresholds, as they were measured in the field, would be analysed separately in relation to exposure in the field study. The symptom score had proved reasonably reproducible between field and clinic, particularly taking account of the time lag (up to 18 months) between the two assessments. The actual measured thresholds showed biases between the field and the clinic, in particular, the hot (factor of two lower in the field) and vibration (factor of two higher in the field) could be explained by the generally low ambient field temperatures during the field survey relative to the controlled temperature in the clinic. However, all three thresholds showed significant linear correlation between field and clinic and no evidence of any additional inter-individual variation in the field.

Main findings in relation to the study group

Of the 995 sheep farm owners sent letters of invitation, 611 (61%) initially agreed to participate in the study. The most common reasons cited for non-participation were that the farmer was not interested, or was too busy. Of those agreeing who were suitable and practicable to visit, 293 (88%) were actually visited by the survey team. Two contract sheep dippers out of five approached also agreed to participate. The majority of workers in both ceramics factories visited were surveyed to reach the target for non-exposed controls.

After exclusions due to reporting having a disease or taking medication that may have confounded a diagnosis of neuropathy, the study group consisted of 612 farmers with sheep-dipping experience (SD farmers), 53 farmers with no sheep dipping experience (NSD farmersanf farm workers) and 107 ceramics workers. SD farmers were six years older, on average, than the other groups, and included the highest proportion of females (14%), who were often additional family members. Alcohol consumption was highest among the ceramics workers.

Among SD farmers, cumulative exposure was found to be highly skewed. Most subjects had experienced fewer than 100 days dipped (median 54 days), although a small number of individuals had experienced over 1000 dipping days. Total dipping days was highly correlated with the model-based exposure index (r=0.92) together with the cumulative concentrate handling and splash score components. Age at survey was not correlated with any of the exposure indices.

Main findings in relation to comparison of occupational groups

In all groups autonomic symptoms were more reported than sensory or motor symptoms. The crude prevalence of reported symptoms overall was highest among SD farmers (19%), followed by NSD farmers (11%) and ceramics workers (5%). Symptoms prevalence was found to be positively associated with age and higher in English farmers than in Scottish farmers. Adjusting for age and country, the prevalence of symptoms among SD farmers remained high compared to ceramics workers (OR=4.3), but was similar to NSD farmers (OR=1.3).

Age was also found to be positively related to all three sensory test thresholds. In addition, males had higher thresholds, on average, than females. There was no effect on thresholds, or on symptoms, of current reported alcohol consumption. Adjusting for age and sex there were inconsistent differences among the occupational groups between the two countries for both hot and vibration thresholds. This was partly due to differences in both thresholds between the two ceramics factories . However, for neither threshold was there a clear difference between SD farmers and ceramics workers across the two countries.

Adjusting for age and sex, cold thresholds among SD farmers were, on average 1.35× higher than among ceramics workers, and 1.65×higher than among NSD farmers.

Main findings in relation to exposure-response analyses

Adjusting for the important confounding variables, only for symptoms among the four neurological response variables was there evidence of a positive relationship with cumulative exposure. The model-based cumulative exposure index did not provide a better fit to the neurological response variables than the total days dipped. The estimated effect predicted a 13% increase in the odds of symptoms per 74 days dipped (inter-quartile range across all SD farmers) and was consistent across the full range of exposures and consistent between the two countries. However, the statistical significance of the gradient depended on the inclusion of the small number of very highly exposed individuals. Restricting the cumulative exposure indices to the period 1984-91, when OP sheep dips were at peak usage, did not improve the fit to the symptoms response. However, the effect of cumulative exposure did not explain fully the higher prevalence of symptoms among SD farmers compared to ceramics workers.

Further analysis of exposure effects revealed that the average concentrate handling intensity, independent of duration of exposure, could explain the difference between SD farmers and ceramics workers in relation to both symptoms reporting and cold threshold. For symptoms, those had ever acted as principal concentrate handler reported more symptoms than those who had not (OR=3.4; 95% CI 1.6—7.2). An effect of duration of exposure, in addition to this effect, was not statistically significant at the 5% level.

Adjusting for concentrate handling also revealed a lower rate of symptoms reporting among males compared to females of the same age, country and exposure.

There remained a much higher prevalence of symptoms among English subjects compared to Scottish subjects (OR=2.0). An analysis of field versus clinic reproducibility among farmers attending the clinic showed that symptoms reporting among English subjects was more reproducible than among Scottish subjects, and indicated that the higher symptoms rates among English farmers were the more reliable result. Subsequent comparisons of the OP sheep dip products recalled by farmers did not reveal any marked difference in product use

On the basis these results, the prevalence of symptoms was predicted to be highest among concentrate handlers in the English regions, for example, 21% (95% CI: 15-27%) at age 40 years, rising to 35% (27-43%) at age 60 years. The corresponding prevalence among ceramics workers was predicted to only rise above 10% for those in their sixties. It is acknowledged that in some cases reported symptoms could be associated with other medical conditions and not necessarily be associated with exposure.

There was a similar effect of concentrate handling intensity on all three sensory test thresholds that was more marked for cold and vibration thresholds. This effect rose from zero intensity and peaked at around the mid-point of the intensity range (4 handling events per day). Adjusting for the other important confounders, this effect could explain the difference in cold thresholds between SD farmers and ceramics workers. There was evidence that the use of gloves while handling concentrate, although estimated to have occurred on less than half of occasions, was increased with increased concentrate handling intensity.

Key findings from Phase 2

- Results showed higher rates of symptoms between OP exposed sheep dippers as a group compared with non-exposed workers. The associations between symptom score and various indices of cumulative exposure to OPs suggest that in at least some of the sheep farmers and farm workers reported symptoms are due to exposure to sheep dip chemicals. Sensory symptoms were more commonly reported than motor symptoms by sheep dippers in the field study.

- The critical exposure factor seems to be contact with concentrate in that markedly higher rates of reported symptoms (adjusted for other factors) were reported among those who had at some time been principal concentrate handlers. These differences generally disappeared when non-exposed groups were contrasted with dippers who had not principally handled concentrate.

- There was no evidence that cumulative exposure to OPs was associated with impairment of measured sensory thresholds. The results suggest a relationship between QST measurements and exposure to concentrate but these are difficult to interpret. The possibility of an associated sensory neurophysiological component to the suggested symptom effect should therefore not be discounted.

The implications of these findings ars considered in more detail in a summary of all three Phases which can be found in the Phase 3 report.

1. INTRODUCTION

1.1 BACKGROUND

In 1994, the then Minister of Agriculture, Fisheries and Food announced that the Government had accepted advice from the Medical and Scientific Panel of the Veterinary Products Committee that there should be further research into the effects on health of organophosphate (OP) sheep dips. Subsequently, the Health and Safety Executive (HSE), the Department of Health and the Ministry of Agriculture, Fisheries and Food (MAFF) jointly commissioned a major epidemiological study into the effects of long-term exposure to OP sheep dips. This study was carried out between November 1995 and April 1999 by the Institute of Occupational Medicine in Edinburgh, in collaboration with the Institute of Neurological Sciences in Glasgow. The conduct and results of the research are being reported in three companion volumes, of which this report is the second.

The issue of OP exposure and health remains important and controversial. For example, since the research began there have been a number of media reports of both physical and psychological ill health among farmers who have used OPs; and in 1998 a 62 year old shepherd was awarded £80,000 compensation for damage to his health in which OPs were implicated. The level of public awareness of and interest in the potential long term health effects associated with OPs was in some respects helpful to the conduct of the study. But it was also a complication, because increased awareness of potential long term health effects might influence recruitment of farmers to the study, and the reported frequency of ill health and the eventual outcomes.

The existing models of mechanisms of action of organophosphate compounds focus on cholinesterase inhibition and the possible formation in solution of neurotoxic compounds. This mechanistic understanding is helpful when considering the acute OP poisoning, i.e. the early, possibly severe but usually transient reaction to extreme OP exposures. However it does not adequately explain how reports of chronic health effects might be caused by repeated low dose exposures to OPs. A recent report by the Royal Colleges of Physicians and Psychiatrists (1998) suggests that reports of chronic low dose effects of OPs are limited by small numbers of cases, selection bias and inadequate controls. It is also considered that some cases may be the result of undocumented episodes of acute exposures. A review by ECETOC (1998) concluded that animal experiments confirm acute and protracted effects on cognitive function, but have not demonstrated effects of prolonged low level exposure. However, although some chronic effects can be predicted from animal studies there are restrictions in their transferability to humans, notably in their capability to test for human mental performance skills. Therefore there is a need to consider a comprehensive range of neurological tests which enable early asymptomatic clinical changes to be detected and cover the spectrum of neuropsychological function. The possible chronic neurotoxic effects of OP exposures, and the methodological difficulties in investigating them, have also been reviewed recently by the MRC Institute for Environment and Health 1998.

1.2 HYPOTHESIS UNDER INVESTIGATION

Despite some uncertainties regarding mechanisms, the design of the present study was based on a working hypothesis of incremental damage; specifically, that repeated exposures to OPs may cause cumulative and irreversible damage to nervous tissue which eventually becomes sufficient to be clinically detectable. If this were the case, then the likelihood of neurological abnormalities would be related to cumulative exposure of OPs, or to some associated index of longer-term exposure. In a sufficiently powerful and well-conducted cross-sectional study, this relationship should show, after suitable adjustment for confounders, as an exposure-response (E-R) relationship between cumulative exposure to sheep dip OPs, and some measure(s) of chronic polyneuropathy.

The present study was designed to identify and describe such a relationship or difference, if it exists. The anticipated difficulties included the retrospective estimation of exposure, the reliability of field measurements of neurological abnormalities and the achievement of adequate numbers of subjects and response rates from the study population.

It may be that cumulative exposure to OPs is not the most relevant exposure index, biologically. It is possible, for example, that damage occurs only following exposure that exceeds some threshold which may vary by individual, or only following exposures which lead to some acute response. In these circumstances, cumulative exposure above some threshold might be a more appropriate index. However, given the substantial difficulties of retrospectively estimating past exposures reliably, we were not confident that we could differentiate between the effects of related indices of cumulative exposure, which in any case were likely to be highly correlated with one another. In fact, it is not really possible to retrospectively estimate exposure peaks reliably, unless these peaks are closely linked with events which are in themselves memorable.

1.3 SPECIFIC OBJECTIVES OF THE THREE PHASES OF THE INVESTIGATION

The broad aim of the study as a whole was to investigate whether cumulative exposure to sheep dip OPs is related to clinically detectable measures of neuropathy; and if so, to estimate that relationship.

The specific objectives of each of the three phases of the investigation were as described below:

a. Phase 1: By means of an investigation at specific farms,

- To develop an improved model for uptake of OPs based on simple task, procedural and behavioural aspects of sheep dipping;
- To validate this uptake model by comparisons with urinary OP metabolites during various dipping procedures; and
- To identify what improvements to working practices might help in reduction of exposures associated with dipping sheep.

b. Phase 2: By means of a cross-sectional field study of sheep farmers and dippers,

- To study the relations between cumulative history of exposure to OPs, as estimated using the above uptake model, and clinically relevant indices of peripheral neuropathy;
- By including some individuals from other occupations, to supplement the numbers of low exposed subjects, and to permit simple comparisons with non-sheep farming populations.

c. Phase 3: By means of a clinical study of subjects with abnormal indices of peripheral neuropathy, and controls, as identified in the cross-sectional field study,

- To classify in terms of clinical disease the subjects with abnormal indices of peripheral neuropathy identified in the Phase 2 field studies
- To explore what neuropsychological profiles, if any, may be associated with neurophysiological damage in the subjects studied;

- To explore what neuropsychological characteristics or profile, if any, may be associated with cumulative exposure to OPs.

1.4 THE STRUCTURE OF THE CURRENT PHASE OF THE STUDY

1.4.1 Overview

The basic design chosen was that of a cross-sectional exposure-response study of sheep dippers, comparing OP exposure indices relevant to uptake, to clinically relevant indices of peripheral neuropathy which are sufficiently simple and robust to be used in the field (see Section 2.1, below). The design and conduct of the cross-sectional study, and its results, form the core of the investigation, and are presented in the present report.

Apart from issues of scale and power, there were two major methodological problems to be overcome in carrying out the cross-sectional study:

a. the estimation of past exposures to sheep dip OPs; and

b. the determination of peripheral neuropathy based on measurements taken in a field study rather than in a clinic.

To help overcome these problems, two linked studies were carried out: a study of exposure to and uptake of OPs while dipping sheep, and a clinical study of neuropathy (and neuropsychology) among cases and controls selected from outcome measurements of the cross-sectional study. These sub-studies were carried out as Phases 1 and 3 respectively of the present investigation (the cross-sectional study being Phase 2); and are reported as Sewell *et al* (1999) and Pilkington *et al* (1999), respectively.

We consider both briefly, to give context to the core cross-sectional investigation reported here.

1.4.2 Estimation of exposures to and uptake of OPs

Separate field studies of exposure of sheep dippers to organophosphates had been completed by IOM prior to the present investigation (Niven *et al*, 1993 and 1994). These workplace studies had demonstrated substantial skin contact with the dilute sheep dip solution (Niven *et al*, 1993), against which recommended protective clothing, when used, seemed to be highly effective against skin contamination (Niven *et al*, 1994). Low levels of urinary OP metabolites could be demonstrated, after dipping, possibly due to skin exposure, but which may also have been the result of exposure by ingestion or from some other source. Higher urinary concentrations were observed amongst workers who handled the OP concentrate, indicating that comparisons with possible health effects should attempt to quantify exposure to the concentrate, as far as possible, in as much detail as exposure to the dilute dip.

One aim of Phase 1 of this study was to develop an uptake model, relating uptake to simple descriptions of task components, and so provide a basis for estimation of past exposures to sheep dip OPs (see Chapter 4, below). A secondary aim was to provide information to the HSE about working practices which might help HSE formulate guidance on the control of exposures during sheep dipping.

1.4.3 Assessment of peripheral neuropathy under field conditions

As described in Chapter 3 below, the best methods for determination of peripheral neuropathy have been designed and validated for use in the clinic by specialist investigators. It was necessary to adapt these methods for use in a field investigation. We considered it important to be able to make a clinical interpretation of the abnormalities and relationships demonstrated in the field studies. Consequently, a clinical study was carried out using a sample of those with neurological abnormalities identified in the field studies, and of control subjects. This investigation had the added aims of giving additional information about the nature of any neuropathies found. It also included a neuropsychological component which had not been practicable in the field investigation.

1.5 THE PRESENT REPORT

The present report is concerned principally with the second phase of the study. Its exposure estimation methods (Chapter 4) draw on the results of the first phase (Sewell *et al*, 1999). It includes in Chapter 5 some results from Phase 3, comparing medical measurements as applied in the field study and in the clinic among subjects who participated in both these phases. It is considered that this information concerning other aspects of the research is essential to the understanding and interpretation of the Phase 2 report.

2. STUDY DESIGN

2.1 OVERVIEW

2.1.1 Choice of a cross-sectional design

The basic design of the current study was a cross-sectional field survey of about 600 individuals actively involved in sheep dipping using OPs in the UK, together with a smaller group of about 200 other workers unexposed to OPs via sheep dipping. Health status was measured in the field by trained personnel, and exposure was measured retrospectively using an exposure history questionnaire in conjunction with a model of OP uptake developed in the earlier phase of the current study.

This cross-sectional design was consistent with the primary objective of examining what is the relationship, if any, between long-term (cumulative) exposure to OPs and clinically relevant indices of peripheral neuropathy.

A longitudinal study of the development of chronic neuropathy among sheep farmers and dippers was impractical for several reasons, including timescale.

A hospital- or clinic-based case-referent study, with people diagnosed as having chronic neuropathy as cases, had been considered. This option was not taken because this type of study would not provide information on the extent of relevant ill health among sheep farmers, or ensure that the cases assessed were representative of all sheep dipping farmers. There was more potential for self-selection among cases due to recent publicity about OPs, and the use of historical cases would have limitations in relation to consistency of health data recorded and the diagnostic criteria applied. It would also have been more difficult to obtain a suitable control population in a clinic setting to be compared with the sheep farmers.

2.1.2 Inclusion of unexposed workers

The inclusion of unexposed was primarily in case it proved impossible to obtain sufficiently reliable estimates of individuals' past exposures to sheep dip OPs. Then, comparison of indices of neuropathy between unexposed and exposed subjects would allow at least a limited investigation of the health effects of exposure. In practice, estimates were made of individuals' past exposures leading to exposure-response analyses. In this context, comparisons between exposed and unexposed workers were used to give supplementary information about possible exposure effects.

2.1.3 Constraints on when the surveys could be carried out

The surveys were carried out during the winter months to avoid the busiest periods of the farming calendar and thus to maximise response rate. Also, between the spring and autumn farmers are more likely to be in contact with a range of pesticides, such as those used in sheep dipping and crop spraying. Therefore in order to avoid confounding from the acute effects of exposure to OPs and other substances such as pyrethroids, the surveys commenced in November 1996, at least two months after peak periods of autumn pesticide usage. The surveys were completed by early June 1997 thus avoiding the spring dipping period, but the survey schedule had to carefully planned between March and May to take account of the busy lambing times in Scotland and England. Inevitably, performing a survey in winter months meant that assessments were performed during cold weather.

2.2 TARGET POPULATIONS, STUDY AREAS AND SAMPLE SIZE

2.2.1 Sheep farmers and dippers; choice of study areas

The study aimed to be informative about exposure to sheep dip OPs and chronic peripheral neuropathy throughout the UK. For practical reasons, however, it was decided to base the study on two areas of the UK where there is a relatively high density of sheep farming. The inclusion of two areas was designed to give some indication of consistency across location, and consequently of ability to generalise the results, without overly complicating the conduct of the study.

The two areas selected were first, the Scottish Borders, Lothians and Ayrshire; and second, Hereford and Worcester. From the MAFF census data these areas had a suitable number of sheep farms which could be included in the study and a range of farm sizes. The inclusion of both Scotland and England also gave a range of low land and hill farms, and varying disadvantage in farming facilities. Therefore, the farms included in the field studies were considered to span the range of sheep farms within the UK.

As the survey was to be performed in winter, it was necessary to ensure as far as possible that access to farms would not be too dependent on the weather. Therefore, in Scotland areas were chosen within less than a day's travelling distance of the IOM. As there were concerns about the response rate for the Phase 3 clinical studies, it was felt that subjects from Scotland would be more likely to participate in the third phase of the study due to their relative proximity to Glasgow and the INS. In reality, recruitment of subjects from England for the clinical studies was not a problem. For convenience, in this report we refer to participants in the two areas as 'subjects (farmers) in Scotland' and 'subjects (farmers) in England', while recognising the inclusion of some Welsh participants in the latter group.

Within the two study areas, the target population comprised all people on farms (farmers, family members, paid workers) actively involved in sheep dipping; augmented with some sheep-dipping contractors from the same areas. It was planned to include a sample of about 600 subjects from this population.

2.2.2 Non-exposed workers

Two groups of workers from the same broad geographical areas were included to provide a comparison with unexposed workers: the first a group of farmers and farm workers, the second a group of other workers in an unrelated occupation.

It was intended that the group of other farmers and farm workers should be as similar as practicable to sheep farmers and workers, but with no exposure to OP sheep dips. Pig and chicken farmers were identified as a suitable group, although some low exposure to OPs was anticipated. Initially, it had been proposed to use beef and dairy farmers for this purpose. However the recruitment would have taken place at the climax of the BSE debate, and it was felt that beef and dairy farmers' concerns over this issue would have adversely affected the recruitment process. It was also considered that the use of pesticides on arable crops and feedstocks by this group of farmers would exclude them from the low exposure to OP category.

Workers in ceramics factories, manufacturing bricks and tiles, were chosen as the second (non-farming) occupational control group. Including a reference group of currently-employed non-farm workers, with little or no exposure to OPs occupationally, would also allow the relative medical significance of any effects found in sheep dippers, or indeed farmers, to be explored. Ceramics (brick) workers were chosen as a group with no anticipated exposure to pesticides, and with the exception of possible exposure to hand-arm vibration were not considered to have other confounding occupational exposures. It was also necessary to recruit low-exposure groups from similar geographical areas as the farmers, and ceramics industries were located in both regions and were willing to participate in the study.

The planned sample size was for 200 non-exposed workers, of whom it was aimed to recruit approximately 80 pig and chicken farmers and 120 ceramics workers.

2.3 RECRUITMENT

2.3.1 Overall strategy

Central to the selection process was that access to subjects was via a sampling frame of farms, not individual subjects. Consequently the sampling method for the recruitment of both sheep dippers and other farm workers was a two-stage design. Firstly, suitable farms were identified from the sampling frame; secondly, contact was made with the farm owner to help recruit all persons employed at the farm.

The priority was to achieve a realistic range of exposures in order to assess any exposure-response relationship, rather than to estimate prevalence of neuropathy. Therefore, it was not essential to treat the sample as a representative census of farms in which measurement of prevalence would be the main aim. This allowed the sampling procedure to be driven mainly by practical considerations, as follows.

The study was carried out mostly during the Winter of 1996/7 and through Spring 1997. It was expected that travel in the study areas would be difficult. Nevertheless, it was important to maintain the momentum of the study: not only to keep to overall timescale, but so that the fieldwork could be completed before the dipping season to avoid the potential confounding from the acute effects of OP exposure present in sheep dip. There were strong practical reasons therefore to organise the fieldwork in a way that kept travel from farm to farm on any given day's fieldwork as low as practicable. Experience from the farm surveys conducted during Phase 1 of the study, also showed that prior agreement to participate did not always mean that the surveys could go ahead at the appointed time. Farming work is vulnerable to unanticipated short-term needs and in many instances these were, understandably, given priority by farmers. On the other hand, where prior agreement to participate had been given, it was sometimes possible to (re-)arrange survey times at short notice, for the same or following day, when arrangements with other farms had to be cancelled. This flexibility was of practical benefit only if the re-arrangements were for nearby farms. Finally, the optimal time between agreement to participate and actual conduct of the surveys was two to three weeks; and so the whole recruitment process was organised as a rolling programme that overlapped significantly with the actual period of carrying out the survey work.

2.3.2 Sampling frame of farm census data

The sampling frame for recruitment of farms (and by implication of sheep dippers and other farm workers) into the study was constructed from databases of annual census data for farms. The information is collected from farm owners on an annual basis; the databases are maintained held by the Ministry of Agriculture, Fisheries and Food (MAFF) for farms in England and Wales and by the Scottish Office for farms in Scotland. Information from census data from 1995 on all sheep farms in Hereford and Worcester, the Scottish Borders, Lothians and Ayrshire, was supplied on diskette by MAFF, to be used solely for the purposes of this study, and subject to appropriate safeguards regarding confidentiality.

The farms were arranged by parish within broader area and the data provided included information on farm size, size of flock (at the middle of June), percentage arable land, and degree of disadvantage was provided. Cross tabulations were performed based on the number of farms per parish and the number of sheep per farm. The farms were categorised as follows:>100-1000 sheep, 1000-2000 sheep and >2000 sheep. These characteristics were expected to be related both to number of exposed workers and to degree of exposure; and so it would be useful to ensure inclusion of farms of different flock sizes, or different overall farm size, etc. In practice it was found later that despite considerable variation in the size of farms by area, the number of staff employed on farms did not vary substantially, and smaller farms with three or fewer staff employed were the most frequent type of farm. This had implications for the number of farms that needed to be visited in order to perform assessments on the desired number of subjects.

Degree of disadvantage, in farming terms, was initially selected as a possible indicator of upland or lowland location. However further exploration revealed that the classification related to the eligibility of the farm for financial benefits, the system used being more complex than purely geographical location, and the systems used differed between England and Scotland. It was therefore decided not to use this criterion in the selection process. In general both upland and lowland farms were well represented in the areas selected for study.

Information was available on names and addresses only of farm owners or tenants, not farm workers. The details recorded for name and address of farm owner were sometimes not sufficiently complete that the farm owner or tenant could be contacted. This limited the number of farms which could be included in the recruitment process. Also, farms were excluded from consideration if there were less than 100 sheep on the farm, and if they were situated in remote areas, for example if situated on an island. These exclusions were on the basis of practicality to ensure that resources were not wasted on travel time, or farms where little dipping was likely to have taken place. It is likely that this will have reduced the number of sheep farmers with lower exposure to OPs. In practice, however, low-exposed sheep dippers were strongly represented in the study group.

Census data is also kept by MAFF and the Scottish Office on pig farms, in a similar manner to that kept for sheep farmers. MAFF also sought and obtained approval from the Office for National Statistics and the Scottish Office for the release of pig farm census data for the same geographical areas covered by the sheep farm data.

2.3.3 Selection of farms

The selection of farms was based on selection within parish for each of the two geographical areas. It was intended that the sample should consist of about 50% Scottish (Borders, Lothians and Ayrshire) and 50% English (Hereford and Worcester) farms.

A simple random selection of farms had the drawback that farms were likely to be geographically widespread and collection of data from farms spread randomly across the target regions would be costly and time consuming. A design which overcomes the practical disadvantages of a simple random sample is the use of clusters of farms. The Scottish data were already grouped into 353 parishes and by selecting 25 parishes (median number of farms per parish = 13) it would be possible to obtain approximately 300 farms. This would allow more efficient collection of data with a visit to one parish involving collection of data from all farms or a subset in the parish. Clustering has some small disadvantages of efficiency in estimating prevalences, but these are irrelevant to the estimation of exposure-response relationships, which was the main focus of the study. The practical gains of clustering far outweighed any disadvantages, which in any case were controlled by including a large number of parishes, with a limited number of farms per parish.

Consequently, farms were selected for inclusion in the study as follows:

a. The sampling frame of suitable farms was stratified into the two study areas of Scotland (Borders, Lothians and Ayrshire) and England (Hereford and Worcester) with 50% of the sample to be obtained from each of these areas.

b. Within area, select the first parish based only on convenience.

c. Select a small number of farms (usually no more than 10) in the parish ensuring a full range of size of farms within the parish.

d. The next parish was chosen on the basis of geographical proximity to ensure that farm visits could be arranged effectively within each location. The process was then repeated for other parishes in different locations, with occasional step-changes to ensure a fresh start that would include parishes some distance away. The process aimed to ensure that other farms were available in the same area, in case of cancellations and to ensure a cost-effective survey schedule.

e. As the process progressed, if there appeared to be, for example, few large farms included in the sample, these would preferentially be chosen in the subsequent parishes, i.e. this is a form of quota sampling. This was expected to ensure coverage of the full range of exposure experienced by sheep dippers.

Within this framework, initial contact was made, letters of invitation were issued, and responses were processed parish by parish. As noted above, the whole recruitment process was organised iteratively, at a rate which allowed a smooth and continuous recruitment process, but with batches of invitation letters timed to allow for an adequate response time from previous parishes. In this way it was known, throughout the survey, which farms had agreed to take part before the survey team moved into the area.

In order to ensure that pig farms were included from the same locations as the sheep farms, and to ensure a smooth survey process, the census data was used to identify pig farms in the parishes due to be visited between March and May 1997. During this period it was more difficult to recruit sheep farms due to the lambing season, and pig farms provided the additional number of visits required for the schedule.

Some larger estates were involved in more than one type of farming, including sheep, pigs and chicken. In these circumstances permission was obtained from the estate manager to approach the individual farm managers. It was necessary to ascertain that the farmers included in the study worked with only one type of animal, particularly to avoid any OP exposure in the pig and chicken farmers. Farm workers were then recruited on the same basis as described below for all other subjects.

2.3.4 Recruitment of sheep and pig farmers, and associated farm workers

Once sheep and pig farms had been selected within parishes, a letter of invitation was sent to the relevant farmers (or tenants), explaining the purpose of the survey and inviting them to participate. All farmers agreeing to participate, or requesting more information, were contacted by telephone by members of the IOM project team who answered any queries about the survey work, determined the precise location of the farm, and ascertained the availability of farm premises with access to a heating source and electrical supply for the performance of the neurological assessment. Telephone calls were made at lunchtime or in the early evening, as experience showed that these were the best times to speak to farmers.

Farms were excluded from the study at this stage if any of the following applied:

a. the farm personnel had never dipped sheep or only used contractors; or

b. there was no relevant livestock on the farm; or

c. it was not practical to carry out the survey at the farm, for example because of limitations in the on-site facilities; or

d. where the farm was single handed; or

e. the farmer had been retired from farming; or

f. the farmer was principally employed in non-farming activities for the majority of the working week.

The IOM contact also asked for details of the names and addresses of farm workers who had worked full or part-time on the farm within the previous twelve months, who were involved in dipping and were available to attend at the time of the survey. Contractors in the area, and their workers, were recruited by the same method. Farmers were also asked to provide information on family members who were involved in sheep dipping, and had at least three days dipping experience. They were asked to include friends who helped from neighbouring farms. None of this information was available from the farm census data.

In general, farmers were only willing to give details of the names and addresses of those workers who would be likely to agree to participate in the study. Equally if the farm was rejected, or the farmer refused to participate, then no farm workers or family members could be included. Therefore it was not possible to obtain accurate details of the number of potential subjects based at each farm. For this reason we have been able to track non-response (non-participation) at the level of farm, but not at the level of individual subjects within participating farms.

In the case of family members it was usually possible to obtain verbal consent to participate during the initial telephone conversation with the farmer. In this case the number and names of additional family members was recorded on the farmers survey control sheet. Recruitment of families in this way ensured that there were no delays in obtaining agreement to participate, and the farm was added to those available for visiting.

Details of names and addresses were sought for the farm workers highlighted by the farmer. Each farm worker was then sent a similar letter of invitation, outlining the purpose of the study and indicating that the farmer had already agreed to participate in the survey.

When there had been no reply to the letters of invitation (either for farmers or farm workers), individuals were followed up by phone approximately two weeks after the letters were sent and given the opportunity to discuss the study in more detail. All subjects agreeing to participate were documented on the farmers survey control sheet and a separate sheet completed for each individual agreeing to take part at any specific farm. For those subjects not wishing to take part, the reason given was recorded. As soon as more than two people at any farm had agreed to participate, it was possible to arrange an appointment with the farmer. In principle this was only done at the point when the majority of responses for any one farm had been received.

Each individual agreeing to participate in the survey had completed a consent form sent with the letter of invitation, and returned it in a pre-paid envelope to the IOM.

All farmers agreeing to participate were contacted nearer to the time of the survey, to confirm suitable times for the survey team to visit. In addition, farmers were informed of the requirement to bring along details of current medication on the day of survey. All information was passed onto the appropriate survey team, along with a contact telephone number for the farm.

To assist response rates, extra efforts were made to recruit farm personnel. These included a brief broadcast on 'Farming Today' outlining the purpose of the study, assistance from the NFU in publicising the field survey at local meetings, and agreement from a local paper in Hereford to publish a brief article summarising the purpose of the study.

2.3.5 Recruitment of chicken farmers

Chicken farmers were recruited in Scotland on the basis of local knowledge of the location of farms, and the IOM having performed previous occupational health and hygiene work at some of these locations. In addition as discussed above, larger estate owners included in the survey were asked about the availability of other types of farming on their estates, and a number of individuals were included in the study, having been shown to be dedicated pig or chicken farmers. Individual consent forms were sent to all those identified at both the chicken farms and the estates, and only those agreeing to participate were included in the study. The recruitment process then followed the same schedule as outlined for sheep farmers.

2.3.6 Recruitment of ceramics workers

The IOM had previously performed surveys of respiratory health of ceramics workers, and therefore had existing contacts in this industry. With the assistance of the British Ceramics Confederation, a number of member ceramics companies in the same broad geographical areas as the farms were approached concerning their willingness to participate in the survey. Two companies were selected and visited, one in south east Scotland and the other in the English Midlands. Neither of these companies had been involved in the previous IOM survey, but were willing to participate. Initial contact was made with the manager at the two sites, and information on the purpose and procedure of the survey was communicated to management and trade union representatives. The information was communicated to employees by their union representatives.

On the basis of the information provided it was agreed that a meeting with employees was not required, and participation in the study would be on a voluntary basis at each site. Due to a significant number of Asian employees at the company in the English Midlands, it was agreed that two interpreters would be available throughout the survey. In practice the interpreter was rarely required.

Each individual who participated in the surveys signed the same consent form as that used for the farmers. This consent form also included a section in which they could specify whether they wished the results of the investigations to be passed onto their general practitioner.

The ceramics companies were contacted approximately two months before the planned date of the survey to arrange a timetable for the visits and assessments based on shift patterns. The feasibility of using company premises was ascertained. Alternatively arrangements were made for the IOM mobile survey unit to visit the sites.

Timetables for the individual assessments were agreed with company personnel, and travel and local accommodation details obtained. This information was passed onto members of the appropriate survey team.

3. CLASSIFICATION OF CHRONIC PERIPHERAL NEUROPATHY

3.1 FIELD SURVEY INSTRUMENTS

3.1.1 Introduction

For the purpose of this epidemiological survey, neurological damage was measured using a symptoms questionnaire in conjunction with a series of quantitative sensory tests (QST) based on the Mayo Clinic Methodology (Dyck *et al*, 1980). The Mayo Clinic methodology included a neurological symptoms questionnaire together with a battery of neurophysiological tests and was designed to improve the diagnosis of, and estimate the prevalence and severity of, polyneuropathy (a disorder of function of more than one nerve) among specific subgroups of the general population. This need had arisen due to the wide variety of reported prevalence of diabetic polyneuropathy using pre-existing definitions and methods.

For this study, the design of the questionnaire was modified, as the original was designed for clinical use, while in this case the questionnaire was to be administered to farm workers in the field by a trained technician. Also, the full battery of neurophysiological tests, particularly the EMG and nerve conduction studies was not appropriate for a field study carried out by a non-specialist. However, two tests for thermal sensation (hot and cold) and another for vibration sensation were suitable for application by a trained technician using portable equipment. All three tests had demonstrated high sensitivity and specificity in a laboratory setting with controlled ambient temperature.

Thermal sensation depends on activation of thermal receptors by adequate, specific stimuli which create impulses reaching the central nervous system (Hansen *et al*, 1988). The impulses are carried in non-myelinated (C) and thinly myelinated (Aδ) peripheral nerve fibres. Vibration sensation is dependent on the integrity of larger diameter myelinated fibres (Aß) and their mechano-receptors (Goldberg *et al*, 1979). Myelin is a substance which coats certain groups of nerve fibres and facilitates the transmission of nerve impulses along these nerve fibres.

Potentially neurotoxic substances impair impulse transmission by damaging nerve fibres, and may require a larger/longer stimulus to be applied before this sensation is detected by the subject. Previous work suggests that both small and large fibres are vulnerable to the effects of OP neurotoxicity. The tests used were complementary, as the hot threshold tests unmyelinated C fibres, the cold threshold test thinly myelinated Aδ fibres, while the vibration threshold tests thicker myelinated Aß fibres, thus assessing the whole range of peripheral nerve fibre populations.

3.1.2 Mayo Clinic methodology

The Mayo methodology compared different clinical tools against a quantitative measure of abnormality in peripheral nerves, called the Index of Nerve Pathology (Ip). The index compared the density of myelinated fibres in nerve biopsies from healthy individuals with fibre density in nerve biopsies from diabetic patients, both with and without neuropathy. Myelin is a substance which forms a coating around certain groups of nerve fibres and facilitates the transmission of nerve impulses. In certain diseases myelin is reduced or unevenly distributed which results in disorders of nerve function, for example as seen in diabetic polyneuropathy. The Ip normalizes the results for age and sex as myelinated nerve fibre density decreases with age, this change being more apparent in men than women. The Ip was found to provide a sensitive and reliable minimum criterion for the diagnosis of polyneuropathy.

The Mayo Clinic method included the following battery of tests:

a. Neurological Symptom Score: This questionnaire includes selected clinical symptoms known to occur in neuropathy, scored on the basis of present (1) and absent (0).

b. Neurological Disability Score: This involves a clinical examination and results are scored on the basis of severity from no deficit (0) to complete loss of function (4).

c. Quantitative Sensory Tests: These used a Computer Assisted Sensory Examination (CASE) for the detection of thresholds for vibration, touch-pressure and temperature sensation in the great toe and foot.

d. Nerve Conduction Studies: This used standard techniques to measure both sensory (sensation) and motor (muscle power) nerve function in the upper and lower limbs.

The Neurological Symptom Score (NSS) scores on the basis of symptoms in:

a. The Peripheral Nervous System (PNS)

   I. *Motor system* by assessing muscle weakness in the upper and lower limbs. (Cranial nerve involvement was not of interest in this study and these questions were omitted.)

   ii. Sensory system by assessing both reduction in a sensory function (a negative symptom), for example, difficulty identifying objects or unsteadiness in walking, and altered sensation (a positive symptom), for example, numbness or pain.

b. The Autonomic Nervous System (ANS)

   This considers symptoms occurring within specific organ groups of the ANS for example bladder function or gastro-intestinal symptoms. (The ANS is a self-regulating part of the nervous system over which the individual has no conscious control).

Abnormality within any two of the clinical tests occurring independently resulted in the same allocation of subjects to normal and abnormal categories as did Ip (Index of Nerve Pathology), (Dyck *et al*, 1980). In assessing the results of quantitative sensory tests, it was found that vibration was the most sensitive test for the detection of polyneuropathy, followed by touch pressure tests, and then thermal cooling using the Mayo Clinic case methods. Recent evidence suggests that thermal cooling is more sensitive than touch pressure, and therefore this test was used with vibrameter assessment in the field studies. The evaluation of sensory tests alone also resulted in a close estimate of neuropathy based on clinical symptoms. Although abnormalities of nerve conduction were found to be sensitive and reliable for the detection of polyneuropathy, none of the nerve conduction measurements alone provided a direct measure of clinical symptoms or signs.

Different combinations of tests were also rated in their ability to predict disease severity and to set minimal criteria for the diagnosis of polyneuropathy. The investigators found that all the tests could be used to assess the severity of polyneuropathy, and determine minimum diagnostic criteria. However, due to the variability in data, it was not possible to use the results from one type of test to predict the others. It was concluded that motor, sensory and autonomic symptoms would be evaluated separately, and judged as normal or abnormal by comparison with appropriate standards.

3.1.3 Neuropathy Symptoms Questionnaire

The questionnaire used in the field studies was a modified version of the Mayo Clinic neurological symptom questionnaire. It was designed specifically to detect possible chronic neurological effects which may be associated with exposure to organophosphates. Questions focussed on symptoms occurring in the upper and lower limbs, and questions on cranial nerve involvement were excluded. It was anticipated that symptoms were more likely to occur in the distal parts of limbs, for example hands and feet rather than more proximal areas. A copy of the questionnaire is shown in Appendix 3.

Symptoms were categorised into three symptom groups relating to muscle weakness and sensory symptoms, which are indicative of damage to the peripheral nervous system, and autonomic symptoms. Within each symptom group, multi-part question targeted symptoms in specific sites of the body, in particular hands, shoulders, legs and feet, or, in the case of autonomic symptoms, specific symptoms experienced, such as, sweating, fainting and impotence, for example. Logical flow charts showing the scoring rules for each question are shown in Appendix 5. Within each symptom group, scores for individual questions were added together to give total scores. An overall symptom score was derived by adding together the total scores for the three symptom groups.

The Autonomic Nervous System questions took account of symptoms occurring in different organ systems as in the original questionnaire, although the weighting given for a positive score was 0.5 rather than 1.0 for those symptoms present for more than one month. It was considered preferable to treat symptoms in one organ group as 'separate syndromes', in that symptoms in one do not increase the probability of symptoms being present in another organ group/system. Whilst any symptom occurring in isolation may be non-specific, the presence of symptoms in two different organ groups/systems greatly increases the specificity. This is the rationale for scoring each section 0.5 if positive symptoms are present. It is felt that the original equal weighting of symptoms between the peripheral and autonomic nervous system may lead to an over-estimation of the cases of possible or probable neuropathy in the study group.

The modified questionnaire also included some sections which were not scored. These sections provided information on other symptoms which could help in excluding confounding medical conditions, or provide additional information on symptoms of interest. Information was also be collected on other possible confounding factors for example, relevant family history of disease, regular exposure to vibration and medication. In addition, individuals were asked about current smoking and alcohol habits. Full details of the questions asked can be found in the copy of the questionnaire reproduced in Appendix 3.

Prior to training of the technicians in administration of the questionnaire, the clinical staff at the INS had administered the neuropathy questionnaire to a number of neurology outpatients as part of a small pilot study. This is described in more detail in the report of Phase 3 of this study (Pilkington *et al*, 1999).

3.1.4 Thermal threshold tests

Heat threshold and cold threshold values are determined by a microcomputer-controlled system and the forced-choice method described below, which is a standard method of test administration. Thermal thresholds are expressed as temperature changes from the basal skin temperature. A microprocessor system controls the stimulating probe (thermode) and presents the forced-choice trials. The thermode operates on the Peltier principle, where the direction of the current flowing in the thermode causes heating or cooling. The amount of current passed gives a measure of the amplitude of the stimulus. The skin temperature beneath the stimulator is maintained at a constant predetermined value (normally 34 ^{0}C +/- 0.2 ^{0}C) when not stimulating.

On the background of a constant skin temperature (34 ^{0}C) the thermode applies a quantified thermal (heat or cold) stimulus to the skin. The stimulus is graded by altering its duration while the power and thus the rate of change of temperature is constant throughout (1^{0}C/s). The thermode is calibrated in each subject to measure the exact amount of power required to obtain this fixed rate of temperature change. The subject is placed in a comfortable position and the thermode is applied with a standardised pressure to the area of skin to be tested (top of the foot). The large thermode probe (12.5cm^2) reduces the variability of the response, and the skin site chosen is most distal site of the lower limb that can be tested.

The stimulus indicator is a small box with two lights (numbered 1 and 2). It is handed to the subject to watch during the test. In the initial manual test, temperature changes between 1 - 10 ^{0}C, in steps of 1^{0}C, can be selected by the operator. This is used to give a rough estimate of the values between which the threshold lies. During the manual test, light one comes on alone with application of the stimulus, and the subject is asked if they could feel the probe becoming warm (or cold if the cold threshold is being measured). The automatic test procedure is started at the lowest reliably identified level.

In the automated test procedure, each light is illuminated in sequence to indicate two separate time periods. During one of the periods there is a null stimulus while during the other a real stimulus is presented to the subject. The order of stimulus application is assigned randomly by the computer and is unknown to both the subject and the operator. The subject must then choose the period during which he/she felt the stimulus (forced-choice method). The answer, whether 1 or 2, is entered into the instrument by the operator. Based on the reply, the computer scores a success(S) or a failure(F). This triggers the computer to give the next stimulus which is of the same, longer or shorter duration according to the up-and-down transform rule (UDTR), which is described in section 3.1.6.

For the purpose of the test the UDTR is applied as follows. The last stimulus duration selected during the manual test, will be the starting point for the automated procedure. The stimulus duration, is reduced in steps of 0.5 second after two S at each level, until the first F which alters the changes of stimulus duration to an upwards direction. It is after this first change in direction that the standard UDTR begins, and the steps of change of stimulus duration are reduced. The stimulus levels follow an exponential scale such that the change between one level and the next is about 10% of that level, subject to a minimum change of 100 ms (corresponds to 0.1 ^{0}C). The standard UDTR programming is such that SSS or SSFS obtained in successive trials causes a change to a lower level of stimulation while F, SF, SSFF causes a change to a higher level. Two changes of direction (excluding the first one following the initial large steps) will be used in determination of thermal threshold.

The threshold is calculated automatically as the mean of the points of change of direction. The threshold value is given as the change from the basic skin temperature (34 ^{0}C). During the field study, measures were taken to ensure the basic skin temperature was held constant at the required level. These included warming the foot during administration of the questionnaire, and wrapping the periphery during sensory testing.

Both hot and cold thresholds increase naturally with age in normal populations. For each test, an individual scored positive or negative for an abnormal age-specific threshold based on comparison with the results from a sample of 68 subjects drawn from a normal population and tested earlier in the clinic at INS (See Appendix 6). The test method was to compare any given threshold with the 95th percentile for the age-specific threshold based on the normal population. If the threshold was higher than this reference value then the subject scored positive for that test, and otherwise score negative. This method has been validated in earlier studies (Appendix 6). Details of the choice of percentiles for defining atypical test results can also be found in Appendix 6.

3.1.5 Vibration threshold test

The equipment used follows physiological principles as the intensity of the vibration stimulus is assessed directly as the amplitude of displacement of the skin. The degree of displacement of the skin is the stimulus to the vibration-sensitive receptors. The procedure described is a standard method of test administration.

The apparatus consists of an electromagnetic vibrator with a 13mm diameter probe that vibrates at right angles to the skin at a frequency of 100Hz. The amplitude of the skin displacement (vibration amplitude) is measured and displayed digitally. The equipment can produce amplitudes in the range 0-399.9 Tm. The test site is on top of the foot in line with the big toe (middle of first metatarsal bone). The vibrator is held against the skin with a force of 500+/- 100g by reference to a force indicator on the vibrameter. The test begins with no vibration to allow the subject to feel and accommodate to the pressure from the weight of the vibrator. The apparatus can deliver two standardised rates of increase or decrease of stimulus intensity: slow or fast. The stimulus is first increased at the fast rate to a level above the threshold, where the subject clearly feels the vibration in order to make him/her familiar with the sensation. The vibration amplitude is then decreased until the subject can no longer feel it.

The actual test is started by increasing the vibration amplitude at the slower rate, and the subject is instructed to indicate when the stimulus is felt. The vibration amplitude is then reduced and the subject asked to report when they no longer feel it. Both these values (the amplitude of appearance and disappearance of the vibration) are recorded, and an average of the two values is taken. Further trials are repeated until three consecutive mean values, with a variation of less than 10%, are obtained. The mean of the last three threshold values is then taken as the vibration threshold (VT).

VTs are affected by surface skin temperature and it is recommended that, where feasible, the skin temperature at which the test is performed is maintained above 31 °C.

VTs also tend to increase with age in normal populations, especially after the sixth decade of life. As with the thermal threshold tests, a positive diagnosis of neuropathy was based on comparison with the 95th percentile for the age-specific threshold derived for a normal population. Details and a graph of the threshold limits against age can be found in Appendix 6.

3.1.6 Up -Down -Transform -Rule in thermal tests

The up-and-down transform response rule is a means of obtaining an estimate of the threshold level in the QST from a sequential series of binary responses (Wetherill GB *et al*,1966). The probability (p) of being at the threshold level L_p, is modelled in a logistic model where:

$$p(x) = 1/1 + \exp^{-(\alpha+\beta x)}$$

0where α is the starting level and β is the step size.

With a starting level of zero and a step size of one this reduces to

$$\ln\left(\frac{p}{1-p}\right) = x$$

The Up-and Down transform response rule (UDTR) is a means of estimating L_p, where $p > ½$. In other words, the aim of the UDTR is to estimate the level at which the stimulus can be felt 50% of the time. With the number of trials, $n_0 = 3$, this corresponds to 75% in forced-choice testing. A pre-determined series of equally spaced levels are used and after each trial, the proportion p' of positive responses at the level used for the current trial is calculated, counting only the trials made since the last change of level.

If $p' > p$ and p' is estimated from n_0 or more trials, decrease the level one step.

If $p' < p$ increase the level one step and if $p' = p$ no change of level is made.

In the thermal threshold test with $n_0 = 3$ and any $p > 0.67$, the following are the criteria for moving up or down one level.

Up : F, SF, SSFF and Down : SSS, SSFS

This procedure can be carried on for 2,4,6 or 8 changes of direction which is set before testing each subject. For the field studies 2 changes of direction was used. In addition, an initial manual test provides a good approximation to the actual threshold so that the operator of the automated test will already have a good idea of the region of the threshold.

3.2 FIELD SURVEY METHODS

3.2.1 Survey teams

The field survey team comprised three technicians, one principally trained in administration of the exposure history questionnaire, one trained in the administration of the neuropathy questionnaire and the third trained to administer both questionnaires and sensory tests. Training for the administration of the neuropathy questionnaire and sensory tests was provided by staff at the Institute of Neurological Sciences, and initial training was provided in the neurology outpatients department. Training for the administration of the exposure history questionnaire was provided by an experienced IOM occupational hygienist and initial training included administration of the questionnaire to local farmers. In both cases the technicians were observed by the senior member of staff and were provided with feedback on their performance. Following this, the technicians administered questionnaires to a number of IOM staff who were provided with mock occupational and symptom histories. The data collected was then checked against the information provided to ensure accurate recording of symptom and job history data. This procedure also allowed the consistency of results obtained from sensory tests to be assessed.

Two teams were operational during the survey. One technician was based in the Hereford and Worcester area, and one was based in Scotland. The third technician, also based in Scotland, travelled between the two survey sites. One of the IOM Occupational Hygienists acted as a specific liaison for each survey team. They ensured that the survey teams were informed of details relating to the farms to be visited, and any changes of plan. They also ensured that information on problems encountered by the survey team was passed onto an appropriate member of the IOM/INS project team.

The technicians were provided with detailed protocols which outlined the procedure required for administration of each questionnaire and the sensory tests. The protocols were incorporated into the training schedule.

3.2.2 Farms

An identical survey procedure was used for both sheep farms and pig and chicken farms. Following recruitment of personnel at a specific farm, the farm owner was contacted by a member of the IOM team to arrange a suitable time for the farm visit to be performed. Visits were arranged where possible in close proximity to each other to ensure that as many subjects could be assessed during each day. The farm surveys took place between November 1996 and the end of May 1997.

The surveys began in the south of Scotland and continued until mid January when the surveys commenced in England and Wales. Surveys continued again in Scotland in April and May. This schedule was arranged to ensure that the continuity of the survey was maintained despite the changing pattern of lambing and other significant tasks between the two geographical areas.

The assessments were performed on farm premises. In general the surveys took place in the living quarters of the farm, the lounge or kitchen, or occasionally in office space. Two rooms were requested so that the data on job history and neurological symptoms could be collected separately. One subject would commence with the job history whilst the second subject began with the neuropathy questionnaire and sensory tests. The technician ensured that, if necessary, the feet were warmed at the start of the questionnaire administration, to attempt to ensure the required skin temperature was reached before performing the sensory tests.

The exposure history questionnaire was administered by one technician to all workers on the farm who had been involved in sheep dipping. The neuropathy questionnaire and sensory tests was performed on the same group by the other technician. The technicians then repeated the procedures at other farms selected in the same parish, before moving onto the next parish.

The same field survey procedure was used for pig and chicken farm personnel. A modified version of the exposure-history questionnaire was administered to this group (See Appendix 2). However, the neurological assessment using the symptoms questionnaire and sensory tests was the same as for sheep farmers.

Subjects were also asked to complete consent forms agreeing to participate in the survey and specifying whether they wished their general practitioner to be informed of the results.

3.2.3 Ceramics companies

The surveys were arranged on the basis of pre-arranged appointments. Suitable facilities were available at one of the ceramics companies to allow the questionnaire and sensory tests to be performed on company premises. There were no suitable facilities available at the other company, and an IOM mobile unit was placed on site and used for the assessments. The unit has separate space available and therefore it was possible to ensure that data was collected on the two questionnaires in privacy. Heating facilities were also available on the unit, although at both companies employees taking part in the survey had often been working in cold environmental temperatures and several had cold peripheries at the time of the survey. One survey took place in early November 1996, and the other in early April 1997.

A modified version of the exposure-history questionnaire was administered to this group (See Appendix 2). However, the neurological assessment using the symptoms questionnaire and sensory tests was the same as for sheep farmers.

Subjects were asked to complete consent forms agreeing to participate in the survey and specifying whether they wished their general practitioner to be informed of the results.

3.2.4 Quality Assurance

In order to ensure a consistent approach by technicians during the survey, the dialogue from a minimum of two assessments performed by the technician were recorded each week. This included the procedure for the sensory testing. A member of the IOM team was nominated to review the tape recordings for one of the questionnaires and sensory tests where applicable, in relation to the appropriate protocol. In the initial stages this resulted in feedback to the technicians on minor aspects of their technique, but as the survey progressed, this procedure confirmed the consistency of the techniques used.

3.2.5 Ethical approval

As the survey took place in more than one geographical area, ethical approval for the study was sought from the HSE Research Committee. All documentation relating to the project and details of survey methodology were submitted and approved.

3.3 NEUROPATHY SCORING SYSTEM

A modified scoring system, based on the Mayo Clinic methodology, was devised to allow subjects to classified on their likelihood of having neuropathy. This scoring system used the combined results of the symptoms score, based on the symptoms questionnaire, and the QST score, based on the sum of positive abnormal thresholds from the three QSTs, to allocate subjects to one of four diagnostic categories labeled 'no', 'possible', 'probable' and 'definite' neuropathy. The score sheets used for assigning individuals to one of the four categories can be found in Appendix 5.

The scores from the results of sensory tests were considered together with the scores from the neuropathy questionnaire, and these were used to assign individuals to the following categories:

	Classification	Criteria
a.	Definite neuropathy	Symptom score ≥ 2 AND QST score ≥ 1
b.	Probable neuropathy	Symptom score ≥ 1 AND QST score ≥ 1
c.	Possible neuropathy	Symptom score ≥ 1 OR QST score ≥ 1
d.	No neuropathy	Symptom score < 1 AND QST score $= 0$

This information was used to compare the classification of neuropathy with indices of exposure to organophosphates, on the basis of historical recall information collected from the same individuals.

4. EXPOSURE ESTIMATION

4.1 INTRODUCTION

The principal objective of the current study was to investigate the hypothesis that repeated exposure to organophosphate (OP) pesticides in sheep dips may cause cumulative and irreversible damage to nervous tissue, which eventually becomes sufficient to be clinically detectable. The principal relevant exposure measure to investigate this hypothesis is cumulative exposure over a working life, that is, the aggregation of exposure that occurs normally during the working lives of farmers and others involved in sheep dipping, at levels usually below those that are likely to result in acute effects. The effects of acute exposure to OPs in general has been relatively widely studied, and it was not a stated objective of this study to investigate these further. Therefore, acute peaks of exposure, where it was possible to quantify them precisely, were not attributed with greater weight than that implied by their contribution to lifetime cumulative exposure. A partial exception (see later) was the separate identification of exposure to concentrate rather than to dilute sheep dip.

The study design involved measuring indicators of neurological damage within a cross-section of sheep farmers, together with a control sample of non-sheep farmers and ceramics workers. These indicators were then analysed, using statistical regression methods, in relation to individual estimates of cumulative exposure to OPs derived using a retrospective exposure history.

Sheep dipping tends to occur on a relatively small number of days set aside per year on each farm. Also, since the usage of OPs in sheep dips prior to 1970 was negligible, potentially relevant exposure was only considered to have occurred in the period since 1970. The exposure estimation strategy was therefore:

a. to use cumulative exposure (CE) as a surrogate measure of the uptake of OP pesticides per dipping day summed across all dipping days from 1970 onwards, for each individual;

b. to estimate that CE from responses to a technician administered questionnaire used to gather information on exposure activities identified in Phase 1 as relevant to uptake.

The first phase of the current study, and earlier work, sought to identify relationships between various activities contributing to the OP exposure of sheep dipping workers, and uptake of OPs. Results have been discussed and reported in detail elsewhere (Sewell *et al*, 1999 and Niven *et al*, 1993 and 1994). Despite considerable inter-individual variation, no evidence was found that uptake, that is the biologically active absorbed dose of OPs, was anything other than linearly related to exposure to sheep dips containing OP compounds. This work was useful in that it showed what sources and measures of exposure could be used as a surrogate, albeit an imperfect one, for the uptake of OPs. It also suggested what kinds of questions might be most useful in gathering information relevant to workers' cumulative past exposures, and suggested how answers to those questions might be used in estimating past exposures.

4.2 REVIEW OF OP UPTAKE MODEL

The exposure history questionnaire that was administered to sheep farm workers had been designed around a simple model of dermal exposure and uptake developed in Phase 1 of the current study (Sewell *et al*, 1999). This earlier phase of the study had involved observation of approximately 60 individuals throughout a single dipping session on a number of farms where sheep dipping with OP sheep dips was in progress. Observations were made of tasks and behaviours of those involved including the use and suitability of personal protective clothing. Exposure to sheep dip, both in its dilute and concentrate form, was quantified. Uptake was measured by the increment in the urinary concentration of two metabolites of OPs from before the dipping session to early the next morning.

Evidence was strongest for a relationship between uptake (U) and exposure to concentrate measured by the number of concentrate handling events (C). There was statistically a much weaker association with exposure to dilute dip in the form of splashing from the dip bath which had been visually quantified by the observing hygienists using a splash score (S). No direct evidence of the effect of protective clothing was found. The basic model took the form:

$$U = aC + bS \qquad (1)$$

where the coefficients *a* and *b* were estimated using regression analysis to be 3.6 and 0.2 respectively. The units of uptake were increments in nmol/mmol of creatinine.

4.3 EXPOSURE HISTORY QUESTIONNAIRE: SHEEP DIPPERS

All people recruited to the study at sheep farms were asked to complete a retrospective exposure history questionnaire administered by a technician. This history questionnaire was designed as a self-contained document. Its administration at survey was kept completely separate from the collection of medical data; within any farm, the two processes of data collection were carried out by different people.

4.3.1 Purpose

The aim of the questionnaire was to allow estimation of each subject's retrospective cumulative exposure to OP in sheep dips, both in terms of the intensity and duration of exposure.

The results from Phase 1 of the study, together with earlier work on exposures during sheep dipping, were central to the development of the questionnaire. Specifically, the questionnaire was designed to allow the simple model of uptake in relation to tasks and behaviours, as described above, to be used to estimate cumulative exposure.

More generally, however, Phase I and the earlier associated studies provided information about what tasks and behaviours were related to exposure and uptake. This allowed questions about past experience of dipping to be constructed based both on their relevance to exposure and uptake, and on their likely reliability in terms of ease and accuracy of recall. For example, in a retrospective assessment of exposure no direct estimates of concentrate handling events or splash scores would be available. It was found in Phase 1 that generally there was a sole person responsible for handling the concentrate. This allowed the development of questions to ascertain whether and under what circumstances the subject had been the designated concentrate handler. The number of concentrate handling events could be estimated indirectly from the flock size, at a rate of approximately one handling event per 100 sheep.

Also, Sewell *et al* (1999) had shown that the splash score was associated with the principal task carried out and, to a lesser extent, with bath type. Specifically, paddlers (or plungers) were exposed to the highest amount of splashing from the dip bath, followed by chuckers, then helpers who were generally worked more distant from the bath. Average splash scores were calculated for each combination of bath type (e.g. linear, circular) and task. It was not thought possible to obtain, by questionnaire, reliable information on bath types used many years in the past. However, by far the most commonly used bath type used over the past three decades was the linear bath and this was used by default when calculating splash score.

4.3.2 Pilot study

The IOM has previously undertaken two major studies of exposure to, and uptake of, organophosphates (Niven *et al*, 1993 and 1994). The knowledge gained from these earlier studies enabled a draft version of the exposure history questionnaire to be piloted in Phase 1 of the present study which included farm workers who were actively involved in sheep dipping. The draft version had been based on the concept of establishing dipping practice within particular time-periods. The experience of the pilot study showed that recall would be better if the questionnaire were based on jobs rather than on pre-defined time periods; and the questionnaire was modified to take account of this and of other improvements suggested by the pilot study and main results of Phase 1.

4.3.3 The questionnaire as administered

A copy of the questionnaire as administered, including the protocol used by the technicians, is shown in Appendix 1. The questionnaire is in three parts. In Part 1, a full occupational history was collected including job title, employer's business and start and end dates for all jobs including casual or part-time work. To aid recall, the administrator began with the subject's current job and then proceeded sequentially back through time to at least 1970. As noted earlier, OPs were not generally used in sheep dips in the UK prior to 1970.

For each job in which an individual indicated that he/she had dipped sheep, a Part 2 was also completed. For each job in Part 2, the number of days in total spent dipping sheep with OPs was recorded. Where necessary, this was done by the technician using estimates of days dipped across the years of each job. For this purpose, three or more days spent dipping in any job, was classified as a sheep dipping job. In part 2 further questions were asked about the nature of the dipping. Otherwise, completion of Part 2 was terminated and the administrator moved on to ask about the next job. This was done because it was felt that details about the nature of the dipping in jobs with only sporadic involvement in dipping would not be reliably recorded retrospectively. It also sought to identify pig or chicken farmers with previous history of sheep dipping.

Within dipping jobs, subjects were asked to quantify the time spent in each of the three main dipping tasks, i.e. paddler, chucker and helper. Other questions relating to use of waterproof clothing and splashing were answered using ordered categorical responses which described the degree of occurrence in words, e.g. 'nearly always'. Subjects were asked specific questions about working with concentrate sheep dip prior to dilution in the bath as this had been identified as a principal route of exposure in the first phase of the current study (Sewell *et al*, 1999); for example, subjects were asked, again using ordered categorical responses, how often within a job they were the principal concentrate handler. Those who had handled concentrate at any time were also asked about the wearing of protective gloves.

In Part 3 of the questionnaire, subjects were asked about specific sheep dip compounds that they could recall having used during their working life. Also, questions were asked about tasks performed during a subject's working life which may have led to exposure to OP compounds through routes other than sheep dipping. These included application of insecticides to crops, cattle or domestically, and use of OP sheep dips via direct application to infested sheep. In addition, for each job notified in the occupational history in Part 1, subjects were asked if the job had involved working with any of vibrating equipment, lead, solvents or insecticides.

4.4 EXPOSURE HISTORY QUESTIONNAIRE: OTHER PARTICIPANTS

Both ceramics workers and pig and chicken farmers were asked to complete a modified questionnaire (shown in Appendix 2). The purpose of the questionnaire was essentially to confirm the low-exposure status of these two groups for comparison with sheep-dipping farmers. Therefore, in Part 1 subjects were asked if they had ever been involved in sheep dipping , although not necessarily with OPs, during their working life. If so, the total number of days was recorded. If this numbered greater than three days, then in the case of ceramics workers the interview would have been terminated. Pig and chicken farmers would have had the Part 2 sheep dip questionnaire administered for all jobs which involved more than three days dipping, and would have been categorised as a sheep dipper. This happened on only a small number of occasions during the study.

For each job, subjects were asked if the job had involved working with any of vibrating equipment, lead, solvents or insecticides. In Part 3, subjects were asked the same questions that sheep-dipping farmers were asked about application of insecticides to crops, cattle or domestically.

When the survey team arrived at a farm categorised as a pig or chicken farm in the MAFF database to find that the farm owner also kept sheep, farm workers completed the same exposure history questionnaire that was administered to the sheep farmers. The same criteria were applied to farm workers on these farms.

4.5 EXPOSURE INDICES

For each individual, the total number of dipping days with OPs per job was recorded on the work history questionnaire. Each day of dipping was assigned to one of up to six possible exposure scenarios, derived from the combination of principal concentrate handler (yes/no), and principal task (plunger, chucker, helper). Specifically, within each job the percentage of days that fall into the different possible exposure scenarios was multiplied by the estimated number of dipping days in that job. Each scenario was assigned a predicted uptake value based on the OP uptake model described earlier, and this predicted value was assumed to be constant across all dipping jobs. Therefore, if *NS* is the number of scenarios, *NJ* the number of jobs and ND_{sj} the number of dipping days under scenario *s* in job *j*, cumulative exposure (CE) was estimated to be:

$$CE = \sum_{s=1}^{NS} \sum_{j=1}^{NJ} \sum_{d=1}^{ND_{sj}} P_s$$

$$= \sum_{s=1}^{NS} \left(\sum_{j=1}^{NJ} ND_{sj} \right) P_s$$

where P_s is the predicted uptake under scenario *s*.

Using this methodology, the following cumulative exposure variables were derived:

a. Total days spent dipping (DAYS),
b. Task-based splash exposure (SPLASH),
c. Concentrate handling (CONC),
d. Exposure index (OPEXP).

These variables all used the OP uptake model from Phase 1 to predict uptake under each scenario, but involved different numbers of distinct scenarios. The following brief description should help to clarify what was done.

Variable DAYS identified only one exposure scenario, that the individual dipped sheep, and is therefore an estimate of the total number of days spent sheep dipping with OPs over a working life.

Variable SPLASH identified three scenarios, that the principal task was a plunger, chucker or helper, and assigns predicted uptake based on the average splash scores of 66, 44 and 10 respectively, assuming a linear bath. This variable can therefore be viewed as the task-weighted total number of days dipped, where the tasks weights are in proportion to the expected exposure to dip wash through splashing.

Variable CONC identified two scenarios, that the individual was principal concentrate handler or not, and assigns an average number of handling events (8) only in the former case. This variable is therefore an estimate of the cumulative number of concentrate handling events across a working life.

Variable OPEXP distinguished between all six exposure scenarios based on the combinations of the two concentrate and three task-based splash scenarios. The predicted uptake values assigned to each of the six scenarios were a weighted sum of the predictions used separately in SPLASH and CONC, using the weights defined for the OP uptake model (equation (1)). Hence, this variable attempted to quantify cumulative daily uptake of OPs in sheep dips and therefore could be expressed in units of nmol.days/mmol of creatinine.

Although the questionnaire was designed to record information on sheep dipping with OP pesticides only, it was envisaged that many of those interviewed would have had difficulty recalling the exact formulations that were used; and so the information sought was limited to recent pesticide usage. Only half of the Phase 2 participants were able to recall products recently used for dipping, these results are presented in Appendix 10. However, prior to 1984 OP sheep dips were not considered to be widely used and after 1991 compulsory sheep dipping ceased, so it was expected that dipping with OPs would be substantial and dominant in the period 1984-91. It was of particular interest therefore to estimate cumulative exposure variables for the specific period 1984-1991 in addition to working life since 1970, and this was done.

Missing data was not anticipated to be a problem since the exposure history questionnaire was administered by a trained technician. However, since the information requested depended on recall by the participant a strategy was devised to deal with any missing data within each job relevant to the estimation of cumulative exposure. The proportion of days spent in each of the three dipping tasks and as principal concentrate handler were calculated across the jobs where this information was available. For any job where this information was not available, these proportions were applied to the number of days dipped to produce estimated values.

5. RELIABILITY OF FIELD MEDICAL MEASUREMENTS

5.1 STRATEGIES FOR INVESTIGATING RELIABILITY

The procedures used in the neurological component of the field survey, although well validated in a clinical setting, had previously been administered in the clinic by professional staff and had never been applied in a field setting. Also, it was also not possible to perform the full range of desirable neurophysiological investigations in the field, and a comprehensive neuropsychological assessment was not possible in this context due to time constraints. It was important therefore to assess as far as practicable the reliability of the field medical measurements, and in particular of the overall neuropathy scoring system (Section 3.3).

Two strategies were available for assessing reliability. First, there were aspects of internal consistency and plausibility to be considered regarding the individual components of the overall neuropathy score. For the QST measurements, these included consistency with the reference values based on clinical measurements, as described in Chapter 3. Examination of consistency in this way was planned from the beginning of the study.

Secondly, as described in Chapter 1, the study was designed from the outset to include a detailed clinical examination of selected subjects who had earlier participated in the field surveys. This clinical study, comprising Phase 3 of the overall investigation, was included in order to assess the reliability of the case identification, to characterise the nature and severity of any abnormalities, and to perform a more comprehensive neurological assessment including neuropsychological assessment. It involved selecting a number of subjects from the field studies on the basis of pre-defined clinical criteria, and inviting them to participate in more detailed neurological investigations at the Institute of Neurological Sciences (INS) in Glasgow. These detailed investigations included re-administration of the symptoms questionnaire and the QST tests that had been applied in the field study, which in turn made possible some direct comparisons on the performance of these tests between field and clinic, despite some (planned) differences in the details of how the medical measurements were made on the two occasions.

5.2 INCONSISTENCIES BETWEEN SOME QST FIELD MEASUREMENTS AND ORIGINAL CLINICAL REFERENCE VALUES

Comparisons at this level of detail between measurements in the field and clinic had not been intended originally. However, checks on the QST measurements during and after the field survey showed unexpected differences between observed values and the clinical reference values. This was true especially for the cold test, and to a lesser extent for the vibration test also. For example, during an initial examination of the field medical outcome data, it had been noted that there were an unexpectedly high number of ceramics workers scoring positive for an abnormal cold threshold (48%). This seemed inconsistent with their status as a control group for comparison with farm workers. It was also noted that, using the scoring system described in Section 3.3, this high level of 'abnormality' for cold threshold automatically resulted in a correspondingly high prevalence of ceramics workers being assigned to the category of 'possible' neuropathy or above (62%), a result which we did not consider to be plausible. Similar difficulties applied to results from the farmers.

There were major inconsistencies between field study QST measurements and the clinical reference values. Measurements had been taken during training by all technicians. Some of these had been in the clinic and others outwith the clinic. None had indicated any likelihood of the problems found. However, none had been taken under the kinds of temperature extremes which occurred later during the actual field survey. There are strong grounds for believing that QST results may be sensitive to individuals' limb temperature and related core temperature. (The field study had taken care to ensure that the required skin temperature had been reached before performing the test; but it had not been possible to control core temperature.)

These results led to serious doubts about the comparability of QST measurements in the field and the available reference values from the clinic, with consequent doubts about the overall neuropathy score as originally envisaged. We decided therefore that it would be useful to compare directly the field and clinical measurements for the medical outcomes individually as assessed for the same subjects albeit on occasions 18 months apart, and with some differences in methods; and on that basis re-consider what medical outcomes might be the most informative to examine in the Phase 2 analysis. These comparisons, and all associated decisions, were made without any knowledge of exposure-response relations, and indeed before any linkage had been made between health and exposure data.

Results of the comparisons are reported in the present Chapter. Full details of the clinical study are given by Pilkington *et al* (1999); a summary of the relevant parts only is included here.

5.3 RELEVANT METHODS FROM THE CLINICAL STUDY

5.3.1 Recruitment

A subset of subjects involved in the field study were invited to participate in the clinical study. To ensure a wide representation of disease status in the clinical study, individuals were to be selected in equal numbers from each of the 'no', 'possible' and 'probable/definite' groups as derived from the field survey data, using the original neuropathy score (Section 3.3) whose relevance to the present study was now in question. (The 'probable' and 'definite' groups were combined for selection due to the small numbers of subjects falling within the latter group across the field study group as a whole.)

In practice, and as described by Pilkington *et al* (1999), a modified neuropathy scoring system was used in selecting subjects for the clinical study. This modified system did not directly use the most questionable of the QST measurements, that for cold threshold, though care was taken to ensure that the subjects selected did include a wide range of cold threshold responses.

In total, 79 subjects actually attended the clinic. This was less than had been envisaged originally. The difference was not due to non-response, the participation rate quite satisfactory, but rather to unexpected delays in getting started on the clinical work in Phase 3. The 79 participants comprised 22, 26 and 31 subjects respectively from the 'no', 'possible' and 'probable/definite' categories in the field study, as classified according to the original definition in Chapter 3.3, i.e. one that made use of the cold threshold score. No ceramics worker was invited to attend the clinical study.

5.3.2 Administration of symptoms questionnaire in Phase 3

The symptoms questionnaire was the same as that used during Phase 2 epidemiological survey, but excluding details of occupation or details of relevant occupational exposure. This was to ensure that the Institute of Neurological Sciences (INS) survey team did not have access to information about the subject which might bias their assessment of neurological status. In Phase 3 the questionnaire was administered by a neurologist in a hospital environment.

The symptoms questionnaire was followed by a clinical assessment based on the Mayo Clinic criteria. In general the neurological assessment was performed on the right side of the body (ie. reflexes, sensation, muscle power) unless the neuropathy questionnaire data for an individual suggested the existence of a right sided injury that was independent of any effects from organophosphates. Both upper and lower limbs were assessed. Further details of these methods can be found in the Phase 3 report (Pilkington *et al*, 1999).

5.3.3 QST measurements in Phase 3

The same range of sensory tests were performed in Phase 3 as in the Phase 2 studies. Sensory testing was undertaken by measuring hot and cold thermal thresholds on the dorsum of the right foot to test for small peripheral nerve fibre function and vibration threshold over the dorsum of the right hand and the right foot to test the large peripheral nerve fibre function. The equipment used was the same as in the Phase 2 field studies, with the addition of the Glasgow Vibration System (GVS). Again, further details of these methods can be found in the Phase 3 report (Pilkington *et al*, 1999).

5.3.4 Statistical methods

Agreement between the field and clinic categorisations was assessed by cross-tabulation. More formal quantifications of the level of agreement was carried out using chi-square tests of association and the kappa statistic (Armitage and Berry, 1994).

The kappa statistic is a means of quantifying the degree of agreement between two grouped variables, conditional on the marginal distributions, that is analogous to the linear correlation coefficient for continuous variables. Therefore, the kappa statistic, κ, lies on a scale from -1 to 1, with chance agreement corresponding to κ=0. Perfect agreement, (κ=1), occurs when all subjects lie on the main diagonal of the two-way table, however, it is to be expected that even by chance some subjects will lie on the diagonal. It is possible that agreement could be worse than chance, i.e. where some sort of aversion is operating between the two classifications, corresponding to negative kappa statistics bounded by κ=-1.

When classifications are ordinal, i.e. the categories can be ranked, as here, then it is possible to use a weighted kappa statistic where, for example, a difference in agreement of only one category is given less weight that a difference or two categories, and so on. As with all one-dimensional summary statistics, however, kappa does not give a complete picture of agreement, being conditional on both marginal distributions, and not invariant to changes in the number of categories used. It is also difficult to determine the precise meaning of absolute values of kappa in terms of what constitutes good and bad agreement. Fleiss (1981) suggests that values higher than 0.75 represents very good agreement, while values lower than 0.4 represent poor reproducibility. In this study emphasis was placed less on absolute levels of agreement and more on the relative performance of several classifications made on the same subjects for which it is ably suited. Statistical analysis was carried out using the Genstat statistical software package (Genstat 5 Committee, 1993).

The level of agreement between the continuous QST threshold measurements was assessed informally using scatter plots. The level of agreement was quantified by analysing the distribution of the individual field versus clinic differences, summarised by the mean and variance.

5.4 COMPARISON OF FIELD AND CLINICAL MEDICAL OUTCOMES

5.4.1 Classification of neuropathy

The comparison of the field and clinical classification of neuropathy using the original (Section 3.3) neuropathy scoring system is shown in Table 5.1, which is based on all 79 subjects who attended the clinic as part of Phase 3. In all, 40 (51%) of the 79 subjects were classified in the same category on both occasions. There was no strong evidence of bias, with 18 (46%) of the 39 off-diagonal elements classified higher in the clinic than in the field, and 21 lower. Overall agreement was however only modestly better than chance, as measured by the kappa statistic (κ=0.26, SE 0.08). A weighted kappa, taking account of the number of categories of difference, was similar at 0.27, suggesting that where differences occurred, they were not necessarily simple movements into the next highest or lowest category. Since the subjects included in the clinical comparison did not include any of those within the field study group with a unsubstantiated positive cold QST outcome, it may be that this measure of agreement has over-estimated reproducibility in the field study group as a whole. The disagreement is noteworthy, for example, in that only 8 (36%) of the 22 subjects classified as 'no neuropathy' based on measurements in the field were again classified as 'no neuropathy' when the same scoring system was applied to measurements made in the clinic. In total, 11% of individuals were classified at opposite ends of the neuropathy scale (e.g none/probable, probable/none) on each occasion.

5.4.2 Agreement of component scores

The reproducibility of each of the four component scores that were combined within the neuropathy scoring system was also investigated in an attempt to highlight any particular principal source for the lack of agreement overall. Comparisons between the field and clinic symptom score and the three QST outcomes are shown in Tables 5.2 to 5.5, respectively.

Exact agreement for the grouped symptom score was found for 51(65%) of the 79 subjects (Table 5.2) with no evidence of bias, the 28 off-diagonal elements being were distributed equally between those with higher scores in the field and those with lower. Overall agreement was significantly better than chance, based on a chi-square test of association. The kappa statistic, κ=0.37 (SE 0.10), suggested reasonable reproducibility of the symptoms questionnaire between the field and clinical studies, while the higher value of the weighted kappa of 0.46, suggested that often disagreement was only by one, rather than two, categories. Table 5.2 shows that 35 (78%) of the 45 subjects with lowest score in the field again had lowest score in the clinic, with similarly high reproducibility of the highest score (13 from 17, or 76%).

Among the three QST outcomes (Tables 5.3-5.5), the proportion on the main diagonal, designating exact agreement, ranged from 60-68%; and this was significantly better than chance for the heat and vibration tests but not the cold test. This corroborated earlier evidence, among ceramics workers, of a lack of comparability between the cold threshold measurements in the field and the clinical reference values. Relative to chance, overall agreement was better for the vibration test (κ=0.30) than for either the hot (κ=0.22) or cold tests (κ=0.18), but, in all three, was poorer than for the symptoms score.

5.4.3 Agreement of measured QST thresholds

The actual measured thresholds for each of the three QSTs were compared between the field and clinic and the results are presented as scatter plots in Figure 5.1. These show Phase 2 versus Phase 3 logarithmic values of hot, cold and vibration thresholds for the 79 subjects that attended the clinic. The positive correlation for each threshold indicate that a patient with a high threshold in the clinic is most likely also to have had a high threshold in the field. Adverse conditions (low temperature) are thought to be the cause of the bias in the field measurement. The use of normative values from the clinic for the field study measurement has been a significant factor in the difference in classification between field and hospital study.

Since inter-individual variation in thresholds tended to increase with the mean threshold, all three thresholds were analysed on the logarithmic scale. These show a significant degree of linear correlation between the field and clinic measurements. Correlation coefficients were 0.71, 0.44 and 0.66, for the hot, cold and vibration measurements respectively. There was evidence of a bias in the hot and vibration measurements. This is summarised in Table 5.6. For the hot QST, thresholds tended to be proportionally lower, by a factor of two, in the field compared to the clinic, although from figure 5.1(a), there was evidence that the bias was greatest for those with the lowest thresholds. For the vibration QST, field thresholds were proportionally higher than clinical thresholds, again by a factor of two. Adjusted for these biases, within individual field-clinic differences varied by, on average, a factor of approximately 2.7, based on the geometric standard deviations (GSD).

Even thresholds measured in the clinic are prone to random measurement error which is exhibited as intra-individual variation in repeated testing of the same subjects. However, if we were to assume that measurements in the clinic in some way represent 'truth', and that the field measurements on the same individual consisted of this truth plus added noise due to poor reproducibility specifically in the field, we would expect to see much greater inter-individual variation in the field than in the clinic, if the same group of individuals were tested in both settings. Comparing the inter-individual variances of the phase 3 subjects as presented in Table 5.6, the ratios of the geometric standard deviations (field v. clinic) were 1.25, 0.99, 0.96 for hot, cold and vibration thresholds respectively. This indicated that inter-individual variation was only slightly higher in the field compared to the clinic for the hot test, but comparable for the other two tests.

5.5 OUTCOMES OF THE COMPARISONS OF FIELD AND CLINIC MEDICAL MEASUREMENTS

5.5.1 Choice of neurological response variables

The Mayo Clinic methodology for the diagnosis of neuropathy has only ever been validated in a clinical setting using professional clinic staff. In a study of this scale, the only practical option was to carry out the various tests and procedures in the field using trained technicians. It was expected that there would be less than perfect agreement between measurements made on the same individuals in the field study and in the clinical study. Although using the chosen method there was clear evidence of association between the classifications of neuropathy made in the two settings, the level of agreement was only modestly better than chance, and resulted in a substantial minority of subjects (11%) being classified at opposite ends of the classification scale on each occasion. Therefore, it was decided that the cross-sectional study of exposure-response relationships would *not* use the modified version of the Mayo Clinic neuropathy scoring system as described in section 3.3. Instead, it was decided to use four distinct neurological response variables, the symptom score and the three continuous QST threshold measurements, in the analysis of exposure-response relationships in the field study data

The symptom score had proved reasonably reproducible and it would be used as a simple indicator (<1 or ≥ 1) of the presence or absence of reported symptoms using the scoring rules described earlier.

Although, in comparison with clinical reference values, the classification of subjects into 'normal' and 'abnormal' groups based on the QST thresholds had proved less reproducible, there was still benefit in using the actual measured thresholds as individual continuous response variables. This is because, if a continuous measurement of a physical quantity, such as a sensory threshold, does in fact correlate with the true level of underlying damage, then there is a substantial loss of information if that variable is instead used to dichotomise the response into binary high/low categories based on comparison with a fixed external reference line. This is most clearly demonstrated using two individuals who, although they have almost identical threshold measurements, fall marginally on either side of the reference line and are therefore categorised differently. This will be compounded by the presence of non-negligible intra-individual variation, as exists for sensory thresholds. This point is particularly pertinent in the current study, where the hypothesis under investigation is that chronic low-level exposure leads to incremental neurological damage. Detection of incremental damage to the nervous system would best be served by retaining the sensory test thresholds on their original, continuous scale.

5.5.2 Implications for the study of exposure-response relationships

The main implication for using four separate neurological response variables was that it required four separate exposure-response regression analyses. Although unifying the results of a number of exposure-response relationships can be sometimes prove difficult, the use of four response variables can be viewed as a benefit in that different manifestations of neurological disease can be identified and related to exposure variables.

Biases were observed in the field QST thresholds in relation to those measured in the clinic. There was evidence that this was due to lack of control of the limb temperatures of the farmers who were principally surveyed during winter months. Comparison of the field and clinic QST thresholds results were consistent with evidence for biases due to low core temperatures. In cold temperatures, increased sensitivity to heat might be expected to reduce hot thresholds, resulting in a bias downwards in the field compared to the clinic. Equally, cold temperatures would reduce sensitivity to both cold and vibration sensations both of which were higher on average in the field compared to the clinic.

However, in a linear regression framework, a bias in the sensory test thresholds, that applied independently of exposure, would not effect the detection of a statistical exposure-response gradient whether one truly existed or not. Random measurement error is an unavoidable component of any measurement system, and in this context, would apply in a clinical setting as well as in the field. In fact, as noted above, there was no evidence that the field measurements incorporated a significant component of *additional* random error relative to the clinical measurements. Therefore, the random scatter in the plots of field versus clinic QST thresholds is likely in the main part, to reflect inherent measurement error in sensory tests of this type. The presence of random error such as this in response variables does not result in biased estimates under a regression framework, but only serves to weaken the power of the analysis to detect an exposure-response gradient where one truly exists.

5.5.3 Further analyses of field and clinic reproducibility

In Chapter 8 of this report, the results of exposure-response analyses are presented using the four neurological response variables as described above. One clear result from the analysis of symptoms prevalence was that subjects, predominantly farmers, in the English regions reported symptoms more often than subjects in the Scottish regions of the same age, sex and exposure, as quantified by an odds ratio of 2.

There was the opportunity, with the clinical data, to compare the reproducibility of symptom reporting between the Scottish and English farmers who attended the clinic. In total, 53 Scottish farmers and 26 English farmers attended the clinic. Therefore, when cross-tabulated by symptoms score (<1, ≥ 1) in the field and clinic, separately by country, the numbers in some of the cells of the tables were small, particularly among English farmers. However, there was evidence that reproducibility of symptoms among English farmers (κ=0.55; SE 0.16) was better than that of Scottish farmers (κ=0.24; SE=0.14).

Table 8.7 shows that the crude prevalence of symptoms among Scottish farmers was 14%, while for English farmers it was 25%. To estimate hypothetical clinical prevalence rates within the field farmer group, a simple adjustment was made by applying the rates of true positives and false negatives found among farmers attending the clinic to the corresponding numbers of positives and negatives found among farmers in the field. In this way, a clinically adjusted prevalence of 29% was estimated for Scottish farmers, with English farmers unchanged at 25%.

Although this crude calculation takes no account of the age and sex of the farmers in the field relative to the clinic, it does suggest that the higher rates of symptom reporting found among English farmers in the field were more reproducible, and, by implication, more reliable, than the lower rates found among Scottish farmers. It is, however, recognised that reproducibility in itself does not guarantee that the measurements themselves necessarily reflect a medical truth. It also suggests that the observed difference in symptoms prevalence between the two countries is not due to a systematic difference in exposures to OP sheep dips, or any other type of exposure that may lead to similar symptoms. This is in line with the comparison of OP sheep dip products used by subjects from the two countries (reported in Appendix 10) which, conditional on products recalled, does not show any marked differences in the type of products used.

The finding of possible relatively depressed rates of symptom reporting among Scottish farmers does not invalidate the results of the exposure-response analyses. By including a term for country differences in the logistic regression models for symptoms, adjustment was made for the relatively lower rates in Scotland, allowing valid comparison of the effects of exposure and other factors both within and between the two countries.

Comparison of field and clinic reproducibility of symptoms reporting between the two sexes, found to have different prevalence rates in e-r analyses, was made difficult by the small number of females attending the clinical study (n=11). However, there was no evidence of markedly different reproducibility between the two sexes.

Comparison of the field and clinic agreement of QST thresholds among farmers in the two countries did not suggest that the biases noted earlier for the hot (lower in the field) and vibration (higher in the field) thresholds in particular differed between the two countries. In fact, these biases were found to be consistent across several other explanatory factors, notably sex, though limited by the low number of females at the clinic, and exposure, when crudely categorised into high and low.

6. DATA ANALYSIS METHODS

6.1 DATA PROCESSING

6.1.1 Data collection and key-entry

There were two streams of data from the field surveys to the IOM. One the medical questionnaires and measurements, the other the occupational histories and related exposure information. The forms were batched at the end of each week of the survey, and returned in separate envelopes.

At the IOM they were inspected for Quality Control by occupational hygienists. In any week the two streams were not inspected by the same person. They were then passed to Systems and Computing Section where the two sets of forms were controlled separately by two people to ensure that the expected, matching, number of forms were received and processed. Identities were not matched at this stage. (There was one, expected, discrepancy as a subject left before completing the medical tests- this person was excluded from the study)

For the medical questionnaires and measurements a set of unique six-digit random numbers was generated, and prefixed with an N, to provide a pseudo-identity. These were printed on labels and stuck to the neuropathy questionnaire before key-entry. The pseudo-identity was keyed along with subject's identifying details from the neuropathy questionnaire. These along with the responses and the QST measurements were keyed using KEIII software. This key-entry software had been programmed to provided checks on valid responses to the questionnaires and valid ranges of measurements.

If there was any inconsistency between the recorded data and the valid responses it was referred to the systems analyst who would determine with the occupational hygienists or an occupational physician an appropriate value to impute for these cases. This value was recorded on the form but distinguished from the original. Usually the attribution would be to treat the doubtful data as missing (which was recorded by a special distinguishable value), but there is one noteworthy exception. For the QST measurements, particularly vibration thresholds, some subjects had no value recorded because the subject could not detect on their foot the highest level producible by the equipment. However, in these cases there was usually a note that the subject could detect the output on their hand, which showed that the equipment was working. In these cases the imputed value was the highest valid value for the threshold. This forced a positive response but would allow these cases to be distinguished in the data from those whose threshold was known.

Processing of medical data through all stages from key-entry to database was carried out before any entry of Occupational History/ Exposure Information was made.

For the occupational history/ exposure information a different set of unique six-digit random numbers was generated, and prefixed with an H, to provide a pseudo-identity. These too were assigned by attaching the labels to the forms. All data including the subjects identity was key-entered. However, the data which contained the subject's identity was reserved in a separate record for subsequent matching, only the pseudo-identity went forward with the substantive data to the database.

The occupational data for some subjects was keyed using the KEIII software. For others the data was keyed by a bureau. This together with the nature of the data meant that the majority of the checks were applied after key entry. However some checks were possible and discrepancies were resolved as described above, with appropriate imputed values being used. In particular, when the start-date for a job did not specify a month then January (01) was imputed.

6.1.2 Database and further data validation

A database was designed and constructed to maintain the data for this project using SIRpc version 3.2 (SIR,1993) on a PC. A hierarchical design was used to facilitate the retrieval of information about individuals. However, in the beginning different pseudo-identities were used for the neuropathy data (N identity) and exposure history data (H identity) so that individuals existed as two cases on the database but with no possibility of matching medical with exposure information. Thus preparatory work could be conducted by the same individual on either stream up to the point of examining the exposure-response relationship. Only after this point was the data loaded to match the two streams. Data was loaded onto the database from the key-entry outputs.

SIR retrievals were written to check the occupational histories. The database contains, in sequence, one record for each distinct job recorded in the subjects work history; and for sheep-dipping jobs a linked record with information about exposure.(It should be noted that where the job involved less than 3 days dipping, no information on exposure was collected other than the number of days.)

Checks were made on the integrity of the records, that is that every dipping job had an exposure record and reflexively every exposure record had a job which ended after 1969. For fifteen individuals no exposure information had been obtained during the survey for their jobs which ended in 1970, otherwise the integrity was complete. Also the start and end dates were checked against the sequence of jobs, and the subjects date-of-birth to confirm there were no gross errors introduced in the processing.

There were apparently both gaps and overlaps in the dates in the work histories. However, in accordance with the protocol, the survey did not attempt to collect a complete work history except for periods of sheep dipping. We therefore did not try to resolve gaps in the history of anyone who did not dip sheep, nor for jobs which ended before 1970. The process of imputing dates when only the year had been given (described above) gave rise to some inconsistencies when there was a sequence of jobs for which only the year was given for start and end dates. These were adjusted by revised imputations which were also marked on the forms without obscuring the original entries. There were also cases where a person may have genuinely worked jobs in parallel.

There was only one subject who reported having two dipping jobs worked in parallel and the stated details were plausible. Both jobs contributed to the accumulated exposure for this subject (who did not have an extreme exposure). Except for an end-date before 1970 (which shows that OP dips were not used), the start and end dates of a job make no difference to the total exposure because it is based on days spent dipping. However, the dates could affect the partitioning of exposure into the years between 1984 1991 inclusive.

6.1.3 Retrieval of data and derived variables

SIR retrievals were written to derive the symptoms scores, QST scores and Neuropathy Outcome Scores according to the scheme described in Chapter 3. Note that even where data was missing a score was still derived for the individual. This was achieved by imputing a value to the missing data during the retrieval. The database continued to record "missing" for the variable. The imputation was always to the value that would avoid the generation of a false positive score for the section in which the data was missing.

The preliminary descriptive statistics for QST scores showed unexpected numbers of positive scores even amongst the ceramic workers. Measures were taken to independently confirm the scores from the manuscripts on a subset of these. Also where at a single farm more than one person was scored as 'probable/ definite neuropathy' the manuscripts were examined by the project leader. The derivation from the retrievals was confirmed in all cases.

In addition other derived outcomes were obtained which were utilised in the process of selecting subjects for Clinical examination in Phase 3 of the investigation.

SIR retrievals were also written to derive measures of exposure according to the model described in chapter 4 and the various confounding measures such as wearing protective clothing, or being exposed to solvents. Also where an exposure or confounder variable was missing then a computation was made of the proportion of the accumulated dipping-days for which the variable was missing. When the dipping-days itself was missing then no exposure could be derived for that job.

The preliminary descriptive statistics for exposure showed some subjects with extreme values. These were reconfirmed against the manuscript records which were plausible by the nature of the jobs (contract dippers, very large flock sizes, or a manager of several farms). All were retained in the data set derived for analysis.

6.1.4 Matching of identities

To prevent derivation of neuropathy outcome being in any way affected by knowledge of an individual's exposure, the project analyst/programmer were kept blind to the match of identities. The matching of identities was carried out by a different analyst/programmer who had access to both sets of forms so that any apparent discrepancies of identity, arising from different transcriptions of names, were successfully resolved. Particular attention was paid to those cases where more than one individual had the same name; all of these were resolvable by date of birth.

Once the phase 2 neuropathy scoring and exposure estimation had been separately completed, and the phase 3 clinical examinations carried out, it was agreed that the exposure-response relationship could be examined. Only at this point was the list matching the neuropathy identity (N identity) and exposure identity (H identity) supplied to the project team. This permitted a match between the previously retrieved data on exposure and neuropathy score, and allowed the database to be updated.

6.1.5 Data protection and confidentiality

The database was protected by a password, and by further access-control words which prevented alteration of the data except by the project analyst/programmer working on the project and his superiors. This also limited the copying of data to project team members on a need- to-know basis. In particular, the data extracted for statistical analysis never included the names of the subjects.

6.1.6 Data archiving

The database was backed-up to off-line tape media. The back-up media of the database, including, for example, derived files for statistical analysis, and manuscript records on which the IOM has collected data from participants will be archived and retained for 10 years.

Within 3 months after the acceptance of the final report all copies of the farm census databases obtained from MAFF and the Scottish Office will be destroyed, as will all derived data. However, any similar data disclosed directly to the IOM by farmers (whether or not they subsequently became subjects) will be treated as project data as described in the previous paragraph.

6.2 STATISTICAL METHODS

6.2.1 Occupational groupings

For comparison of responses among groups of exposed and unexposed groups, individuals were assigned one of three occupational groups (OGs):

a) sheep-dipping farmers (subsequently labeled SD farmers),
b) non-sheep-dipping farmers (subsequently labeled NSD farmers),
c) ceramics workers.

Although the first two groups of farmers broadly corresponded to the distinction between sheep farms and pig and chicken farms as they were labeled in the MAFF databases, it was felt more appropriate to distinguish a control group of farmers on the basis of their having had no reported exposure to OP sheep dips. This was necessary because, during the field survey, it was found that some of the farms labeled as pig farms also held some sheep and that often workers at these, and other farms without sheep, had helped in dipping the sheep of friends and neighbours.

6.2.2 Exclusions

Based on criteria established prior to the field study, individuals were excluded from the final analysis study group if, during the field survey, they reported positively for any one of the following criteria that were included in the symptoms questionnaire:

a) ever diagnosed for a neurological disease by a GP/hospital,
b) had any other disease associated with the effects of a neurological disease,
c) were on medication which may cause side effects associated with the effect of neurological disease, or which indicated a condition which was associated with the effects of a neurological disease,
d) had a relevant family history of muscle weakness, sensory loss or high arches (with or without curly toes).

6.2.3 Comparisons of occupational groups

At the most basic level, an exposure effect, though not necessarily cumulative exposure, could be tested by comparing responses across the three defined occupational groups: SD farmers, with some experience of sheep dipping, NSD farmers, with no experience of dipping, and ceramics workers, also with no experience of sheep dipping.

Four indicators of neurological damage were compared across these three groups: a binary symptoms score (≤ 1, >1) based on the symptoms questionnaire, and thresholds measured for the hot, cold and vibration sensory tests. The differences in the four neurological response variables among the three occupational groups were estimated using a regression model based approach. This allowed the significance of differences between the groups to be tested not only directly, but also while simultaneously adjusting for all potential confounding variables.

Informal comparisons between OGs were based on tabulated symptoms prevalences grouped by 10-year age bands. Linear logistic regression was used to calculate odds ratios (ORs) and test the significance between the occupational groups (Collett, 1991). By fitting models that included the relevant variables, odds ratios were adjusted for potential confounders of neurological symptoms, prominent among which were expected to be age and alcohol habit. More details about the form of the logistic regression models used are given in Appendix 9. Regional differences in reporting of symptoms were also investigated by including a indicator variable to distinguish the country (England or Scotland) of residence.

The three QST thresholds were compared initially graphically across the range of ages using a scatter plots that included the LOWESS scatter plot smoothers (Cleveland, 1979), a form of locally-weighted moving average to aid the comparison of trends with scattered data. More formal comparisons were made using multiple linear regression (Draper and Smith, 1981) of the log-transformed thresholds. On the log scale a constant difference effect equates to constant proportional effect on the measurement original scale. As with the symptoms score, effects were adjusted for potential confounders such as age and alcohol habit. More details about the form of the regression models used are given in Appendix 9.

The emphasis in the statistical analysis was in the estimation of the size of effects, i.e. differences, ratios and regression coefficients, and their standard errors. Where relevant, the statistical significance of effects was assessed using Wald tests (ratio of effect size to its standard error) for individual effect sizes. Unless otherwise stated, a 5% level was used to determine statistical significance, although P-values for individual tests lying between 5-10% were not ignored but noted as of borderline significance.

6.2.4 Exposure-response Relationships

The relationship between the four indicators of neurological damage and cumulative exposure to OPs in sheep dips was investigated using the same regression framework described in the section above: logistic regression for symptoms, multiple linear regression for log-transformed QST thresholds. Using regression models allowed the effect of exposure variables to be estimated while simultaneously adjusting for important confounding variables.

The indices of cumulative exposure described in Chapter 4 were included in regression models both before and after adjusting for significant confounders and occupational group differences, as described in 6.2.3. To check on the linearity of the exposure-response relationship to be explored, cubic spline smoothing splines were used, in place of simple linear terms for some exposure variables. A cubic smoothing spline is a form of nonparametric curve where the degree of smoothness is controlled by a smoothing parameter, in this case corresponding to the effective degrees of freedom. With an effective degrees of freedom of one the smoothing spline is constrained to be equivalent to a simple linear term. By increasing the effective degrees of freedom, the constraints are relaxed and the spline is determined by the more and more by the underlying trends in the data. Unless otherwise stated, in this report, an effective degrees of freedom of four was used as a suitable trade-off between a relatively smooth shaped spline, and one that characterised the main trends in the observed data. Models that contain smoothing splines in place of linear terms are no longer technically linear models, but are referred to as additive models (Hastie and Tibshirani, 1990).

Residual plots were used to investigate potentially outlying observations and influential values. In regression analysis, influential points tend to have high leverage and small residual (observed minus predicted) differences, and can contribute more than the other data points to the determination of parameter estimates (e.g. gradients). The leverage is a statistic that can be determined for each data point in the regression that quantifies how distant each point is in relation to all others along the scales of all the explanatory variables simultaneously. Normal probability plots (multiple linear regression) and half-normal plots (logistic regression) were used to assess the distribution of the residuals after models were fitted to the observed data.

Regression models were fitting using Genstat version 5.4.1 (Genstat 5 Committee, 1993). Diagnostic plots and other data descriptions were carried out using MINITAB version 12 (MINITAB Inc., 1998). Figures were produced using Sigmaplot version 3 (Kuo and Fox, 1993).

7. RESULTS 1: DESCRIPTION OF THE STUDY POPULATION

7.1 RECRUITMENT

7.1.1 Recruitment of sheep farms

Letters of invitation were sent out to 995 sheep farms selected from the databases provided by MAFF and the Scottish Office. Where there had been no reply to the letter of invitation, farmers were phoned approximately two weeks after the letters were sent. Often the farmer had been too busy to open the letter, or had assumed it was a consumer based survey. Given the opportunity to discuss the survey in more detail, many of the farmers who had not returned the reply slip agreed to participate.

An agreement to take part was obtained for 611 farms, an overall response rate of 61%. However, not all of these farms were surveyed, as is illustrated in the flowchart of the recruitment outcomes (Figure 7.1). Approximately 17% were not followed up either because they did not meet in the criteria for inclusion set out in Chapter 2, or because the required quota of farms had been reached and the field survey terminated before responses could be processed.

It can be seen from the flowchart that of the 508 farms contacted for further details, 335 (66%) were deemed suitable for survey. Table 7.1 shows the reasons for excluding 173 farms at this stage. The most common reason, accounting for around half of the exclusions, was that the farm personnel had never themselves dipped sheep. Of the 335 farms deemed suitable for survey, a survey actually took place in 293 (88%) of these. The reasons for surveys not taken place at the remaining 42 farms is shown in Table 7.2. The most common reason was that, despite the farmer's acceptance, the farm workers were unwilling to take part.
As can be seen in Figure 7.1, 308 farms replied to the initial letter that they did not want to take part. The reasons for their negative response, where they were given, are shown in Table 7.3. In the main the farmers claimed not to be interested or were too busy to participate.

7.1.2 Recruitment of non-sheep farms

Pig farms were selected from the databases provided by MAFF and the Scottish Office, chicken farms approached directly based on previous contact with the IOM. Letters of invitation were sent to 94 farms. Where there had been no reply to the letter of invitation, farmers were phoned approximately two weeks after the letters were sent.

An agreement to take part was initially obtained at 58 farms, an overall response rate of 61.7%. However not all of these farms were surveyed, as is illustrated in the flowchart of the recruitment outcomes (Figure 7.2). Of the 56 farms contacted for details, it was determined that 35 (62%) were suitable for survey. All of these 35 farms deemed suitable for survey were in fact surveyed.

As shown in the Figure 7.2, 21 of the 56 farms contacted after agreement proved unsuitable for survey, and would not have been selected if the information given by the farmer had been available on the database. The reasons for exclusion were as follows: eight had no relevant livestock on the farm, three were not a farmer (or worked full-time at another job) and there were ten miscellaneous reasons (including being a small-holding).

7.1.3 Recruitment of dipping contractors

The IOM contacted five people whose current employment was dipping contractor. Two of these took part in the survey. These individuals were contacted with the help of the National Farmers Union. The reason for non-participation was the difficulty in scheduling an appointment given the unpredictability of their own timetables and demands for their services.

7.1.4 Recruitment of ceramic workers

As discussed in Section 2.3, ceramics workers were recruited with the assistance of the British Ceramics Confederation. Two companies were selected and visited, one in south east Scotland and the other in the English Midlands.

The Scottish ceramics company employed less than 60 people, some of whom were absent at the time of the survey. Despite this participation rates of over 80% were achieved at this site. The second company in the English Midlands employed approximately 150 individuals. As it was only necessary to obtain sufficient subjects to reach the target number of 120 ceramics workers, the survey stopped when approximately 60% of employees had participated.

7.2 STUDY GROUP

Following the recruitment process, a total of 609 sheep farm workers, 80 pig and chicken farm workers and 121 ceramic workers were successfully surveyed by the field survey team. Of these, 31 were excluded from the final study group because, on the basis of reported conditions and medications, they did not meet the inclusion criteria set out in chapter 2. Of these, 11 had insulin-dependent diabetes, 4 advanced rheumatoid arthritis, 2 chronic fatigue syndrome/ME, 2 Menières disease, and there were single reported cases of Parkinsons disease, thyrotoxicosis and ulcerative colitis. A further 6 took were taking medication which may cause postural hypotension and two had a relevant family history of high arches. Seven ceramics workers were excluded from the final study group because the had experienced at least one day of sheep dipping. Therefore the final study group for analysis consisted of a total of 772 subjects. Of these, 107 were ceramics workers with no experience of sheep dipping, 53 were farmers or farm workers with no experience of sheep dipping, and 612 were farmers or farm workers with experience of sheep dipping.

Table 7.4 shows a summary of the study group broken down by occupational groups. The majority of ceramics workers were recruited from the English factory (66%), whereas a proportionally smaller majority of sheep-dipping farmers were recruited from Scottish farms (56%). Almost all the non-sheep-dipping farmers were recruited from Scottish farms (87%). The IOM had contact with chicken farms in Scotland, and pig farmers were surveyed during the busiest period of lambing, and the sheep farms included in the survey at this time were mostly in Scotland.

There was a higher proportion of subjects older than 55 years at survey among sheep-dipping farmers (25%) than among other farmers (9%) or ceramic workers (6%). Consequently, the mean age among sheep-dipping farmers (45 years) was higher than the mean age among other farmers and ceramics workers (both 39 years). There was also a higher proportion of female subjects among sheep-dipping farmers (14%) than among other farmers (6%) or ceramics workers (3%). Among sheep dipping farmers these were often family members that were used as additional helpers. Among farmers generally, a higher proportion had experienced college or university education (36%) compared to ceramics workers (23%), and correspondingly, a slightly lower proportion had been presented no educational certificates.

Ceramics workers included a higher proportion of drinkers of more than 30 units of alcohol per week (19%) compared to farmers generally (4%) and a lower proportion of non-drinkers (2%) compared to farmers (7%). Consequently, the mean units of alcohol consumed per week for ceramics workers (19 units/wk) was approximate double that among farmers generally. A small number of subjects consumed greater than 45 units per week (n=12), with a maximum of 92 units per week recorded for one individual ceramics worker. Although the number of ex-smokers was similar among the three groups (19%), there were fewer current smokers among sheep-dipping farmers (20%) than among other farmers or ceramics workers (34%).

In addition, there was no significant difference in either average height (males: mean 1.78 m, SD 0.07 m) or weight (males: mean 80.6 kg, SD 11.6 kg) among the occupational groups. All subjects in the study group indicated that they ate meat or fish or poultry so it was unlikely that dietary deficiencies resulting from a vegan/ vegetarian diet would be responsible for any cases of neuropathy. The prevalence of left-handedness was approximately 8% across the study group and this differed little among the occupational groups. This factor was of more relevance in the clinical assessment where handedness might have influenced the findings of the clinical examination.

7.3 EXPOSURE ESTIMATION

By definition, those in the ceramics worker and non-sheep-dipping farmer groups all were estimated to have zero exposure. Therefore, as described in Section 4.5, four exposure indices were calculated for each subject in the sheep-dipping farmer group. Summary statistics for the four indices within this group are shown in Table 7.5. The simplest of these indices, DAYS, estimates the total number of days dipped since 1970. This ranged up to a maximum of 1350 days, but the majority of estimates were below 100 days, and a significant minority, approximately 25%, were below 30 days. The highly skewed nature of this variable can be seen in the histogram in Figure 7.3. Since the other three variables differ in the weights assigned to each estimated day of dipping, they are also highly skewed in distribution. Variable CONC is an estimate of the number of handling events across all dipping days, and clearly there was a significant minority who handled the concentrate very little or not at all. Variable OPEXP, which is a weighted sum of the SPLASH and CONC variables is an estimate of overall OP exposure based on the phase 1 model and can be expressed as nmol.days/mmol of creatinine.

Since all four variables are weighted sums over all days dipped, there was generally a high degree of correlation among them. Figure 7.4 shows a scatter plot matrix of each variable against every other, together with the linear correlation coefficient. The lowest correlation was between DAYS and CONC (r=0.86), reflecting the fact that a substantial susbset would have handled the concentrate not at all or very little. The highest correlation was between CONC and OPEXP (r=0.99), and this is a consequence of the high weight attached to the concentrate handling component of exposure, relative to the splash score component, in the phase 1 model. The two individuals with the greatest number of days dipped also score the highest in all the other exposure variables.

A total of 55600 dipping days were recorded across the study group. Of these, 35% were estimated to have taken place between the years 1984-91 when OP sheep dips were licensed and widely used. The period prior to this, back to 1970, accounted for 42% of days dipped, while the period since, up to survey in 1997, accounted for 23% of days dipped. Therefore, there was evidence that dipping rates using OP sheep dips were higher during the period 1984-91, although this is based on crude estimates of dipping rates per year that do not take account of periods when individuals were actively employed in sheep-dipping.

The median number of days dipped between 1984 and 1991 was 17 (inter-quartile range: 10—36). There was high correlation between exposure indices calculated over the full research period (1970 onwards) and the restricted period 1984-1991. For both DAYS and OPEXP variables the correlation coefficient was 0.94.

8. RESULTS 2: EXPOSURE-RESPONSE RELATIONSHIPS

8.1 OVERVIEW

This chapter describes the results of the analysis of exposure-response relationships, using the four neurological response variables: a symptoms indicator, and the hot, cold and vibration sensory test thresholds. Primarily, a regression-model based approach was adopted; first to compare responses across occupational groups; second to compare across the groups adjusting for important confounding variables; and third, to quantify the direct relationship between the responses and indices of cumulative exposure, also adjusting for important confounders. Subsequent analyses using other, non-cumulative, exposure indices are described later in the chapter, together with evidence of the effects of other potential sources of OP exposure. The statistical methods employed are described in more detail in chapter 6.

The unadjusted group differences are shown in Table 8.2. The same differences, adjusting for important confounding variables and interactions, are shown as the first (left most) model output in each of Tables 8.3-8.6, which correspond to each of the response variables in turn. Having identified potential confounding variables for each of the four response variables, the effect of variables representing cumulative exposure was investigated by adding a further terms to the regression models that included terms for the important confounders previously identified. The remaining models in each of Tables 8.3-8.6 show models which show the results of these analyses of cumulative exposure indices.

Models in Tables 8.3-8.6 and later tables are shown column-wise, with effect sizes (ORs, × effects) and 95% confidence intervals for each term included in the model. By including multiple terms in each model, each term is adjusted for all others in the model. At the base of each model column is given the overall fit statistic or deviance, which quantifies the unexplained variation after fitting the model to the observed data. Each model fitted also included a constant term, corresponding to the predicted response when all explanatory variables equaled zero. Since the emphasis was on looking for effect sizes and gradients, the estimated constant parameter has been omitted from the tables of model output.

For symptoms, represented by a binary (yes/no) indicator variable, the effects are presented in these tables as odds ratios (ORs) which are directly estimable from the parameters of the fitted model. For the three QST thresholds, the effects presented are multiplicative factors since these response variables were analysed on the logarithmic scale.

The estimated effects in Table 8.2 onwards are based on a slightly-reduced subset of the full study group which omits the small number of subjects for whom, either no response variable was recorded, or for whom no relevant exposure data was recorded. This means that, for example, estimates (e.g. ORs) in Table 8.2 are based on the same group of subjects as for estimates in the corresponding Tables 8.3-8.6 which incorporate exposure variables, allowing valid comparison of parameter changes due to inclusion of additional variables for adjustment.

8.2 COMPARISON OF OCCUPATIONAL GROUPS

8.2.1 Prevalence of symptoms

The prevalence of reported symptoms among the three occupational groups is presented in Table 8.1 for each of the three symptom groups together with the overall symptom score. For the former, the prevalence of a non-zero score is shown. For the latter the prevalence of a score of 1 or more is shown, based on the neuropathy scoring system described earlier, which assigns a score of 0.5 to each basic autonomic symptom. For all three symptom groups and the overall score, SD farmers reported a higher prevalence of symptoms than either NSD farmers of ceramics workers. In addition, NSD farmers consistently reported a higher prevalence of symptoms than ceramics workers. Reported prevalences were, on the whole, much higher for autonomic symptoms than for either muscle weakness or sensory symptoms. Reporting of symptoms generally increased with age, and there tended to be a marked increase among the oldest age group (≥55 years). The prevalence of the individual symptoms that contributed to each of the three symptom groups is shown in Appendix 11.

Overall, approximately 20% of SD farmers were assigned a symptom score of 1 or more, which was almost twice the rate for NSD farmers, and almost four times the rate for ceramics workers. The consistency of these differences with age was difficult to ascertain due to the small numbers of ceramics workers and, in particular, NSD farmers, within specific age groups. However, there was a clear trend in reported symptoms with age among the more numerous SD farmers, that rose to a prevalence of over 30% in the oldest age group.

Odds ratios (ORs) were estimated from parameters of the linear logistic model fitted to the observed data, and were used to compare the difference in prevalence rates among the three occupational groups (see section 6.2.3). Table 8.2 shows unadjusted ORs which compare directly the odds of symptoms among SD farmers relative to the odds among both NSD farmers and ceramics workers. Without adjustment for potential confounders, there was an almost 5-fold increase in the symptoms reporting among SD farmers compared to ceramics workers generally, and a smaller increase (approximately 2-fold) compared to NSD farmers.

Model S/1 in Table 8.3 shows ORs for the same group comparisons but after adjusting for statistically significant confounders. Age was found to be an highly significant effect with, on average, a 43% increase in the odds of symptoms for every 10 years of age. Using a cubic spline smoother, there was no evidence that, under the linear logistic model, this effect was anything other than linear with age. Since, prior to the analysis it was thought possible that there could be differences in responses among farmers in different areas of the UK, a term for country of residence was included in the model-fitting process. In fact, there was a statistically significant higher prevalence of symptoms in England, higher by a factor of almost 2, compared to Scotland. The effect of alcohol consumption (number of units per week) was not found to be significant and therefore was no included in the reported models. There was no evidence of any statistically significant interaction between age and either OG or country, or between OG and country. The ORs between the OGs show a significantly higher prevalence of symptoms in SD farmers compared to ceramics (OR=4.4), and a higher prevalence, though non-significant, in SD farmers compared to NSD farmers (OR=1.3). Therefore, in comparison with the unadjusted ORs in Table 8.2, the potential confounding effects of age, and country account only a small fraction of the large difference between SD farmers and ceramics workers.

8.2.2 Hot QST Threshold

A plot of the hot QST thresholds, on a logarithmic scale, against age at survey is shown in Figure 8.1. The three OGs are plotted using different symbols and a LOWESS smoothed trend line has been fitted across the age ranges of each OG to aid comparison. The layered effect at lower thresholds is a consequence of the precision with which threshold measurements were recorded (to the nearest 0.05 °C). Despite the wide variation among individuals, even within the same group, there is a clear increasing trend with age in all three groups, but little or no separation in mean thresholds between the three groups. There is some evidence, most noticeably among SD farmers, to suggest that thresholds rise more steeply after approximately age 45 years.

The relative mean differences between the occupational groups were estimated using multiple linear regression of the log-transformed hot thresholds. Table 8.2 shows that, before adjustment for any potential confounders, thresholds among ceramics workers were, on average, lower than among both groups of farm workers. Thresholds among SD farmers were a factor of 1.54 (CI: 1.17—2.04) higher than ceramics workers, and 1.25 (CI: 0.85—1.83) higher than among NSD farmers.

Model H/1 in Table 8.4 shows the result of a single regression model fitted including the statistically significant confounders and OG differences. Both age and sex, but not alcohol consumption, were found to be significantly related to the hot threshold. Age was modeled using a cubic spline smoother (with 4 d.f.) to allow for any non-linear trends as suggested in Figure 8.1. The approximate linear equivalent effect predicted than 10 years of age resulted in a 63% increase on average in the hot threshold, while thresholds among males were on average over twice those among females (the vast majority of whom were sheep dippers).

Although main effects for OG and country were not significant, after adjustment for age and sex, the inclusion of an interaction between OG and country was significant (F=3.9; P=0.021). A country effect was included in the analysis because of the evidence, presented in the previous section, that symptoms prevalences differed by country. The lack of consistency in the size of the differences between groups in the two countries, relative to Scottish ceramics workers can be seen in the effects that make up the country×OG interaction term in Model H/1. Although in Scotland farmers generally had lower thresholds than ceramics workers, in England, the reverse was true. Thresholds among English SD farmers were 1.60× higher than English ceramics (P=0.002), but also 1.40× higher than Scottish SD farmers (P<0.001). However, thresholds among English SD farmers were not significantly higher than among Scottish ceramics workers. Thresholds among Scottish ceramics workers were, on average, 1.48× than their English counterparts although this difference was not statistically significant (P=0.11).

There was no evidence of any further significant interactions among the fitted confounders, or between OG and the confounders.

8.2.3 Cold QST Threshold

A plot of the cold QST thresholds, on a logarithmic scale, and age at survey is shown in Figure 8.2. The three OGs are plotted using different symbols and a LOWESS smoothed trend line has been fitted across the age range for each group to aid comparison. The layered effect at lower thresholds is a consequence of the precision with which threshold measurements were recorded (to the nearest 0.05 °C). Despite the wide variation among individuals, there is a clear increasing trend with age in all three groups. Only among ceramics workers was there evidence of a steeper increase in later years (> 40 years); prior to this there was evidence to suggest higher average thresholds among SD farmers in comparison with both NSD farmers and ceramics workers.

The relative mean differences between the occupational groups were estimated using multiple linear regression of the log-transformed cold thresholds. Before adjustment for other covariates (Table 8.2), thresholds among SD farmers were, on average, higher than among both other groups. Thresholds among SD farmers were a factor of 1.55 (CI: 1.28—1.86) higher than among ceramics workers, and a factor of 1.87 (CI: 1.46, 2.39) higher than among NSD farmers.

Model C/1 in Table 8.5 shows the result of a single regression model fitted that includes the statistically significant confounders and OG differences. Both age and sex, but not alcohol consumption or country, were found to be significantly related to the cold threshold, although the size of the effects, particularly the sex difference, were lower in relation to those for the hot threshold. Age was modeled using a cubic spline smoother (with 4 d.f.) to allow for any non-linear trends as suggested in Figure 8.2. The approximate linear equivalent effect predicted that 10 years of age resulted in an average 30% increase in the cold threshold, while thresholds among males were on average 38% higher than among females. Adjusting for these confounders, there was a significant difference among the three occupational groups (F=13.8; P<0.001). In particular, thresholds among SD farmers were 1.35× higher than among ceramics workers (CI: 1.14—1.60), and 1.65× higher than among NSD farmers (CI: 1.31—2.07). There was no evidence of a significant interaction of these effects with country of residence, or with the other important confounders.

8.2.4 Vibration QST Threshold

A plot of the vibration QST thresholds, on a logarithmic scale, and age at survey is shown in Figure 8.3. The three OGs are plotted using different symbols and a LOWESS smoothed trend line has been fitted across the age range for each group to aid comparison. Despite the wide variation among individuals, there is a clear increasing trend with age in all three groups. Within all three groups was there evidence of a steeper increase in thresholds after the age of 50 years. From the figure there was no strong evidence of a difference in average vibration thresholds among the three groups.

The relative mean differences between the occupational groups were estimated using multiple linear regression of the log-transformed vibration thresholds. Prior to adjustment for any covariates (Table 8.2), thresholds among SD farmers were higher than among both other groups. Relative to NSD farmers, thresholds among SD farmers were 1.47× higher (CI: 1.06—2.03), while relative to ceramics workers, thresholds among SD farmers were 1.68× higher (CI: 1.32—2.14).

Model V/1 in Table 8.6 shows the result of a single regression model fitted that includes the statistically significant confounders and OG differences. As for the other thresholds, age and sex, but not alcohol consumption, were found to be significantly related to the vibration threshold. Age was modeled using a cubic spline smoother (with 4 d.f.) to allow for any non-linear trends as suggested in Figure 8.3. The approximate linear equivalent effect predicted that 10 years of age resulted in a 63% increase, on average, in the vibration threshold, while thresholds among males were on average 21% higher than among females. Although the main effect for OG was not significant, after adjustment for age and sex, the inclusion of an interaction between OG and country was highly significant (F=4.8; P=0.008). The country×OG interaction term in Model V/1 of Table 8.6 shows the lack of consistency in the size of the differences between groups in the two countries, relative to Scottish SD farmers. The basic pattern was a reversal of that found in the two countries for the hot threshold. In Scotland, SD farmers, and NSD farmers, were significantly higher than ceramics workers, while in England, both SD farmers, and NSD farmers, were lower on average than the ceramics workers. Although there was no significant difference between the Scottish and English SD farmers, there was evidence of a significant difference between the two groups of ceramics workers. Vibration thresholds among English ceramics workers were, on average, 1.63× higher (CI: 1.11—2.40) than among Scottish ceramics workers, and this meant that, although thresholds among Scottish SD farmers were higher than among Scottish ceramics workers, there was no clear difference between Scottish SD farmers and English ceramics workers.

8.3 ANALYSIS OF CUMULATIVE EXPOSURE

8.3.1 Descriptive Statistics

Table 8.7 shows the prevalence of symptoms among individuals grouped by total number of days dipped and split by country. This reveals the higher prevalence in symptoms reported in England generally and a suggests a trend towards a higher prevalence with increasing days dipped in both Scotland and England. However, this comparison take no account of other important variables that may vary between individuals, in particular, age.

Figures 8.4(a)-(c) show scatter plots of thresholds against cumulative exposure, expressed as total days dipped, for the three QSTs. These show a large degree of inter-individual variation at all levels of exposure, but no evidence of a trend with exposure.

The regression results for each of the four response variables are discussed in more detail in the following sections.

8.3.2 Prevalence of Symptoms

Models S/2 and S/3 in Table 8.3 show the estimated effects from the models fitted that include the important confounders, OG differences and cumulative exposure indices DAYS, the total number of days dipped, and OPEXP, the model-based cumulative exposure index, respectively. Both variables were scaled to show the gradient of the linear effect, transformed to an OR, over the inter-quartile range (IQR) which was 74 for DAYS and 2350 for OPEXP. Since both variables were highly correlated, the gradients, and model deviances, were very similar. Therefore, it was not possible to state with confidence that one variable was a more accurate reflection of exposure than the other. Both linear effects were statistically significant at the 5% level.

A further, more detailed, investigation of the shape of the relationship of symptoms reporting and cumulative exposure was carried out using a nonparametric cubic spline smoother in place of the simple linear term in the logistic regression model. Figure 8.5(a) shows the resulting smoothed effect of the variable DAYS, relative to zero exposure and adjusted for all the terms shown in model S/2, and expressed in units equivalent to the log odds of symptoms being present. Also shown for comparison is the simple linear effect from Model S/2 in Table 8.3. Although the smoothed line deviates from the linear effect towards the high end of the exposure scale where subjects are sparse, at less than 400 days dipped, where that vast majority of subjects lie, the smoothed effect is very close to the simple linear effect. Therefore, the simple linear term and its corresponding OR, appeared to be valid summaries of the cumulative exposure effect.

Before inclusion of cumulative exposure, an increase in symptoms reporting had been noted among SD farmers relative to NSD farmers (non-significant) and ceramics workers (significant). There was also much higher symptoms reporting in England compared to Scotland.

Even after adjusting for cumulative exposure, comparison of models S/1 and S/2 showed that, the much higher symptoms prevalence among SD farmers relative to ceramics workers remained (OR=3.85, CI: 1.51—9.82) and had only marginally been reduced. The difference between SD farmers and NSD farmers, although non-significant before cumulative exposure was also marginally reduced (OR=1.07, CI: 0.43—2.68). The higher prevalence of reported symptoms in England marginally increased however (OR=1.93, CI: 1.27—2.92). The effect on the age, of including an exposure term was negligible reflecting the low correlation between these two variables noted earlier.

8.3.3 QST Thresholds

Hot Threshold

Models H/2 and H/3 in Table 8.4 show the estimated effects from the models fitted that include the important confounders, OG differences and cumulative exposure indices DAYS, the total number of days dipped, and OPEXP, the model-based cumulative exposure index, respectively. It is clear that neither exposure index is estimated to have a positive gradient with respect to the hot threshold. In fact both suggest a small, but statistically significant, negative relationship. To explore the full extent of this relationship, a cubic spline smoother was fitted in place of the simple linear term. The smoothed effect plus the linear effect are shown in Figure 8.5(b), relative to zero exposure, and in logarithmic units. This indicated that the negative gradient was consistent across the exposure range and not the product of a small number of highly influential points.

Comparison between Models H/1 and H/2 showed that, after adjusting for cumulative exposure, the significant interaction between OG and country noted earlier remained, with little difference in the size of the effects. Therefore, the higher thresholds among English SD farmers relative to Scottish SD farmers could not be explained by differences in cumulative exposure. Also, there remained a significant difference between English SD farmers and English ceramics workers, but not between the former and Scottish ceramics workers.

Cold Threshold

Models C/2 and C/3 in Table 8.5 show the estimated effects from the models fitted that include the important confounders, OG differences and cumulative exposure indices DAYS, the total number of days dipped, and OPEXP, the model-based cumulative exposure index, respectively. It is clear that neither exposure index has an estimated gradient that is significantly different from zero. When a cubic smoothing spline effect is fitted in place of a linear term (Figure 8.5(c)), there is no evidence of any positive relationship between cumulative exposure and the size of the cold threshold over the full range of exposures.

Before inclusion of cumulative exposure, significant age and sex effects had been found. Also, SD farmers were found to have significantly higher cold thresholds than both ceramics workers and NSD farmers. Not surprisingly, since there was no evidence of an exposure effect, after inclusion of cumulative exposure (models C/2 and C/3), none of these significant effects, including the higher thresholds among SD farmers, were greatly altered.

Vibration Threshold

ModelsV/2 and V/3 in Table 8.6 show the estimated effects from the models fitted that include the important confounders, OG differences and cumulative exposure indices DAYS, the total number of days dipped, and OPEXP, the model-based cumulative exposure index, respectively. As for the cold threshold, there was no evidence of a gradient in thresholds that was significantly different from zero. Fitting a cubic spline smoother in place of the linear term for cumulative exposure (Figure 8.5(d)), did not reveal any consistent effect of cumulative exposure across the range of exposures within the study group. An initial steep positive gradient is not sustained after around 100 days dipped, and thereafter the gradient becomes negative. This did not suggest a real effect that reflected an hypothesis of cumulative and irreversible damage to nervous tissue.
Comparison of Model V/1 and either of Models V/2 and V/3 in Table 8.6 shows that, after inclusion of a term for cumulative exposure, the estimated effects of the interaction between OG and country, together with the effects for age and sex, remained virtually identical. Therefore, allowing for differences in cumulative exposure, there was no significant difference between the vibration thresholds of English and Scottish SD farmers. However, thresholds among English ceramics workers remained over 60% higher than their Scottish counterparts.

8.3.4 Comparison of cumulative exposure models

The previous sections have described the results of regression models fitted between the four neurological response variables and two indices of cumulative exposure, adjusting for covariates found also to have a significant effect on each response.

These regression models showed that, when scaled by a factor equal to the inter-quartile range of exposure across the study group, the estimated gradients and width of confidence intervals for the exposure variables DAYS and OPEXP, were virtually identical across the four neurological responses.

This similarity was a consequence of the strong positive correlation between them. While DAYS was an estimate of the total number of days spent dipping during the research period, OPEXP was a weighted total over the same number of days, with weights for each dipping day, reflecting intensity of exposure, being determined by predicted exposure to both concentrate and dilute dip. Nevertheless, for all four responses, the simple sum of days dipped, DAYS, resulted in a marginally better fit, corresponding to a lower residual deviance, than the cumulative exposure index OPEXP. Therefore, if a real cumulative exposure effect existed, index OPEXP was no better an explanatory of each response than the cumulative days dipped.

Only for symptoms was there evidence of a positive statistically significant relationship with cumulative exposure. This relationship was adequately modeled, in relation to the log odds of symptoms prevalence, using a simple linear term for cumulative exposure. To place the magnitude of this effect in context by using the effect of age as a guide, 22 days of dipping was approximately equivalent to one year of aging in terms of in creasing symptoms prevalence.

There was a statistically significant, but small, negative relationship between hot threshold and both cumulative exposure variables. For both cold and vibration thresholds there was no evidence of any significant relationship with cumulative exposure. These findings are summarised in Table 8.8 which, for the full regression data set, shows the estimated effects for DAYS and OPEXP from the models (-/2) presented in Tables 8.3-8.6.

To test whether the inclusion of country differences in symptoms and both hot and vibration threshold models could also have accounted for differences in cumulative exposure, the models including DAYS were re-fitted excluding the terms that related to country differences. The estimated gradients for DAYS did not change for both hot and vibration threshold models, while for the symptoms model, the gradient (OR) for DAYS reduced from 1.13 to 1.09 and was no longer statistically significant even at the 10% level. Therefore, magnitude and significance of the exposure gradient for symptoms depended on adjustment also for country.
The exposure history questionnaire asked specifically about dipping using OP products back to 1970. However, it was known that peak usage is likely to have occurred between 1984 and 1991 when OP sheep dips were licensed. Therefore, the exposure variables corresponding to DAYS and OPEXP, but cumulated only over the period 1984-91 were calculated and substituted into models that included the important confounders (Models -/2 in Tables 8.3-8.6). The estimated gradients for these effects are shown in Table 8.8, both variables being scaled by the same number of days (74) and units (2350) as the original variables. For symptoms, the gradients of both restricted-period variables were higher than the corresponding full-period variables, although only the cumulative days dipped variables was significant at 5% (OR=1.35). Among the three threshold responses there negligible differences in the gradients of the restricted-period and full-period exposure variables.

In terms of the fit of the models to the observed symptoms data, neither of the restricted-period exposure variables resulted in a lower residual deviance, and hence a better fit to the data, than the corresponding full-period variables. Although gradients for the restricted period variables appear steeper in Table 8.8, variables have been scaled by the inter-quartile range of the unrestricted variables which are higher than the inter-quartile range for the restricted period variables. For example, if the gradient for restricted-period DAYS variable were scaled by its own IQR of 26 days, the gradients of both the full period and restricted period variables would be almost identical. Therefore, there was no additional evidence of a cumulative exposure effect when exposure was restricted to the period 1984-91 when peak usage was expected to have occurred.

8.3.5 Sensitivity of estimated cumulative exposure effects

Analysis of the residuals of from all of these fitted models showed that several individual data points had high leverage, due in the main to their being at the upper extreme of the cumulative exposure scale. In the main, these consisted of a small number of the most highly exposed individuals on the extreme upper end of the highly skewed distribution of cumulative exposure. Since the points with the highest leverage were not in the main also outliers, the models were re-fitted excluding those points with high leverage as a check for potential highly influential values.

Table 8.8 shows the fitted cumulative exposure gradients when data points found to have high leverage (h>0.05) in models using the full data set were omitted. In the models fitted here, those omitted had a leverage value over 6 times the average leverage of all points, although a factor of 2 is often suggested as a useful cut-point (Collett, 1991). Due to the highly skewed distribution of exposures in this study group, however, this cut-point would have required omission of a significant fraction of all the full data set.

Using the above criterion for high leverage resulted in the exclusion of 4, 17, 10, and 18 data points in the regression models of symptoms, hot, cold and vibration thresholds respectively. Exclusion of these points made little difference to the estimated exposure regression coefficients for the three QST thresholds. There was, however, a slight reduction in the size of the cumulative exposure effects for symptoms, from and OR of 1.13 to 1.07 for DAYS. Also, despite excluding only four subjects from among a study group of almost 800, the gradient for cumulative exposure would no longer be deemed statistically significant as can be seen from the inflated confidence interval. Therefore, the statistical significance of the cumulative exposure gradient was highly dependent on the inclusion of a very small number of subjects, much more highly exposed than the vast majority of the study group.

8.4 FURTHER ANALYSES OF EXPOSURE EFFECTS

8.4.1 Exposure Intensity

The models presented for each of the four response variables in Tables 8.3 to 8.6, show the close similarity between the estimated effect of the simplest exposure index (DAYS) and the most complex (OPEXP). The high correlation between these two variables, which are both weighted sums of the same number of days dipped but using different weights, made it very difficult to determine whether the more complex index based on the Phase 1 model did, in fact, reflect any important attribute of exposure in addition to total duration of exposure. To answer this, a new variable was formed by dividing OPEXP by DAYS to give an estimate of the average OP exposure intensity per day dipped. This variable was grouped in four equal-sized groups by quartiles based on the observed distribution of exposure among SD farmers. This grouped variable, labeled 'Ave. OPEXP', was then added to the exposure-response regression model for each response variable described in the previous section, that included the important confounders plus adjusted for cumulative days dipped (DAYS). These results are presented as models S/4, H/4, C/4 and V/4 in Tables 8.3-8.6 respectively.

Relative to the group with lowest average exposure intensity (<10 units), symptoms, cold and vibration thresholds were estimated to be higher among those in the higher intensity groups. Addition of this grouped effect was of borderline statistical significance for vibration threshold (P=0.07) and symptoms (P=0.09). For these three response variables, the difference did not appear to increase consistently with average exposure intensity, but appeared to peak at the second highest intensity group. For the hot threshold, there was no evidence of a statistically significant difference between the intensity groups.

For all four variables there was no evidence of a significant interaction between average intensity group and cumulative days dipped. This meant that there was no evidence that the average intensity effects were different among subjects with different cumulative days dipped.

Adjusting for average exposure intensity as well as cumulative days dipped appeared to reduce the size and significance of the difference between SD farmers and ceramics workers without affecting greatly the age and country effects (Model S/4). The same was also true for the cold threshold (Model C/4). However the average intensity grouping was not able to explain the higher hot thresholds in English SD farmers relative to Scottish SD farmers (Model H/4).

8.4.2 Comparison of exposure intensity of concentrate and splash components

In phase 1 of the current study, concentrate handling had been identified as the major route of exposure to OP sheep dips and this had been reflected in the model derived for phase 2 of the study. The large weight given to a small number of concentrate handling events in the model used to derive the exposure index OPEXP meant that, among SD farmers, there was a very high correlation (r=0.98) between average OP exposure intensity, and average concentrate handling intensity. The latter was calculated by dividing CONC, the total number of concentrate handling events, by DAYS. The correlation between average OP exposure intensity and average splash intensity was high but lower (r=0.69).

To investigate to relative importance of both the concentrate handling and splash score components of OP exposure intensity, models similar to S/4, H/4, C/4 and V/4 were fitted replacing grouped average OP exposure intensity by, in turn, grouped average concentrate handling intensity and grouped average splash intensity. The resulting improvements in model fits by adding each average intensity effect separately after adjustment for total days dipped and the important confounders are summarised in Table 8.9. The results for the average OP index correspond to models -/4 described above.

For the threshold response variables, variance ratios greater than 1 signify an improvement in model fit that can be tested for significance against standard distributions. Equally, this is true for mean deviances greater than 1, which are relevant to the symptoms response variable modeled using logistic regression. This shows that for both symptoms and vibration threshold, grouped average concentrate handling intensity per day produces a better fit to the response data than average OP exposure intensity based on the full exposure model. For both these response variables, the inclusion of an effect for average concentrate handling intensity, in addition to total days dipped and the important confounders, was statistically significant at the 5% level.

For none of the models fitted and summarised in Table 8.9, was there a significant interaction between average intensity and total days dipped, indicating that the apparent effects of average intensity per day dipped were not dependent on the total number of days dipped. Therefore, there was evidence that the significant concentrate handling intensity effects were independent of duration of exposure. This explained why these effects did not show up in strongly significant cumulative exposure effect in earlier models.

8.4.3 Effect of Concentrate Handling

The comparison between the effects for average intensity due to concentrate handling, splashing and overall OP exposure described above pointed to concentrate handling as potentially having the most significant effect on at least two of the neurological response variables. Since this comparison had been based on a crude, and arbitrary, grouped of the average exposure levels, a more detailed examination of the relationship between average concentrate handling intensity and neurological response was carried out. As for the analysis of the cumulative exposure indices described in Chapter 4, a cubic spline smoother was fitted in place of the grouped concentrate handling intensity in the models described in Table 8.9. This allowed true shape of the relationship between average concentrate handling and each response to be quantified.

For each of the four neurological response variables, the cubic spline effect fitted to the average concentrate handling intensity term, after adjustment for total days dipped and the important confounders, has been extracted and is shown in Figure 8.6. In each of these figures, the effect of average concentrate handling intensity is shown relative to individuals similar with respect to all other modeled variables. Average concentrate handling intensity, quantified as the average number of handling events per day dipped, is on a scale from 0 (never handled concentrate) to 8 (always principal concentrate handler). This was a consequence of assuming 8 concentrate handling events per day for the principal concentrate handler in the model used to estimate exposure to OP sheep dips.

In earlier analyses of cumulative exposure, sex had been found to be a significant effect on all three QST thresholds but not on symptoms prevalence. However, with the inclusion of a term for average concentrate handling intensity, it was found that sex also became a highly significant predictor of symptoms, with males reporting symptoms less often than females of the same given exposure, age and country. Therefore, the cubic spline effect in Figure 8.6(a) has been adjusted also for sex.

For symptoms (Figure 8.6(a)), the odds rise sharply from zero intensity and then appear to plateau, with a slight drop at the highest average intensity. The three threshold variables are similar in pattern, rising sharply from zero as for symptoms, but then falling away at higher average intensity. All three appear to peak around an average of 3 concentrate handling events per day. For the hot QST, the effect falls fully to zero intensity levels at the highest average intensity. However, for vibration and cold QSTs, the effect remains higher than zero intensity levels at the highest average intensity.

As with the grouped average concentrate handling intensity, the cubic spline intensity effects for symptoms and vibration threshold, with 4 d.f., are significant at the 5% level . While P-values for both the hot and cold thresholds were lower ($0.05 < P < 0.10$), it is the consistent shape of the smoothed effects across the three threshold variables that was notable.

8.4.4 Predicted prevalence of symptoms

The shape of the average concentrate handling intensity effect in Figure 8.6(a) suggested, principally, a distinction between these who had, and those who had never, been principal concentrate handlers.

Of the SD farmers included in the exposure-response regression analyses, 78% had been, at some point, principal concentrate handlers A difference in the frequency of principal concentrate handlers was noted within both sexes of SD farmers. Among men, 87% were reported to have been principal concentrate handlers, while among women, the corresponding figure was only 25%. Therefore, the joint and independent effects of gender and concentrate handling on the response variables were investigated.

A binary variable which indicated those individuals who had been principal concentrate handlers was added to the logistic regression model of symptoms that included the effects of total days dipped and the important confounders, including sex, in place of the cubic spline term. The estimated effects are shown under Model S/5 in Table 8.10.

As noted earlier, both concentrate handling and sex were highly significant terms when included together in a regression model of symptoms. Since there was no significant interaction between these two terms, the effects within the logistic model can be treated as applying independently. Although sex was not a significant effect prior to the inclusion of concentrate handling, clearly its effect had been masked by its association with concentrate handling. Males reported far fewer symptoms than females given the same exposure, age and country (OR=0.34; CI: 0.17—0.70) and concentrate handlers reported far more symptoms than those who had never been concentrate handlers (OR=3.43; CI 1.63—7.23). Since these effects are almost reciprocal, an earlier difference between males, who tended to be concentrate handlers, and females, who tended not to handle concentrate had not been apparent.

With inclusion of effects for concentrate handling and sex, the term for cumulative days dipped was slightly reduced and was no longer statistically significant at the 5% level (P=0.08). Without days dipped in the model, the effect of concentrate handling is slightly increased to 3.7, so the two effects are only very slightly confounded. More notably, adjusting for concentrate handling decreased the large difference in symptoms prevalence between SD farmers and ceramics workers (OR=1.27; 95% CI: 0.40— 4.00). Therefore, SD farmers with no experience of handling concentrate were estimated to have the same prevalence of symptoms as ceramics workers of the same age, sex and country.

The prevalence of symptoms predicted by this regression model is shown in Figure 8.7(a). The estimated parameters of the model, which were used to calculate odds ratios in earlier tables, were used to predict the log odds, and in turn, the probability, of symptoms for specific values of the fitted terms. Figure 8.7(a) shows the predicted prevalence (or probability) of symptoms for male SD farmers aged 20 to 65 years under the four combinations of country (England or Scotland) and concentrate handler (ever or never). Although days dipped is not technically statistically significant in Model S/5, all predictions in Figure 8.7(a) are based on 50 days dipped.

Among non-concentrate handlers, the predicted prevalence only increases above 10% for English subjects in their sixties. However, among concentrate handlers, and in England specifically, prevalence had reached 21% (95% CI: 15—27%) by age 40 years and, at age 60 years, 35% (95% CI: 27—43%). Figure 8.7(a) also shows, for comparison, the predicted prevalence among male English ceramics workers which is always marginally higher than Scottish SD farmers who had never handled concentrate. Note however that, due to the smaller number of ceramics workers and generally lower prevalence, confidence intervals for prevalence are relatively wider than for SD farmers. For example, at 40 years of age, the predicted prevalence of symptoms in English ceramics workers is 5% with a 95% CI 2—12%.

8.4.5 Predicted prevalence of QST thresholds

Figures 8.6(b)-(d), corresponding to the three QST thresholds suggested a parabolic shape to the effect of average concentrate handling intensity. Therefore, both linear and quadratic terms for average concentrate intensity were included in models that contained the important confounders noted earlier and cumulative exposure and are shown as models H/5, C/5 and V/5 in Tables 8.10(b),(c) and (d) respectively.

Hot QST

At it the peak of the parabolic concentrate handling effect, hot thresholds were predicted to be, on average, 1.12× higher than for non concentrate handlers. However, as noted earlier, using both grouped variable and cubic spline smoother, the effect of concentrate handling intensity was not statistically significant, the same was true therefore when using a quadratic term. Neither did inclusion of the terms for concentrate handling intensity effect the estimates of the important confounders, and, in particular, did not explain the higher thresholds among English SD farmers relative to Scottish SD farmers.

Cold QST

At it the peak of the parabolic concentrate handling effect, cold thresholds were predicted to be, on average, 1.31× higher than for non concentrate handlers. With the inclusion of linear and quadratic terms for concentrate handling intensity (Model C/5), the magnitude of the sex effect was reduced slightly in comparison with Model C/3 which included on cumulative days dipped. This was a consequence of the concentrate handling effect being principally a male effect, as described earlier. Adjustment for concentrate handling intensity could also explain the difference between SD farmers and ceramics workers, now reduced to factor of 1.21 (CI: 0.98—1.49). There remained however higher thresholds (×1.49) among SD farmers relative to NSD farmers. The predicted thresholds from this regression model are shown in Figure 8.7(b) for particular parameter combinations. The separate lines show the predicted thresholds on the original scale for male sheep dippers ranging from age 20 to 65, for three concentrate handling intensities, together with the predicted threshold for ceramics workers. The three concentrate handling intensities were 0 (non-handlers), 4.3 (corresponding to the maximum effect from model C/5) and 8 (corresponding to the maximum intensity) events per day dipped. The age effect used was the approximate linear effect rather than the cubic spline smoother.

Vibration QST

At the peak of the parabolic concentrate handling effect, vibration thresholds were predicted to be, on average, 1.55× higher than for non concentrate handlers As for cold threshold, inclusion of linear and quadratic terms for concentrate handling intensity (Model V/5) reduced to sex effect, from ×1.21 in Model V/3 to ×1.03 in Model V/5. Effects representing the country and OG interaction, which was principally due to a difference between ceramics workers in England and Scotland, remained with very little change. The predicted thresholds from this regression model are shown in Figure 8.7(c) for particular parameter combinations. The separate lines show the predicted thresholds on the original scale for male Scottish sheep dippers ranging from age 20 to 65, for three concentrate handling intensities, together with the predicted threshold for English ceramics workers. The three concentrate handling intensities were 0 (non-handlers), 4.4 (corresponding to the maximum effect from model V/5) and 8 (corresponding to the maximum intensity) events per day dipped. The age effect used was the approximate linear effect rather than the cubic spline smoother. This shows that it is only near the peak of the parabolic concentrate handling intensity effect (around 4 handling events per day) that there is a separation between concentrate handling sheep dippers and English ceramics workers.

8.5 OTHER FACTORS AFFECTING DETECTION OF EXPOSURE-RESPONSE RELATIONSHIPS

8.5.1 Protective clothing

In phase 1 of the study, sheep dippers were observed while working normally by occupational hygienists who assessed the amount and quality of personal protective equipment (PPE) used. It was not anticipated that use, and quality, of PPE could be quantified adequately for individuals based solely on a retrospective questionnaire, since it was not possible to quantify and summarise the protection afforded by PPE worn concurrently with episodes of exposure. However, questions regarding the use of waterproof trousers and waterproof footwear were included in the exposure questionnaire within sheep dipping jobs (Appendix 1; section 2.2d). In addition, those who indicated that they had acted as principal concentrate handler within a sheep dipping job were asked about the use of gloves whilst pouring out the concentrate (Appendix 1; section 2.3b). The categorical responses to these questions, although corresponding on textual descriptions, were based on quantitative guidelines, in the protocol, on the proportion of time relating to each response category. This allowed quantitative estimates to made of the proportion of time spent wearing PPE whilst dipping within each dipping job. A weighted average of these estimates across dipping job was then calculated, weighted by the number of dipping days within each job.

Figure 8.8 shows scatter plots of the average percent use of PPE (self-reported) against average exposure intensity among all sheep dipping farmers. Smoothed average trend lines, using LOWESS, have been superimposed to aid interpretation. The banding in these figures correspond to the values substituted for the four possible categorical responses: 5% ('hardly ever'), 25% ('less than half the time'), 75% ('more than half the time')and 95% ('nearly always'). Figures 8.8(a) and (b) show, respectively, average use of water proof trousers and waterproof footwear against average splash score intensity. Almost all individuals claimed to wear waterproof footwear at all times when dipping. However, use of waterproof trousers was reported to be less frequent, though rising, on average, to almost 100% with increasing splashing intensity.

Figure 8.8(c) shows average use of gloves whilst handling concentrate against concentrate handling intensity, among all those who claimed to have been principal concentrate handlers. On average, use of gloves was estimated to occur with a frequency of less than 50%. However, there was some evidence that those with the highest exposure to concentrate made greater use of gloves while handling and therefore may have experienced greater protection from exposure to concentrate.

8.5.2 Other Sources of Exposure

The neuropathy symptoms questionnaire included questions about current exposure to vibration, both occupationally, as in the number of hours per day using different types of vibrating equipment, and at leisure, as in the numbers of hours per week spent in hobbies with potential exposure to vibration (Appendix 3).

Table 8.11 summarises the extent of daily exposure to vibrating equipment among the three occupational groups split by country. This shows that most sheep dipping farmers (77%) spent several hours every day driving tractors, although this was less prevalent among non-sheep dipping farmers (36%) who mostly farmed pig and chickens. In all the other variables, there was little difference among groups in average usage. Earlier analyses had revealed higher symptoms reporting and higher hot thresholds among English as opposed to Scottish sheep dippers. There was no evidence that these differences were due to any variable measured in Table 8.11. Only for sawing machinery was exposure more prevalent among English sheep dippers than their Scottish counterparts, but overall prevalence of exposure was only 9%. It had also been found that English ceramics workers had higher vibration thresholds than Scottish ceramics workers. From Table 8.11 it can be seen that 32% of English ceramics workers spent over 4 hours per day on fork lift trucks, over twice the prevalence among Scottish workers. Also, relatively more of the English workers participated in motor cycling and mountain biking outside of work (17% compared to 3%).

The exposure history questionnaire included basic questions regarding general use of pesticides and insecticides, either occupationally or domestically, during the working life of each subject (Appendix 1, Section 3). In addition, sheep dippers were asked about use of sheep dips other than in dip baths (e.g. direct application). All subjects were asked if their current jobs included working with lead, solvents or insecticides.

Table 8.12 summarises the prevalence of those who indicated that they had undertook the various activities and therefore were potentially exposed to OPs, in addition, or in place of, OP sheep dips. Current work with solvents was high in all three groups, and unsurprisingly, insecticide use was much higher among the farmer groups. A majority of the sheep dipping farmers had used sheep dips other than for dipping (71%), and had treated cattle for warble fly (63%). All subjects had used insecticides domestically to some degree.

None of these variables could be used as additional quantitative indices of exposure to OPs. However, each variable was added individually to the models S/5, H/5, C/5 and V/5 described above to determine whether there was evidence that the significant non-cumulative exposure effects estimated for OP sheep dips could be explained by simple indicators of both exposures to other sources of OPs, and other exposures which result in similar neurological responses.

Symptoms

The only effects that were statistically significant when added to Model S/5 (which included confounders plus cumulative exposure plus concentrate handling) were use of sheep dips other than for dipping among sheep dippers and the treatment of stored grain. Of these only the former was partially confounded with concentrate handling, the estimated OR of which reduced from 3.4 to 2.5. This reflected the fact , indicating that relatively more concentrate handlers had used dips other than for dipping compared to non-concentrate handlers. However, even this reduced effect remained statistically significant. No other exposure variables confounded the effect of concentrate handling or, could explain the sex and country differences found earlier.

QST thresholds

For hot threshold, only the hours per week in hobbies using vibrating equipment (sum of variables corresponding to the last three rows of Table 8.11) showed a significant linear relationship when included after model H/5. However, neither this variable nor any other, when included, was confounded with the parabolic effect of concentrate handling intensity. For cold threshold, only the hours per day using vibrating machinery (sum of variables corresponding to the first four rows of Table 8.11) showed a significant linear relationship when included after model C/5. However, neither this variable nor any other, when included, was confounded with the parabolic effect of concentrate handling intensity. For vibration threshold, none of the alternative exposure variables were significant when included after Model V/5. No variable was confounded with the parabolic effect of concentrate handling intensity.

9. DISCUSSION

The discussion will overview the main findings of the study in the light of the initial hypothesis and the reliability of the study. The relevance of the findings will be discussed in the light of current knowledge of the possible long-term effects of exposure to OPs, and will consider the possible mechanisms which may have led to the results found. The potential implications of the study findings will then be considered.

9.1 REVISITING THE HYPOTHESIS

The hypothesis under investigation in this study was that repeated exposures to OPs may cause cumulative and irreversible damage to nervous tissue which would eventually become sufficient to be clinically detectable. If this were correct, it was therefore anticipated that in a cross-sectional study, the likelihood of neurological abnormalities would be related to cumulative exposure ('dose') of OPs, after taking account of confounding factors.

Studies investigating whether long term low dose exposure to OPs causes chronic ill health have suggested impaired attention and reaction time (Fiedler *et al*, 1997); increased psychiatric morbidity (Stephens *et al*, 1995); minor sensory changes (Beach *et al*, 1996); and EMG abnormalities (Drenth *et al*, 1972 and Stalberg *et al*, 1978). A recent report by the joint working party of the Royal College of Physicians and the Royal College of Psychiatrists found that the evidence that long term low dose exposure to OPs causes chronic ill health is still the subject of much research.

9.2 SUMMARY OF THE MAIN RESULTS

9.2.1 Recruitment

The recruitment of sheep farm workers was based on letters of invitation sent out to 995 sheep farm owners across regions of Scotland (Borders, Lothians and Ayrshire) and England (Hereford and Worcester) who were listed in the MAFF farm census database. Of those sent letters, 61% (611) agreed to participate in the study. Among the most common reasons stated for not participating was that the farmer was not interested in the study or was too busy. Of those agreeing who were suitable and practicable to visit, 88% (293) were actually visited by the survey team. Approximately half of those not surveyed were due to the farm workers being unwilling to cooperate despite the farm owners agreement. In addition, two contract sheep dippers out of five approached agreed to included in the study.

Pig farms were also recruited by letter and the numbers of potentially low-exposed farm workers was augmented with chicken farm workers already known to the IOM. Of the total of 94 farm owners sent letters, 62% agreed to participate. All those agreeing to participate were visited by the survey team.

Two ceramics plants were visited; one in Scotland (SE) the other in England (Midlands). Over 80% of the smaller Scottish factory staff were surveyed, and the target number of ceramics workers included was met by surveying a further 60% of employees at the English factory.

9.2.2 Study group

In total 690 sheep farm workers, 80 pig and chicken farm workers and 121 ceramics workers were surveyed in the field. Since many of those who worked at the pig and chicken farms had also dipped sheep, farm workers were divided into two occupational groups: sheep-dipping (SD) farmers with some experience of dipping sheep, and non-sheep-dipping (NSD) farm workers, with no experience of dipping sheep. Subjects were omitted from the final study group if they had reported having a condition or taking medication that may confound a diagnosis of neuropathy. Ceramics workers with past sheep-dipping experience were also excluded. The final study group consisted of 612 SD farmers, 53 NSD farmers and 107 ceramics workers.

Marginally more of the SD farmers (56%), and almost all of the NSD farmers (87%) were from Scotland. Approximately two-thirds of the ceramics workers in the study group were from the larger English factory.

On average, SD farmers were 6 years older than the other two groups (mean age 45 yrs). They also included a higher proportion of females, although even among SD farmers the overall number was low (14%). Ceramics workers included a higher proportion of current drinkers, and higher mean consumption among those that did, compared to the farmers.

The distribution of cumulative exposure among SD farmers was highly skewed towards the lower end of the exposure scale, with a median of 54 dipping days (inter-quartile range 74 days). A small number of individuals had experienced greater than 1000 days of dipping. The model-based exposure index, OPEXP, was highly correlated with the total number of days dipped (r=0.92). Since the most significant route of exposure was via the handling of concentrate, the index OPEXP was also very highly correlated with the estimated total number of concentrate handling events (r=0.99). Age was not correlated with any cumulative exposure variable.

9.2.3 Reproducibility of field and clinic medical measurements

After the field survey had been carried out, a subset of farmers surveyed (n=79) had been invited to attend for a clinical assessment where the medical measurements that were carried out in the field were repeated and additional measurements taken. This allowed the reproducibility of the field medical measurements to be quantified in relation to clinically determined values.

For the modified version of the Mayo Clinic neuropathy scoring system that had originally been proposed as a method of scoring likelihood of neuropathy status in the field, reproducibility between field and clinic was found not to be sufficiently better than chance to warrant use as the principal response variable in exposure-response analyses. When the specific component scores that were combined in the scoring system were analysed separately, it revealed that it was the scoring of the sensory test thresholds relative to a clinical reference values that were least reproducible. This lent weight to earlier suspicions that the high proportion of ceramics workers in the control group scoring 'abnormal' for cold and vibration thresholds, in particular, could not be plausible.

Since the use of the clinical reference values to detect abnormality in the sensory test thresholds measured in the field could not be justified, it was decided that the symptoms score and the three sensory test thresholds as they were measured in the field would be analysed in relation to exposure in the field study. The symptom score had proved reasonably reproducible between field and clinic, particularly taking account of the time lag (up to 18 months) between the two assessments. The actual measured thresholds showed biases between the field and the clinic, in particular the hot (factor of two lower in the field) and vibration (factor of two higher in the field), that could be explained by the generally low ambient field temperatures during the field survey relative to the controlled temperature in the clinic. However, all three thresholds showed significant linear correlated between field and clinic and no evidence of any additional inter-individual variation in the field. There was more information in using the measured thresholds as markers of increment nerve damage as opposed to using the same variables dichotomised in to normal and abnormal categories relative to 95th percentiles of a clinical reference sample.

9.2.4 Group comparisons

Crude reported prevalence was highest among SD farmers for all three symptom groups (autonomic, sensory, muscle weakness). Within all three occupational groups prevalence was highest for autonomic symptoms followed by sensory symptoms. The crude prevalence of the overall symptom score was highest among SD farmers (19%), compared to NSD farmers (11%) and ceramics workers (5%).

The four neurological response variables (symptoms score plus the three QST thresholds) were compared across occupational groups prior to inclusion of exposure estimates for SD farmers. Unadjusted for any covariates, proportionally more SD farmers reported symptoms than either NSD farmers (OR=1.8, not sig.) and, in particular, ceramics workers (OR=4.8). Thermal and vibration thresholds among SD farmers were also, on average, higher than among NSD farmers and higher still (except for cold threshold) than among ceramics workers.

Age was found to be strongly related to all four neurological responses, with increasing symptoms prevalence and QST thresholds with increasing age. There was evidence among the QST thresholds that the gradient with age steepened at older ages.

For symptoms, there was also a strong regional difference, with a higher prevalence in England (OR=1.8) compared to Scotland, among subjects of the same age and occupational group. Adjusted for age and country, prevalence of symptoms among SD farmers was similar to NSD farmers but remained high in comparison with ceramics workers (OR=4.3).

In addition to an age effect, there was also evidence of a sex effect across the three QST thresholds, with males having higher thresholds, on average, than females. This effect was greatest for hot threshold (OR=2.2).

Current alcohol consumption, measured as number of units of alcohol per week, was found not to be related to any of the four neurological response variables, and was not included as a potential confounding variable in regression analyses.

Adjusting for age and sex, there were found to be inconsistent differences among occupational groups between countries for the hot and vibration thresholds. For hot threshold, ceramics workers in Scotland had higher average thresholds than ceramics workers in England (×1.5, non-sig), while English SD farmers had higher average thresholds than their Scottish counterparts (×1.5). The net effect was that there was very little difference in average hot thresholds between English SD farmers and Scottish ceramics workers. For vibration threshold, there was no difference in average threshold between English and Scottish SD farmers. However, since ceramics workers in England had higher average thresholds than ceramics workers in Scotland (×1.6), there was no clear difference in average thresholds between Scottish SD farmers and English ceramics workers.

Comparisons were between SD farmers and NSD farmers were weakened statistically by the low numbers of NSD farmers generally, and particularly in England. However, after adjustment for age and sex, cold thresholds remained higher, on average, among SD farmers compared to both NSD farmers (×1.6) and ceramics workers (×1.3).

9.2.5 Effect of cumulative exposure

Of the four neurological responses, only for symptoms was there evidence of a positive relationship with cumulative exposure. The estimated effects for the different exposure indices were very similar. The model-based exposure index, OPEXP, was no better an explanatory variable than the exposure duration variable, DAYS. The estimated effect predicted a 13% increase in the odds of symptoms per 74 days dipped and was consistent across the full range of exposures and consistent between the two countries.

However, the statistical significance of the gradient depended on the inclusion of the small number of very highly exposed individuals. Restricting the cumulative exposure indices to the period 1984-91, when OP sheep dips were at peak usage, did not improve the fit to the symptoms response.

Adjusting for cumulative exposure in addition to age and country, the odds of symptoms remained almost four times higher among SD farmers than among ceramics workers.

Neither the cold or vibration thresholds had estimated gradients for cumulative exposure that were significantly different from zero, while for hot threshold, a slight negative gradient with exposure was estimated. Adjusting for cumulative exposure in addition to age and sex, did not explain the inconsistent differences among occupational groups between countries in relation to hot and vibration thresholds, nor the higher average cold threshold among SD farmers compared to NSD farmers and ceramics workers.

9.2.6 Other exposure effects

The model-based exposure index, OPEXP, did not explain more of the variation of the neurological responses than the duration of exposure variable, DAYS. To investigate the relationship between exposure, other than simple cumulative exposure, and response, average exposure intensity was analysed in conjunction with exposure duration. The effect of grouped intensity variables corresponding to the concentrate handling and splash score components of the model, together with the intensity of their combination were compared across the four neurological responses after adjustment for the important confounders plus exposure duration (DAYS).

There were statistically significant differences within grouped concentrate handling intensity for symptoms and vibration threshold, more so than for average splash intensity or for the combined OP exposure. None of the grouped intensity effects showed evidence of a dependence on duration of exposure, suggesting that the effects were not necessarily of a cumulative nature.

Further analysis, using a cubic smoothing spline in place of the grouped intensity, showed that the effect of concentrate handling on symptoms prevalence could be succinctly summarised as a difference between those who had, and those who had not, ever acted as principal concentrate handler (OR=3.4; 95% CI 1.6—7.2). This effect was independent of and of greater significance than the duration of exposure. With adjustment for concentrate handling, together with the important confounders, sex was also shown to affect symptoms prevalence, with females being over three times more likely to report symptoms than males of the same exposure, age and country. Prior to adjustment for concentrate handling, this sex effect had been masked, since male SD farmers were over three times more likely to have been principal concentrate handlers compared to females.

Based on the fitted regression model for symptoms, the prevalence of symptoms was predicted to be highest among concentrate handlers in the English regions, corresponding to, for example, 21% (95% CI: 15-27%) at age 40 years, rising with age to 35% (95% CI: 27-43%) at age 60 years.

Having adjusted for concentrate handling together with age, sex and occupational group, there remained a much higher prevalence of symptoms among English subjects compared to Scottish subjects (OR=2.0). An analysis of field versus clinic reproducibility among farmers attending the clinic showed that symptoms reporting among English subjects was more reproducible than among Scottish subjects, and indicated that the higher symptoms rates among English farmers were the more reliable result. Subsequent comparisons of the OP sheep dip products recalled by farmers did not reveal any marked difference in product use.

Further analyses of the effect of concentrate handling intensity on the three QST thresholds indicated, for all three, a peak effect at the mid point of the intensity range, relative to non-handlers. For all three thresholds, this effect diminished towards the highest intensities, although only for the hot threshold was the effect at the highest intensity comparable with non-handlers.

At the intensity corresponding to the peak effect, cold thresholds were, on average, ×1.3 higher among concentrate handlers compared to non-handlers. Adjusting for this peaked effect of average concentrate handling intensity, in addition to the important confounders such as age and sex, could explain the difference in average cold threshold between SD farmers and ceramics workers.

At the intensity corresponding to the peak effect, vibration thresholds were, on average, ×1.5 higher among concentrate handlers compared to non-handlers. Adjusting for this peaked effect of average concentrate handling intensity, in addition to the important confounders such as age and sex, and given the inconsistent differences among occupational groups in different countries, it was only near the peak of the concentrate intensity effect that there was evidence of higher average thresholds among sheep dippers compared to the English ceramics workers.

9.2.7 Other factors affecting exposure

The use of gloves when handling concentrate was estimated to be have occurred on less than 50% of occasions. There was some evidence that usage increased with exposure to concentrate and this could help explain the low concentrate handling effect at high intensity exposure. Waterproof leggings and footwear was estimated to have been used more often than not, again with evidence of increased usage at higher exposure intensity.

A large proportion (77%) of sheep-dipping farmers, more so than among NSD farmers, spent several hours per day driving tractors, a source of vibration exposure. Also, similarly large proportions could have been exposed to OPs by using sheep dip products other than for dipping (71%) and by treating cattle for warble fly (63%). There was evidence that a greater proportion of English ceramics workers drove fork-lift trucks on a daily basis, but exposure to vibrating machinery occupationally at the two ceramics factories was comparable. Very few of the additional exposures variables showed evidence of positive relationship with the neurological responses. No variable could explain the effect of average concentrate handling intensity.

9.3 RELIABILITY OF THE STUDY METHODOLOGY AND FINDINGS

9.3.1 Representativeness of study participants

Representativeness and variety of sheep farms

In attempting to identify exposure-response relationships, what is needed is a wide range of exposures, and that the people studied are representative of the wider group of sheep dippers, not in terms of prevalences in an absolute sense, but representative in how they have responded to OP exposure (again conditional on age, sex and other non-exposure factors).

The census data provided by MAFF and the Scottish Office allowed selection from a large number of farms in both Scotland and England, and although some farms initially selected could not be contacted due to missing data on current address, these formed only a small percentage of all the farms contacted.

The selection of farms on the basis of parishes aimed to limit selection bias whilst ensuring a cost-effective survey strategy. There was also opportunity to include larger farms within the parish, if these were not considered to be adequately represented among the farms already visited in that parish. We consider that the farms selected were broadly representative of the regions from which they were selected, and there is no evidence to suggest that they were not representative of other sheep farms nationwide.

Representativeness of sheep farmers and farm workers

Sheep dipping farmers were on average six years older than the other farming groups and ceramics workers. In order to address the aims of the study, the selection of farms needed to ensure that the range of exposures which would be included, covered the likely range found within farming groups. It was not necessary to ensure that the distribution of exposures mirrored that of sheep farmers in general. However, it was also common to find that younger members of the family were not involved in farming on a full time basis, which possibly reflects the pressures which farmers have faced in recent years, and the perceived need of younger individuals to seek alternative employment.

Due to the inclusion of families for sheep dipping farmers, there were also more women among this group than the other farming groups. In general other family members might be expected to have experienced less days dipping than other farm workers, and might have increased the number of individuals in the group with less than 100 days dipping. However as most farms relied on family members to provide assistance during busy periods in the year, it is not considered that this distribution of dipping days is unrepresentative of farming groups.

On the basis of the background information on factors such as farm size, age groups and level of education, there is nothing to suggest that the farmers from Scotland and England differ significantly other than by region of domicile.

Other participants

A consistent recruitment method was used for sheep farmers, but recruitment of ceramics workers and pig and chicken farmers differed in some cases. Participation rates were higher for pig and chicken farmers, as in several cases, surveys were coordinated via a farm manager, as part of a normal working day. There was less of a problem with competing demands in these circumstances, and less likelihood of appointments being cancelled than had been the case with sheep farmers. It is considered that a more direct approach was necessary, in order to ensure low-exposure groups were recruited from the same areas as the sheep dippers, and as there were less obvious advantages for these groups in taking part in such a survey. The difference in recruitment methods used for pig and chicken farmers is not thought likely to influence the results from these two groups. They were also groups with negligible exposure to OPs, and in the case of pig and chicken farmers represented similar socioeconomic groups to the sheep farmers.

9.3.2 Reliability of sensory tests and symptoms questionnaire

Assessing the reliability of results is always difficult where there is limited published data from similar studies to compare against the findings of the study. However, a strength of this study is that we designed in an assessment of the reliability of the tests applied in the field. This was a clearly stated aim of the project and the results provide insight into ways of improving reliability in future studies of this type.

The Mayo neuropathy symptoms questionnaire used in the study was designed as a physician administered questionnaire. All components used have been well validated (see supporting text), and were performed according to a strict protocol.

The questionnaire and sensory tests were administered by a technician in the field. The use of a technician means that there is less opportunity for informed interpretation of the response of participants, although this could also be seen as an advantage, reducing the degree of subjectivity applied by the interviewer. The technicians who took part in this study all received training in administration of the symptoms questionnaire and sensory tests from neurological specialists. Quality control checks were also built into the survey procedure. The survey was also planned to ensure that as far as possible the same technician performed the same aspect of the assessment in each geographical region, in order to limit the degree of inter-observer bias.

Due to the use of a technician in the field and the time constraints of assessment in the farmers homes, the clinical examination and nerve conduction studies were not included in the field study. The Mayo methodology however supports the use of sensory testing and questionnaire as a diagnostic screening test for neuropathy, and it was always a stated aim to follow up a subgroup of field participants with a complete battery of test in the third phase of the survey. It is therefore considered that the choice of tests used was fit for the purpose intended.

Due to a limited period of time between the completion of Phase 1 and the commencement of Phase 2 it was only possible to conduct a brief pilot of the neurological questionnaire and sensory tests. This pilot took place in the month prior to the commencement of the field studies and did not reveal any difficulties with test administration. As previously discussed the use of the sensory tests in the field setting proved to be problematic due to the cold environmental conditions which were encountered. It was necessary to perform the field studies over the winter months in order to avoid peak OP usage periods and potential confounding from acute OP effects. The subjects had often been working outdoors prior to the test and had cold peripheries. The room temperature in many of the farms was below that recommended in a clinic setting. It is also possible that subjects had more distractions in the home environment than in the clinic environment This could not have been anticipated from the results of the pilot trial, and there was no previous data available on the use of the sensory tests in a field setting. There is also no reliable information on the performance of the equipment at varying environmental temperatures.

During much of the field survey the equipment was used out with the recommended operating range for skin temperatures in a clinic setting. Whilst all steps were taken to address this problem, the range of thresholds recorded during the field studies differed from those which might have been anticipated from the reference data. This was also true for ceramics workers and pig and chicken farmers working in cold conditions. It was only possible to seek to control the temperature of a small area of the limb, and not possible to control for limb temperature as a whole, or any underlying changes in core temperature. Data are not available to reliably predict what the size of measurement error might be, particularly in view of the range of temperatures measured in the field. It is possible that the three tests might be influenced to different degrees by cold temperatures, although the results suggest a consistent trend in the way in which the sensory test results have been influenced.

As this problem casts doubt on the reliability of these measures, it was considered appropriate in analysing the results to use the actual measured thresholds as response variables, as opposed to using the indicators of abnormality derived from the reference population. This approach was further supported by finding a similar inter-individual variance for the field sensory tests results compared with the variance for results obtained from the clinic, for those individuals taking part in the third phase of the study.

9.3.3 Reliability of exposure assessments

The exposure history questionnaire was piloted during phase 1 of this study, and this proved helpful in structuring the questionnaire to ensure better recall. It was found that individuals had better recall in relation to a specific job, rather than over a specific period of time, which had no special significance for them. In general, only the concentrate handler had any specific knowledge about the type of OP used, and this related to recent product, even when prompts were provided on specific product names.

Therefore questions on product usage where limited to products currently used within the final questionnaire.

Phase 1 of the study involved careful observations of task and working practice in relation to uptake of OPs as assessed by urinary OP metabolites. The exposure history questionnaire was developed on the basis of relatively stable and easily identifiable features of the sheep dipping roles, and these were used to provide surrogates of exposure. These factors included: flock size (as an indicator of number of days dipped); principal task/job (also considered an indicator of likelihood of concentrate handling); concentrate handling; use of gloves; and other personal protection.

It is difficult to assess the reliability of the exposure data obtained or the degree of recall bias. However, from the pilot study, the surrogates chosen were found to be memorable aspects of job. The surrogates were also linked to those tasks which had been identified from the Phase 1 study as being associated with uptake of OPs. The model derived in Phase 1 of the study has been used to derive exposures as discussed in Chapter 4. It is also difficult to assess the impact of changes in awareness of potential health issues associated with OPs, and whether this varied across the sample of sheep dippers. It was noted that there was more media coverage of the issue in England during the period of the survey and this could in part explain the differences in reported level of symptoms between the two areas.

The same quality control checks were again built into the survey procedure for the exposure-history as described above for the neuropathy data.

Analysis of the exposure data showed that number of dipping days were skewed towards the lower end of the range observed, with most individuals having been involved with less than 100 days during their working life. It was only possible to recruit a small number of contractors during the study, and they represent the higher end of the days dipped range. There is no evidence to suggest that the distribution of dipping days is atypical for sheep farmers in general, although it is possible that consideration of exposure-response could be influenced by the more highly exposed outliers. For this reason a leverage technique was used in the analysis to ensure that the gradient for symptoms is consistent over the main body of the exposed individuals.

9.3.4 Protection against unaware biases

To prevent derivation of neuropathy outcome being in any way affected by knowledge of an individual's exposure the project analyst/programmer and the statisticians were kept blind to the match of identities. The matching of identities was carried out by a different analyst/programmer who had access to both sets of forms so that any apparent discrepancies of identity, arising from different transcriptions of names, were successfully resolved.

At the request of the Steering Committee the exposure data was not processed until the Phase 3 clinical investigations were completed. During this time the Phase 2 neuropathy scores were derived by the relevant member of the IOM team, in order to allow the selection of subjects for Phase 3. This individual was therefore blind to any data relating to exposure. When the Phase 3 clinical examinations had been carried out, and the exposures calculated by the model from Phase 1, it was agreed that the exposure-response relationship could be examined. Only at this point was the Matching List supplied to the project team.

9.4 RESULTS IN RELATION TO CHARACTERISTICS OTHER THAN OP EXPOSURE SURROGATES

9.4.1 Age

The age difference between the three groups has been previously discussed, and for sheep dipping farmers was found to associated with an increased tendency to report symptoms. There was also an increase in sensory threshold with age, which would be expected physiologically. However, the group differences were still present after accounting for age.

All groups of farmers had experienced more higher education than ceramics workers, but this was considered to be less important than ensuring that a suitable control group of non-exposed individuals was included from a similar geographical area. Perhaps more importantly, there was little difference in levels of education between the farming groups.

9.4.2 Lifestyle

In relation to lifestyle factors, ceramics workers consumed twice as much alcohol on average than farmers, although the average levels of alcohol intake for farmers was low and therefore a doubling of intake in ceramics workers was not considered to be sufficient to cause a significant increase in the prevalence of neuropathy among the ceramics workers.

English ceramics workers also included a higher proportion of Asian subjects than either the Scottish ceramics workers or the farmers. It is plausible that the difference in ethnic group could account for an apparent increased sensitivity to cold in the English ceramics groups, and in part explain the higher vibration and lower cold thresholds than expected among this group. There was no evidence to suggest that different dietary factors were responsible for these findings.

9.4.3 Gender

There was a gender difference for both reported symptoms and sensory test results, with higher values recorded in females. Biologically it is plausible that females may have a lower threshold for detecting applied sensory stimuli, and in the sheep farming group females were less likely to have been exposed to cold environments prior to sensory testing. In general male sheep dippers reported less symptoms than the female sheep dippers, but this might be a cultural bias in this occupational group.

9.4.4 Other medical conditions

Only a small number of individuals taking part in the field studies were considered to have co-existing conditions or be taking medication which might lead to an increase in reported symptoms, or influence the results of the sensory tests. These conditions included insulin dependent diabetes, hereditary neuropathy, thyrotoxicosis and certain cardiovascular medication. All subjects were excluded from the Phase 2 analysis, and a check was made to ensure that these subjects were not recruited to Phase 3.

9.4.5 Regional differences: Scotland and England

As previously discussed even after adjusting for exposure there was twice the reported prevalence of symptoms in the English farmers compared with Scottish farmers. However, there were no consistent regional differences among the sensory threshold results, except for English ceramics workers. It is possible that greater awareness of health issues, due to increased media reporting, might have led to selection or reporting bias, although these results might reflect a true difference in the prevalence of symptoms.

Based on information obtained from sheep farmers during Phase 2 on recall of recently used OP products (see Appendix 10), there is no evidence to suggest a significant difference in the general pattern of OP usage between England and Scotland.

9.4.6 Other occupational exposures

Other occupational exposures might also account for the sensory test findings for the three groups. Ceramics workers reported more exposure to workplace vibrating equipment than the other two groups, and this may vary between task and between companies. There may also be common factors among farmers as a group, such as the use of pesticides for other purposes (e.g. treatment of grass-land or warble fly), which might explain the lack of significant differences between sheep farmers and pig and chicken farmers.

9.5 MAIN RESULTS RELEVANT TO WHETHER THERE IS AN OP EFFECT

9.5.1 Exposure-response relationships: symptoms

After adjustment for confounding factors, symptoms score was associated with cumulative exposure, as estimated via the uptake model, although the gradient was not large in comparison with the effect of age, for example, and the statistical significance depended on inclusion of a very small number of individuals with high estimated cumulative exposure. Further examination showed that, among sheep dippers with the same number of days dipped, average intensity of exposure was additionally related to symptoms reporting. Average intensity of exposure was largely determined by whether or not the sheep dipper had been a principal concentrate handler. Classification of sheep dippers into those who had, and who had not, been principal concentrate handlers showed a strong difference between the two groups in reported symptoms: after adjustment for other factors, including gender and days dipped, the concentrate handlers showed a 3.4-fold increase in odds of symptoms relative to non-handlers. The difference was highly significant statistically (95% CI 1.6 - 7.2) and was principally independent of, and of greater statistical significance than, the remaining weak effect of cumulative days dipped.

As discussed earlier, the estimates of exposure to sheep dip chemicals are recognised to have limited accuracy because they are based on individual recollection, and the questions asked at survey could cover only some of the aspects relevant to past exposure. On the other hand results from Phase 1 (Sewell *et al*, 1999), together with earlier IOM studies, showed that the characteristics studied in Phase 2 had an important influence on uptake. This was true in particular of concentrate handling. Furthermore, whether or not a participant sheep dipper had ever been a principal concentrate handler is an aspect of past history which might reasonably have been recalled with quite high accuracy: it refers to a defined event which might well be remembered well. Also, random errors in exposure estimation (or the associated classification of sheep dippers into ever principal concentrate handler or not) would be expected to reduce, not increase, the chances of finding relationships with health indices.

Reports of symptoms of peripheral neuropathy are of course subjective, and may be influenced by many factors, including perception of health risks. Risk perception could have influenced the prevalence of reported symptoms in this study; and indeed we conjecture (see earlier) that it may be a contributory factor in the observed difference in reported prevalences between sheep dippers in England and Scotland. The study participants did not, however, know how exposure was to be calculated, and in particular were not aware of the key role of concentrate handling in estimating past exposure. Indeed, publication of the results from Phase 1 was kept back while the field survey was in progress, so that the basis of exposure estimation in the study did not become common currency. It is possible that some participants might have allowed their reporting of symptoms to be influenced by knowledge of their past exposure via, for example, number of days dipped. It is less plausible that reporting was influenced by awareness both of concentrate handling and its importance.

All in all, the evidence of relationships between symptom score and various indices of past exposure to OPs, notably both days dipped and exposure to concentrate, is unlikely to be an artefact of methodology in the study.

9.5.2 Group differences between exposed and non-exposed workers: symptoms

These findings are supported by results concerning symptoms when sheep dippers are contrasted with non-exposed workers, taking account of other factors. In particular, when adjustment is made for gender, days dipped and concentrate handling, in addition to age and country, then the non-exposed groups are contrasted with low-exposed sheep dippers who had never been principal concentrate handlers. These sheep dippers had lower (adjusted) symptom scores than non-exposed farmers, and only slightly higher prevalences than ceramics workers: the difference might easily have arisen, even if chance were the only explanation.

As discussed earlier, the reliability of these contrasts may have been affected by the study selection effects via non-participation of some selected subjects. However, the reasons for non-participation seem plausibly not to be strongly health-related; and though some selection bias cannot be excluded, there is no positive indication that results have been in any serious way distorted by it.

These between-group comparisons are very interesting supplementary findings, showing similar symptom prevalences between low-exposed sheep dippers and non-exposed comparison groups, having adjusted for other factors.

9.5.3 QST measurements and OP exposure

In a sufficiently powerful and reliable study, we would expect to find similar relationships among the QST thresholds as were found for symptoms, on the grounds that, biologically, sensory threshold effects should be detectable before the subject is aware of sensory symptoms.

Although unadjusted, thresholds were higher among sheep dippers than among the non-exposed groups, when adjusted for age and sex, only for the cold threshold was there evidence that thresholds remained higher among sheep dippers. The inconsistent differences in hot and vibration thresholds among the occupational groups in the two regions surveyed, although not easily explained in terms of possible exposure effects, do not point to an important effect among sheep dippers relative to the non-exposed groups.

Unlike symptoms, there was no evidence of a cumulative exposure effect on any of the three QST thresholds individually. Similar to symptoms however, there were strong exposure effects in relation to average exposure to concentrate, although these effects were not as marked among the highest average exposed as for symptoms. The estimated peak effect, higher at moderate exposure intensities than at very low or very high intensities, was of strikingly similar shape across all three QST thresholds. This size of the effect at the peak was most marked for cold and vibration thresholds, and this may be a consequence of the generally lower hot thresholds measured in the field relative to the clinic. A possible reason for a low effect at high concentrate exposure intensities was suggested by the evidence of greater use of protective gloves with increased exposure, possibly due to greater awareness of the potential hazards using sheep dip products. However, it is unclear why any possible protective effect should be more apparent for measured sensory thresholds than for symptoms.

All three QST measurements were positively associated with age, as would be expected, and this effect was independent of all other covariates including exposure. This provides some evidence that the QST measurements were informative and the associated results were meaningful. There are no strong reasons to expect a gender effect on QST measurements, and it is possible that this effect was acting as a surrogate for some other unquantified factor.

Taken as a whole, the results of the sensory test thresholds do not give a coherent picture. The results indicate, however, as they do for symptoms, that the principal evidence of a neurological effect is in relation to exposure to concentrate, and is not necessarily the result of a purely cumulative relationship.

9.6 KEY FINDINGS

- Results showed higher rates of symptoms between OP exposed sheep dippers as a group compared with non-exposed workers. The associations between symptom score and various indices of cumulative exposure to OPs, suggest that in at least some of the sheep farmers and farm workers reported symptoms are due to exposure to sheep dip chemicals. Sensory symptoms were more commonly reported than motor symptoms by sheep dippers in the field study.

- The critical exposure factor seems to be contact with concentrate in that markedly higher rates of reported symptoms (adjusted for other factors) were reported among those who had at some time been principal concentrate handlers. These differences generally disappear when non-exposed groups are contrasted with dippers who had not principally handled concentrate.

- There was no evidence that cumulative exposure to OPs was associated with impairment of measured sensory thresholds. The results suggest a relationship between QST measurements and exposure to concentrate but these are difficult to interpret. The possibility of an associated sensory neurophysiological component to the suggested symptom effect should therefore not be discounted.

The implications of these findings are considered in more detail in an over-arching summary which can be found in the Phase 3 report.

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TABLES

TABLE 3.1 Neuropathy scoring system

	Classification	Criteria		
1	No neuropathy	symptom score < 1	AND	QST score = 0
2	Possible neuropathy	symptom score ≥ 1	OR	QST score ≥ 1
3	Probable neuropathy	symptom score ≥ 1	AND	QST score ≥ 1
4	Definite neuropathy	symptom score ≥ 2	AND	QST score ≥ 1

TABLE 5.1 Comparison of field and clinic neuropathy classification

	Clinic			
Field	**none**	**poss**	**prob/def**	**all**
none	8	9	5	22
poss	5	17	4	26
prob/def	4	12	15	31
all	17	38	24	79

TABLE 5.2 Comparison of field and clinic symptoms score

	Clinic			
Field	**0-0.5**	**1-1.5**	**≥2**	**all**
0-0.5	35	6	4	45
1-1.5	10	3	4	17
≥2	4	0	13	17
all	49	9	21	79

TABLE 5.3 Comparison of field and clinic heat QST results (0=normal, 1=abnormal)

Field	Clinic 0	Clinic 1	all
0	46	21	67
1	4	8	12
all	50	29	79

TABLE 5.4 Comparison of field and clinic cold QST results (0=normal, 1=abnormal)

Field	**Clinic 0**	**Clinic 1**	**all**
0	20	17	37
1	15	27	42
all	35	44	79

TABLE 5.5 Comparison of field and clinic vibration QST results (0=normal, 1=abnormal)

Field	**Clinic 0**	**Clinic 1**	**all**
0	37	2	39
1	26	14	40
all	63	16	79

TABLE 5.6 Comparison of field and clinic QST thresholds (log scale)

QST	**Field**			**Clinic**			**Ratio (Field/Clinic)**		
	GM	**GSD**	**n**	**GM**	**GSD**	**n**	**GM**	**GSD**	**n**
Hot	0.77	3.88	79	1.73	3.10	78	0.44	2.65	78
Cold	0.68	2.76	76	0.54	2.80	75	1.28	2.86	73
Vibration	3.64	3.35	76	1.81	3.48	77	2.06	2.77	75

geometric mean (GM), geometric standard deviation (GSD)

TABLE 7.1 Reasons for sheep farms being excluded from the survey by the IOM.

Reason for exclusion	Number of farms	% of contacted farms
Farm personnel never dipped or they used contractors	81	15.9
No relevant livestock on the farm	40	7.9
Farmer was single handed or otherwise impracticable	29	5.7
Not a farmer or worked full-time at another job	9	1.8
Miscellaneous	14	2.8
Total	173	34.1

TABLE 7.2 Reasons for not proceeding with suitable sheep farms which were not surveyed.

Reason for not proceding with survey	Number of Farms	% of suitable farms
Workers unwilling	24	7.2
Cancelled appointments	2	0.6
Declined at time of visit	7	2.1
Miscellaneous	9	2.8
Total	42	12.5

TABLE 7.3 Reasons for non-participation fo sheep farms after initial letter.

Reason for non-participation	Number of Farms	% of letters sent
Too busy	74	7.4
Not interested	103	10.4
Retired	19	1.9
Duplicate / farmer already recruited	16	1.6
Did want to contemplate visit to Glasgow	4	0.4
Not specified	92	9.2
Total	308	31.0

TABLE 7.4 Summary of final study group

Variable	Ceramics (n=107)		NSD Farmers (n=53)		SD Farmers (n=612)	
country:						
Sco	36	*34*	46	*87*	344	*56*
Eng	71	*66*	7	*13*	268	*44*
age:		%		%		%
15-24	11	*10.3*	9	*17.0*	35	*5.7*
25-34	30	*28.0*	15	*28.3*	131	*21.4*
35-44	40	*37.4*	7	*13.2*	142	*23.2*
45-54	19	*17.8*	17	*32.1*	149	*24.3*
55-64	7	*6.5*	5	*9.4*	113	*18.5*
65-74	0	*0.0*	0	*0.0*	37	*6.0*
≥75	0	*0.0*	0	*0.0*	5	*0.8*
mean	38.6		39.2		45.1	
SD	10.2		12.7		13.4	
sex:		%		%		%
M	104	*97.2*	50	*94.3*	524	*85.6*
F	3	*2.8*	3	*5.7*	88	*14.4*
alcohol: (units/week)		%		%		%
non-drinker	2	*1.9*	3	*5.7*	41	*6.7*
≤5	16	*15.0*	22	*41.5*	293	*47.9*
5-15	35	*32.7*	16	*30.2*	176	*28.8*
15-30	34	*31.8*	10	*18.9*	78	*12.7*
30-45	14	*13.1*	1	*1.9*	19	*3.1*
>45	6	*5.6*	1	*1.9*	5	*0.8*
(drinkers only) mean	19.1		10.1		8.2	
SD	16.2		12.8		10.2	
smoking: (cigs/day)		%		%		%
never smoked	50	*46.7*	24	*45.3*	375	*61.3*
ex-smoker	22	*20.6*	10	*18.9*	116	*19.0*
≤10	11	*10.3*	4	*7.5*	54	*8.8*
10-20	17	*15.9*	10	*18.9*	48	*7.8*
20-30	6	*5.6*	2	*3.8*	15	*2.5*
>30	1	*0.9*	3	*5.7*	4	*0.7*
education: (highest)		%		%		%
no certificates	46	*43.0*	19	*35.8*	226	*36.9*
certificates	36	*33.7*	16	*30.2*	162	*26.5*
tertiary	25	*23.5*	18	*34.0*	224	*36.6*

TABLE 7.5 Summary of exposure variables among sheep-dipping farmers (n=612)

statistic	DAYS	SPLASH ($\times10^{-3}$)	CONC	OPEXP ($\times10^{-3}$)
minimum	1	0.00	0	0.00
25th %-ile	28	1.08	9	0.35
median	54	2.44	185	1.25
75th %-ile	102	5.00	484	2.70
maximum	1350	75.77	9348	48.81
mean	91	4.48	418	2.40
SD	127	7.26	816	4.28

TABLE 8.1 Prevalence of reported symptoms (non-zero scores)

Symptom group	Age (years)				
	<35	35-44	45-54	≥55	All
a) muscle weakness					
ceramics	0.0	0.0	0.0	0.0	0.0
NSD farmers	4.2	0.0	0.0	0.0	1.9
SD farmers	3.0	7.0	7.4	14.2	7.8
b) sensory					
symptoms	0.0	2.5	0.0	14.3	1.9
ceramics	0.0	14.3	5.9	20.0	5.7
NSD farmers	5.4	11.3	11.4	18.7	11.6
SD farmers					
c) autonomic					
ceramics	17.1	5.0	5.3	14.3	10.3
NSD farmers	25.0	28.6	17.6	0.0	20.8
SD farmers	26.5	24.6	26.8	35.5	28.4
d) overall					
ceramics	4.9	5.0	0.0	14.3	4.7
NSD farmers	12.5	14.3	5.9	20.0	11.3
SD farmers	9.0	16.9	20.1	31.0	19.1
e) age distribution (denominators)					
ceramics	41	40	19	7	107
NSD farmers	24	7	17	5	53
SD farmers	166	142	149	155	612

TABLE 8.2 Unadjusted differences between occupational groups showing multiplicative effects (×effect) and 95% confidence intervals (CI).

SD farmers v.	Symptoms		Hot threshold		Cold threshold		Vibration threshold	
	OR	CI	×effect	CI	×effect	CI	×effect	CI
NSD farmers	1.89	(0.79, 4.52)	1.25	(0.85, 1.83)	1.87	(1.46, 2.39)	1.47	(1.06, 2.03)
Ceramics	4.82	(1.97, 12.26)	1.54	(1.17, 2.04)	1.55	(1.28, 1.86)	1.68	(1.32, 2.14)

TABLE 8.3 Odds ratios (OR) and 95% confidence intervals (CI) for prevalence of reported symptoms between occupational groups.

Terms	Model S/1		Model S/2		Model S/3		Model S/4	
	OR	CI	OR	CI	OR	CI	OR	CI
Age ($\times 10^{-1}$ years)	1.42	(1.22, 1.66)	1.42	(1.22, 1.66)	1.41	(1.21, 1.65)	1.40	(1.19, 1.65)
Country (Eng v. Sco)	1.76	(1.18, 2.64)	1.93	(1.27, 2.92)	1.90	(1.26, 2.88)	2.05	(1.34, 3.12)
SD farmers v.								
NSD farmers	1.29	(0.52, 3.16)	1.07	(0.43, 2.68)	1.12	(0.45, 2.78)	0.68	(0.24, 1.89)
Ceramics	4.39	(1.74, 11.09)	3.85	(1.51, 9.82)	3.99	(1.57, 10.14)	2.52	(0.90, 7.11)
DAYS ($\times IQR^{-1}$)			1.13	(1.01, 1.25)			1.11	(1.00, 1.24)
OPEXP ($\times IQR^{-1}$)					1.11	(1.01, 1.23)		
Ave. OPEXP								
10—22 v. <10							1.73	(0.89, 3.38)
22—35 v. <10							2.23	(1.16, 4.29)
>35 v.<10							1.46	(0.75, 2.87)
Deviance (df)	637.5 (758)		633.0 (757)		633.3 (757)		626.6 (754)	

IQR= inter-quartile range (74 for DAYS, 2350 for OPEXP).

TABLE 8.4 Hot QST threshold: adjusted differences between OGs showing multiplicative effects (×effect) and 95% confidence intervals (CI).

Terms	Model H/1		Model H/2		Model H/3		Model H/4	
	×effect	CI	×effect	CI	×effect	CI	×effect	CI
Age*								
($x10^{-1}$)	1.63	(1.53, 1.74)	1.64	(1.54, 1.75)	1.64	(1.54, 1.75)	1.65	(1.54, 1.76)
Sex								
(Male v Female)	2.11	(1.64, 2.73)	2.15	(1.67, 2.78)	2.18	(1.69, 2.83)	2.21	(1.67, 2.91)
Country×OG interaction:								
(Sco SD farmers v.)								
Sco NSD farmers	0.88	(0.62, 1.25)	0.96	(0.67, 1.37)	0.93	(0.65, 1.33)	1.02	(0.68, 1.52)
Sco ceramics	0.79	(0.53, 1.18)	0.86	(0.57, 1.30)	0.83	(0.55, 1.25)	0.91	(0.59, 1.42)
Eng SD farmers	0.71	(0.59, 0.86)	0.74	(0.61, 0.89)	0.73	(0.60, 0.88)	0.74	(0.61, 0.89)
Eng NSD farmers	0.94	(0.40, 2.22)	1.03	(0.44, 2.43)	1.00	(0.42, 2.36)	1.10	(0.46, 2.63)
Eng ceramics	1.15	(0.86, 1.54)	1.26	(0.93, 1.72)	1.22	(0.90, 1.66)	1.35	(0.95, 1.92)
DAYS								
($\times IQR^{-1}$)			0.94	(0.89, 1.00)			0.95	(0.89, 1.00)
OPEXP								
($\times IQR^{-1}$)					0.96	(0.91, 1.01)		
Ave. OPEXP								
10-22 v. <10							0.87	(0.66, 1.13)
22-35 v. <10							0.97	(0.74, 1.29)
>35 v. <10							0.90	(0.67, 1.20)
Residual SS	978.9		973.3		975.3		971.5	
(df)	(748)		(747)		(747)		(744)	

* cubic spline fitted, approx. linear effect

IQR= inter-quartile range (74 for DAYS, 2350 for OPEXP).

TABLE 8.5 Cold QST threshold: adjusted differences between OGs showing multiplicative effects (×effect) and 95% confidence intervals (CI).

Terms	Model C/1		Model C/2		Model C/3		Model C/4	
	×effect	CI	×effect	CI	×effect	CI	×effect	CI
Age*								
($x10^{-1}$)	1.30	(1.24, 1.35)	1.30	(1.24, 1.36)	1.30	(1.24, 1.36)	1.29	(1.24, 1.35)
Sex								
(Male v Female)	1.38	(1.15, 1.65)	1.39	(1.16, 1.66)	1.39	(1.16, 1.67)	1.31	(1.08, 1.59)
OG (SD farmers v.)								
NSD farmers	1.65	(1.31, 2.07)	1.68	(1.33, 2.11)	1.67	(1.32, 2.09)	1.51	(1.17, 1.96)
Ceramics	1.35	(1.14, 1.60)	1.37	(1.15, 1.64)	1.37	(1.15, 1.63)	1.23	(1.00, 1.52)
DAYS								
($\times IQR^{-1}$)			0.99	(0.95, 1.03)			0.98	(0.95, 1.02)
OPEXP								
($\times IQR^{-1}$)					0.99	(0.96, 1.03)		
Ave. OPEXP								
10-22 v. <10							1.17	(0.97, 1.41)
22-35 v. <10							1.23	(1.01, 1.50)
>35 v. <10							1.07	(0.87, 1.31)
Residual SS	476.0		475.7		475.8		472.5	
(df)	(746)		(745)		(745)		(742)	

* cubic spline fitted, approx. linear effect
IQR= inter-quartile range (74 for DAYS, 2350 for OPEXP).

TABLE 8.6 Vibration QST: adjusted differences among OGs showing multiplicative effects (×effect) and 95% confidence intervals (CI).

Terms	Model V/1		Model V/2		Model V/3		Model V/4	
	×effect	CI	×effect	CI	×effect	CI	×effect	CI
Age* (x10^{-1})	1.63	(1.54, 1.72)	1.63	(1.54, 1.72)	1.63	(1.54, 1.72)	1.62	(1.53, 1.71)
Sex (Male v Female)	1.21	(0.97, 1.51)	1.21	(0.97, 1.50)	1.21	(0.97, 1.50)	1.10	(0.87, 1.39)
Country×OG interaction: (Sco SD farmers v.)								
Sco NSD farmers	1.09	(0.81, 1.46)	1.07	(0.79, 1.46)	1.08	(0.80, 1.46)	0.94	(0.67, 1.31)
Sco ceramics	1.76	(1.26, 2.46)	1.74	(1.24, 2.44)	1.74	(1.24, 2.44)	1.52	(1.05, 2.19)
Eng SD farmers	1.10	(0.94, 1.29)	1.10	(0.93, 1.29)	1.10	(0.93, 1.29)	1.08	(0.92, 1.27)
Eng NSD farmers	1.96	(0.95, 4.00)	1.93	(0.94, 3.99)	1.94	(0.94, 4.00)	1.70	(0.81, 3.54)
Eng ceramics	1.08	(0.84, 1.38)	1.06	(0.82, 1.38)	1.07	(0.83, 1.38)	0.92	(0.68, 1.23)
DAYS (×IQR^{-1})			1.01	(0.96, 1.06)			1.00	(0.96, 1.05)
OPEXP (×IQR^{-1})					1.01	(0.96, 1.05)		
Ave. OPEXP								
10-22 v. <10							1.12	(0.89, 1.41)
22-35 v. <10							1.37	(1.08, 1.75)
>35 v. <10							1.12	(0.87, 1.43)
Residual SS (df)	684.7 (741)		684.6 (740)		684.6 (740)		678.0 (737)	

* cubic spline fitted, approx. linear effect

IQR= inter-quartile range (74 for DAYS, 2350 for OPEXP).

TABLE 8.7 Prevalence of reported symptoms by OG and number of days dipped.

Days dipped	Scotland			England			All		
	N	n	%	N	n	%	N	n	%
Ceramics									
0	36	2	5.6	71	3	4.2	107	5	4.7
Farmers									
0	46	5	10.9	7	1	14.3	53	6	11.3
1-100	218	26	11.9	231	56	24.2	449	82	18.3
101-200	81	15	18.5	25	7	28.0	106	22	20.8
201-400	30	6	20.0	7	3	42.9	37	9	24.3
>400	15	1	6.7	5	3	60.0	20	4	20.0

TABLE 8.8 Regression coefficients for cumulative exposure variables adjusted for important confounders. Confidence intervals (95%) are in parenthesis. DAYS and OPEXP variables have been scaled by 74 days and 2350 units respectively.

Exposure	**Symptoms (OR)**	**Hot QST (×effect)**	**Cold (×effect)**	**Vibration (×effect)**
Full regression data set:				
DAYS	1.13** *(1.01, 1.25)*	0.94** *(0.89, 1.00)*	0.99 *(0.95, 1.03)*	1.01 *(0.96, 1.06)*
OPEXP	1.11** *(1.01, 1.23)*	0.96* *(0.91, 1.01)*	0.99 *(0.96, 1.03)*	1.01 *(0.96, 1.05)*
DAYS (1984-91)	1.35** *(1.03, 1.77)*	0.90 *(0.78, 1.03)*	0.98 *(0.89, 1.07)*	1.02 *(0.91, 1.15)*
OPEXP (1984-91)	1.26* *(0.99, 1.59)*	0.93 *(0.82, 1.05)*	0.99 *(0.91, 1.08)*	1.02 *(0.92, 1.13)*
Subset omitting high leverage:				
DAYS	1.07 *(0.92, 1.24)*	0.92** *(0.86, 0.99)*	0.98 *(0.94, 1.03)*	1.03 *(0.97, 1.09)*
OPEXP	1.06 *(0.91, 1.24)*	0.93** *(0.86, 1.00)*	0.98 *(0.93, 1.03)*	1.04 *(0.97, 1.10)*

* 0.05 < P < 0.10
** P < 0.05

TABLE 8.9 Summary of improvement to model fits after adding each average intensity term (grouped by quartiles) after adjustment for total days dipped and important confounders.

Intensity effect	Symptoms (mean deviance)	Hot threshold (variance ratio)	Cold threshold (variance ratio)	Vibration threshold (variance ratio)
ave. CONC	4.3**	0.3	0.6	3.0**
ave. SPLASH	0.8	0.5	1.9	1.3
ave. OP	2.1*	0.5	1.7	2.4*

* $0.05 < P < 0.10$
** $P < 0.05$

TABLE 8.10(a) **Odds ratios (OR) and 95% confidence intervals (CI) for prevalence of reported symptoms including the effects of sex and concentrate handling.**

Terms	Model S/5	
	OR	CI
Age ($\times 10^{-1}$ years)	1.43	(1.22, 1.67)
Country (Eng v. Sco)	1.98	(1.30, 3.03)
SD farmers v.		
NSD farmers	0.37	(0.12, 1.15)
Ceramics	1.27	(0.40, 4.00)
DAYS ($\times IQR^{-1}$)	1.10	(0.99, 1.23)
Sex (Male v. Female)	0.34	(0.17, 0.70)
Conc. handler (Ever v. never)	3.43	(1.63, 7.23)
Deviance (df)	619.4 (755)	

IQR= inter-quartile range (74 for DAYS)

TABLE 8.10(b) **Hot QST threshold: estimated multiplicative effects and 95% confidence intervals (CI) including the effects of important confounders, cumulative exposure and average concentrate handling intensity.**

Terms	**Model H/5**	
	× effect	**CI**
Age ($\times 10^{-1}$ years)	1.64	(1.54, 1.75)
Sex (Male v. Female)	2.09	(1.58, 2.78)
Country×OG interaction:		
(Sco SD farmers v.)	0.91	(0.61, 1.36)
Sco NSD farmers	0.82	(0.53, 1.27)
Sco Ceramics	0.73	(0.60, 0.89)
Eng SD farmers	0.99	(0.41, 2.37)
Eng NSD farmers	1.20	(0.85, 1.70)
Eng Ceramics		
DAYS ($\times IQR^{-1}$)	0.94	(0.89, 0.99)
Ave. CONC	1.80	(0.42, 7.64)
$(\text{Ave. CONC})^2$	0.47	(0.08, 2.92)
Residual SS (df)	972.4 (745)	

IQR= inter-quartile range (74 for DAYS)

TABLE 8.10(c) **Cold QST threshold: estimated multiplicative effects and 95% confidence intervals (CI) including the effects of important confounders, cumulative exposure and average concentrate handling intensity.**

Terms	Model C/5	
	×effect	CI
Age ($\times 10^{-1}$ years)	1.30	(1.24, 1.36)
Sex (Male v. Female)	1.26	(1.04, 1.54)
OG (SD farmers v.)		
NSD farmers	1.49	(1.15, 1.91)
Ceramics	1.21	(0.98, 1.49)
DAYS ($\times IQR^{-1}$)	0.98	(0.95, 1.02)
Ave. CONC	3.50	(1.28, 9.58)
$(\text{Ave. CONC})^2$	0.23	(0.06, 0.82)
Residual SS (df)	472.1 (743)	

IQR= inter-quartile range (74 for DAYS)

TABLE 8.10(d) **Vibration QST threshold: estimated multiplicative effects and 95% confidence intervals (CI) including the effects of important confounders, cumulative exposure and average concentrate handling intensity.**

Terms	**Model V/5**	
	× effect	**CI**
Age		
($\times 10^{-1}$ years)	1.62	(1.53, 1.71)
Sex		
(Male v. Female)	1.03	(0.81, 1.31)
Country×OG interaction:		
(Sco SD farmers v.)	0.86	(0.62, 1.20)
Sco NSD farmers	1.40	(0.98, 2.01)
Sco Ceramics	1.07	(0.91, 1.25)
Eng SD farmers	1.57	(0.76, 3.27)
Eng NSD farmers	0.84	(0.63, 1.12)
Eng Ceramics		
DAYS		
($\times IQR^{-1}$)	1.00	(0.95, 1.05)
Ave. CONC	7.41	(2.18, 25.18)
$(\text{Ave. CONC})^2$	0.10	(0.02, 0.48)
Residual SS	674.7	
(df)	(738)	

IQR= inter-quartile range (74 for DAYS

TABLE 8.11 **Summary of the reported daily exposure to vibrating equipment. Shown are the percent of subjects with non-zero exposure (%) and, in parenthesis, the mean number of hours per day among those with non-zero exposure. Means in italics are based on fewer than five subjects.**

Vibrating equipment		Ceramics			NSD farmers			SD farmers		
		Sco (n=36)	Eng (n=71)	All (n=107)	Sco (n=46)	Eng (n=7)	All (n=53)	Sco (n=344)	Eng (n=268)	All (n=612)
Saws/	%	3	1	2	0	0	0	2	9	5
wood machines		*(2.0)*	*(2.0)*	*(2.0)*	*(-)*	*(-)*	*(-)*	(1.0)	(2.0)	(1.8)
Hammers/	%	6	1	3	2	0	2	1	1	1
drills		*(1.0)*	*(1.0)*	*(1.0)*	*(1.0)*	*(-)*	*(1.0)*	*(1.0)*	*(2.3)*	(1.8)
Grinding/	%	11	6	7	0	0	0	3	4	3
rotary tools		*(1.3)*	*(1.3)*	(1.3)	*(-)*	*(-)*	*(-)*	(1.0)	(1.0)	(1.0)
Riveting	%	0	0	0	0	0	0	0	0	0
		(-)	*(-)*	*(-)*	*(-)*	*(-)*	*(-)*	*(-)*	*(1.0)*	*(1.0)*
Fork lift	%	14	32	26	13	0	11	27	12	20
		(4.8)	(4.2)	(4.3)	(1.5)	*(-)*	(1.5)	(1.8)	(1.6)	(1.7)
Tractor/	%	8	1	4	33	57	36	83	71	77
quad biking		*(6.0)*	*(1.0)*	*(4.7)*	(2.2)	*(1.3)*	(2.0)	(3.1)	(3.0)	(3.1)
Motorcycling/	%	3	17	12	9	0	8	3	2	3
mountain biking		*(3.0)*	(3.2)	(3.2)	*(4.5)*	*(-)*	*(4.5)*	(2.4)	(2.7)	(2.5)
Wood working	%	3	6	5	6	14	8	5	4	5
		(2.0)	*(1.8)*	(1.8)	*(2.7)*	*(6.0)*	*(3.5)*	(2.9)	(8.0)	(4.9)
Vehicle	%	19	16	17	17	14	17	20	19	19
maintenance		(1.7)	(1.5)	(1.6)	(3.5)	*(2.0)*	(3.3)	(2.0)	(3.5)	(2.6)

TABLE 8.12 Percent of subjects reporting participation in activities with potential exposure to OPs.

Exposure	Ceramics			NSD farmers			SD farmers		
	Sco (n=36)	Eng (n=71)	All (n=107)	Sco (n=46)	Eng (n=7)	All (n=53)	Sco (n=344)	Eng (n=268)	All (n=612)
Currently work with:									
lead	3	6	5	0	0	0	7	3	5
solvents	36	48	44	65	14	58	53	16	37
insecticides	3	0	1	26	71	32	60	70	65
Tasks over working life:									
use of sheep dips other than for dipping	0	0	0	0	0	0	72	70	71
treatment of warble fly	6	6	6	13	43	17	59	68	63
use of insecticides on crops	11	6	8	13	29	15	43	48	45
treatment of stored grain	3	1	2	4	14	6	16	22	19
use of insecticides on farms	0	1	1	24	29	24	43	17	31
use of insecticides on garden	25	31	29	26	57	30	41	33	38
use of insecticides in home	100	100	100	100	86	98	99	99	99

FIGURES

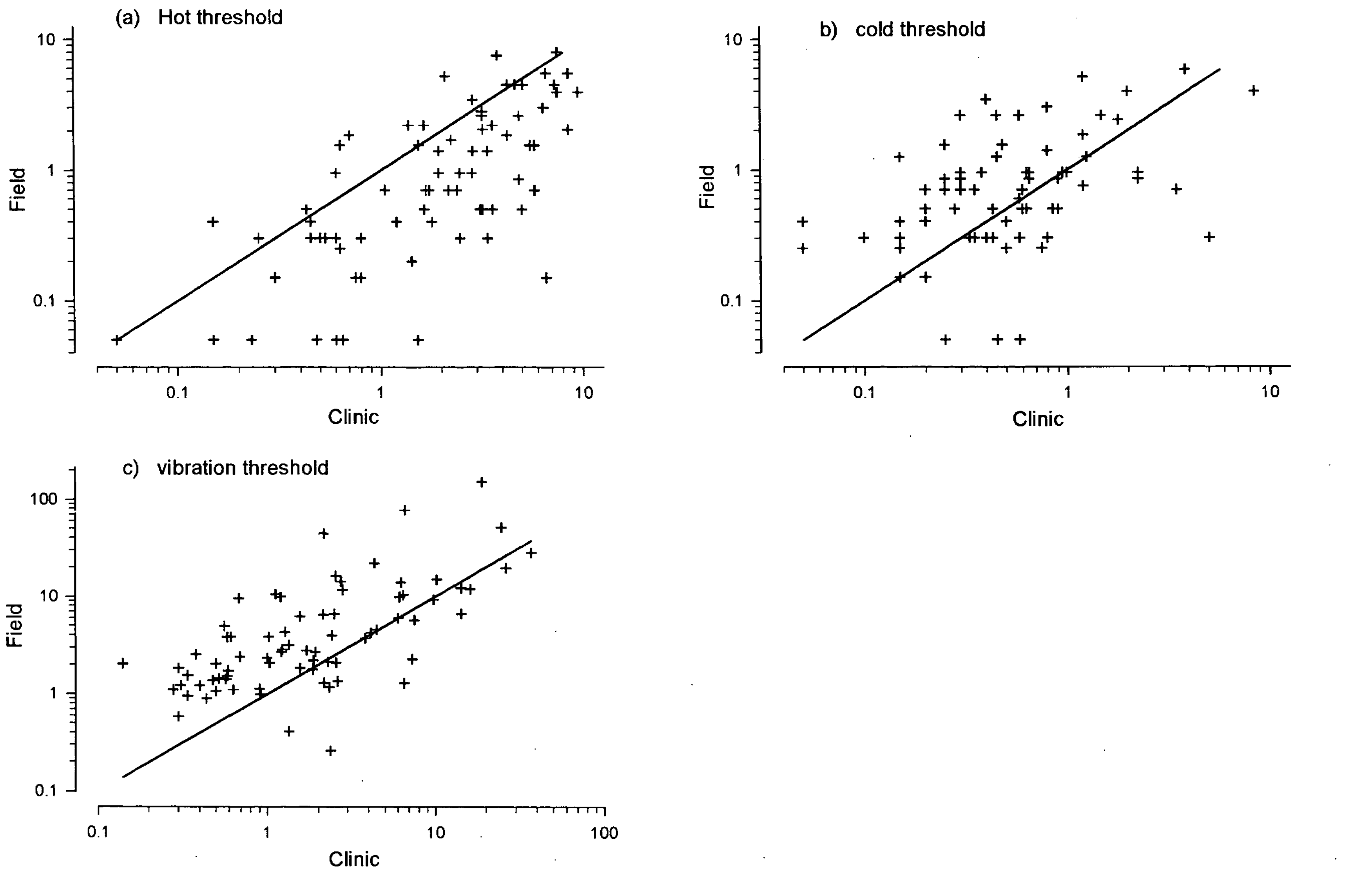


Figure 5.1 Comparison between field (phase 2) and clinic (phase 3) measurements of sensory thresholds

Figure 7.1 Flowchart of Recruitment Outcomes for Sheep Farms

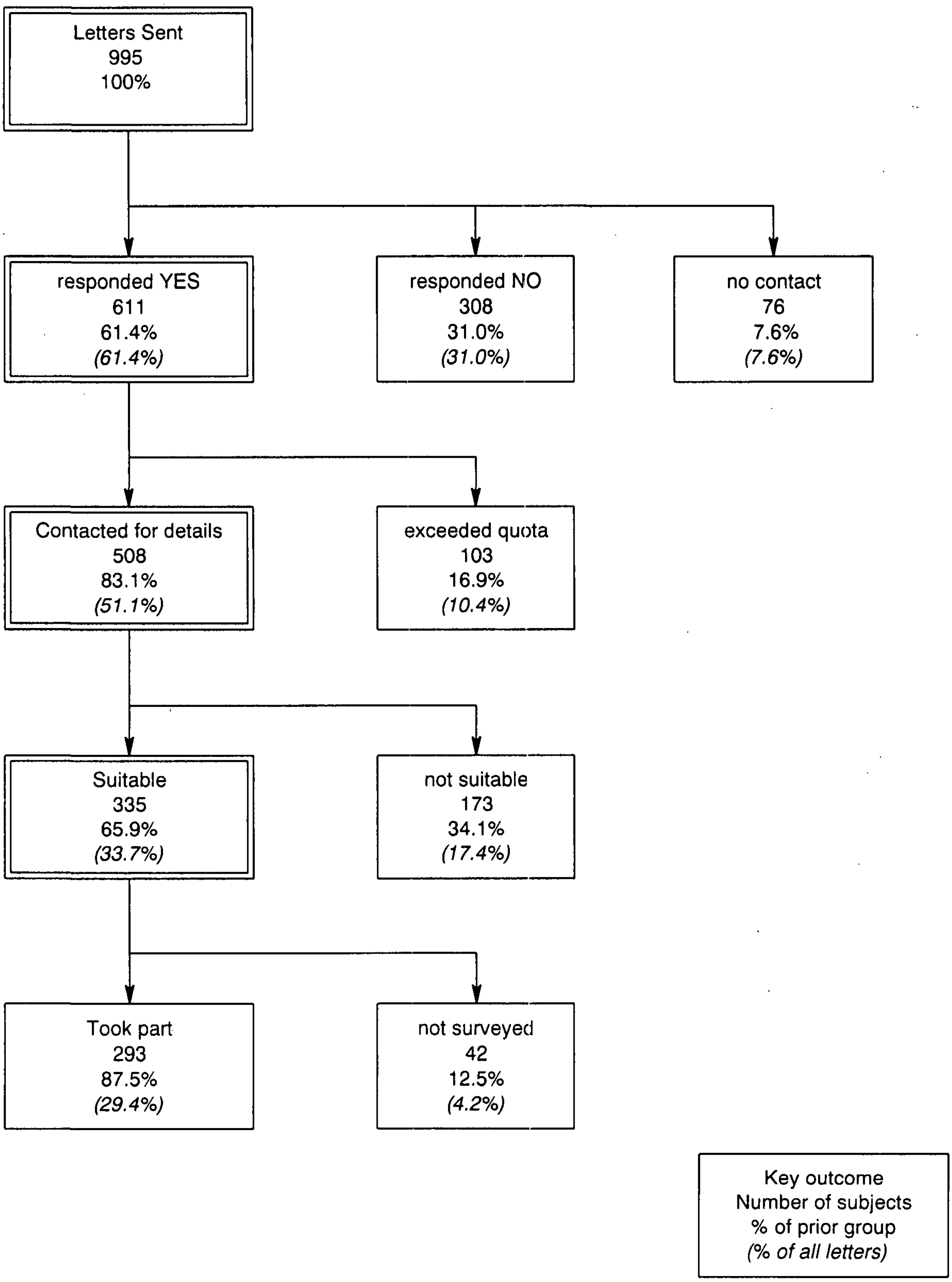
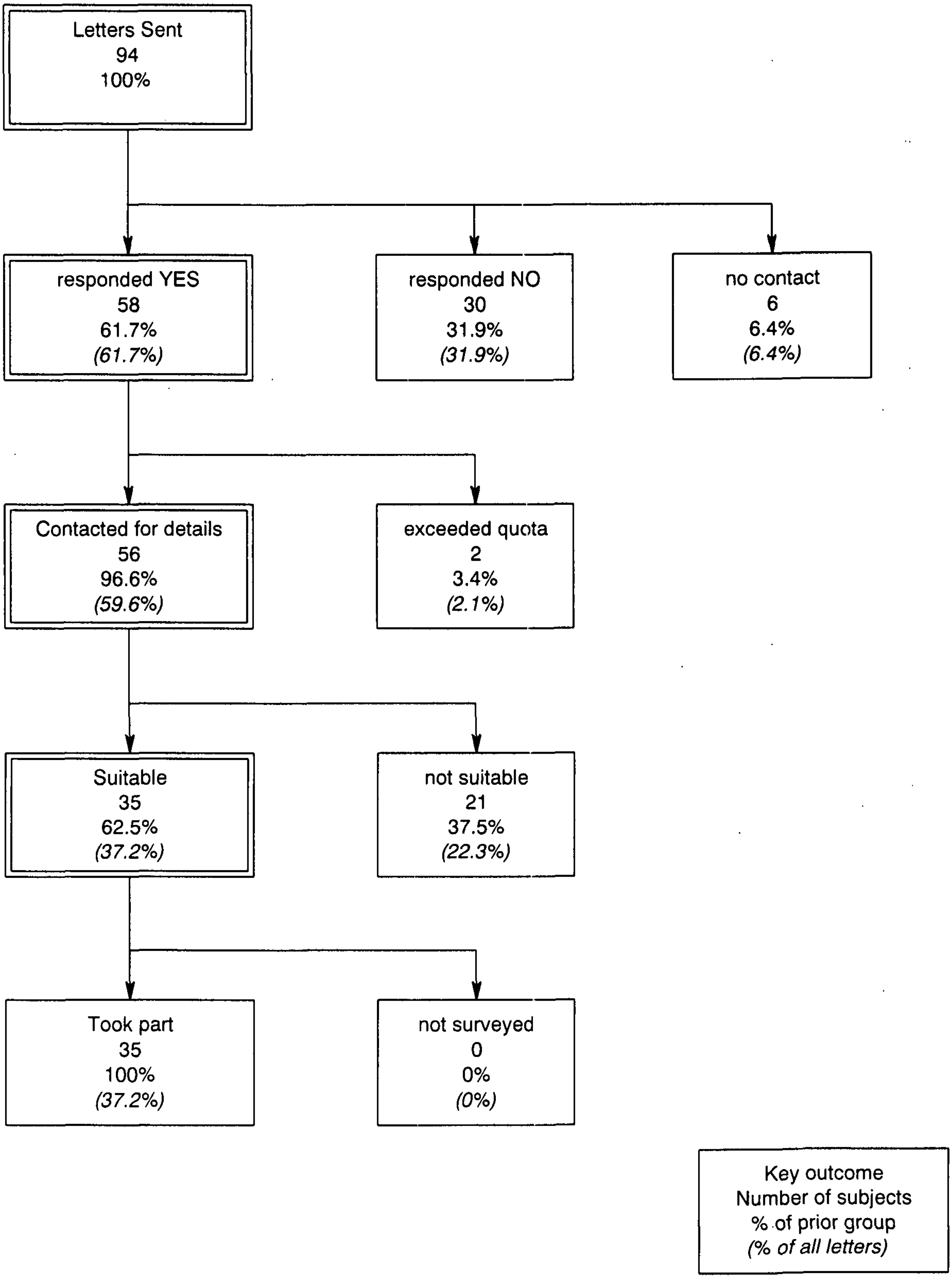


Figure 7.2 Flowchart of Recruitment Outcomes for Non-Sheep Farms



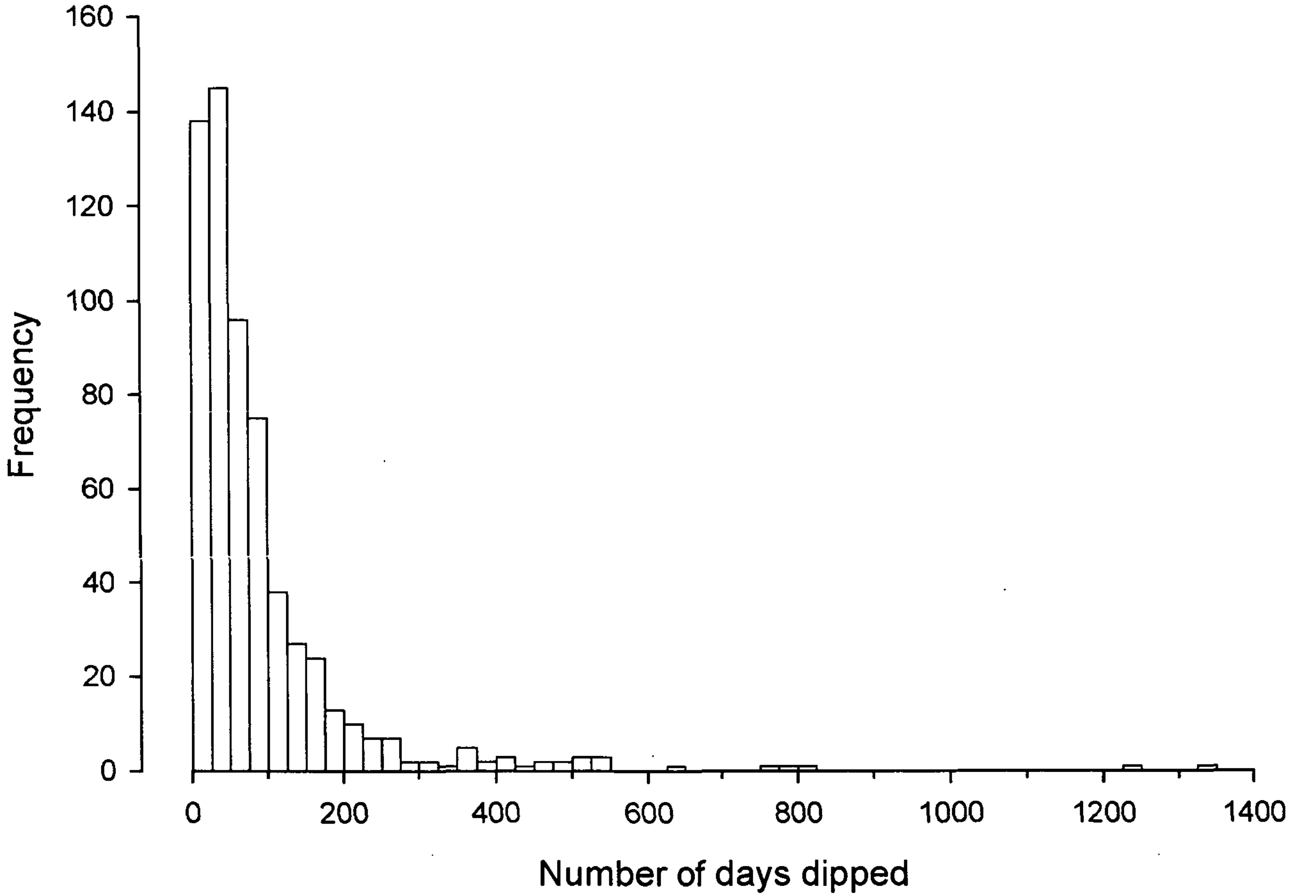


Figure 7.3 Histogram of days dipped among sheep dippers since 1970

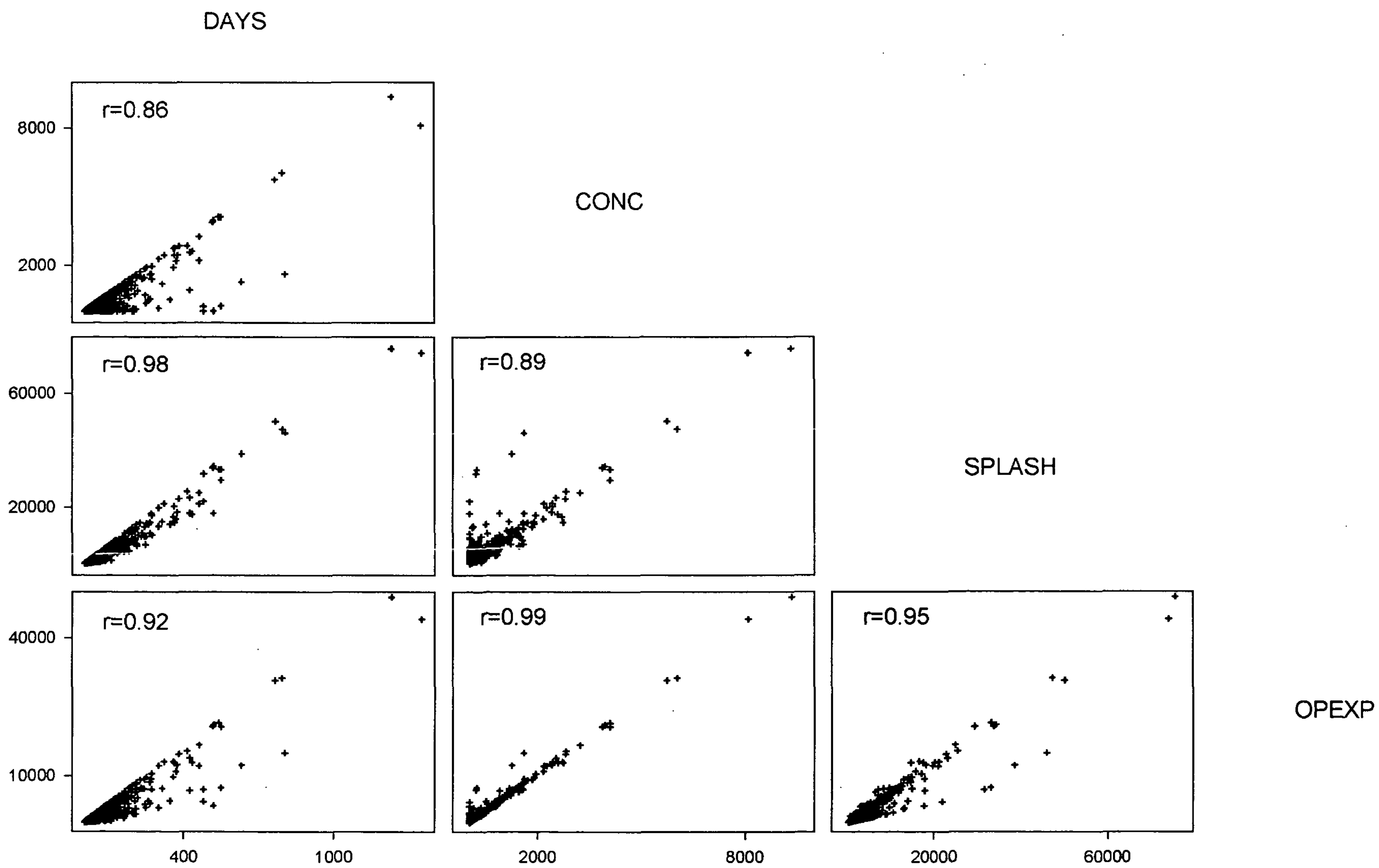


Figure 7.4 Scatter plot matrix of cumulative exposure indices showing linear correlation coefficients (r)

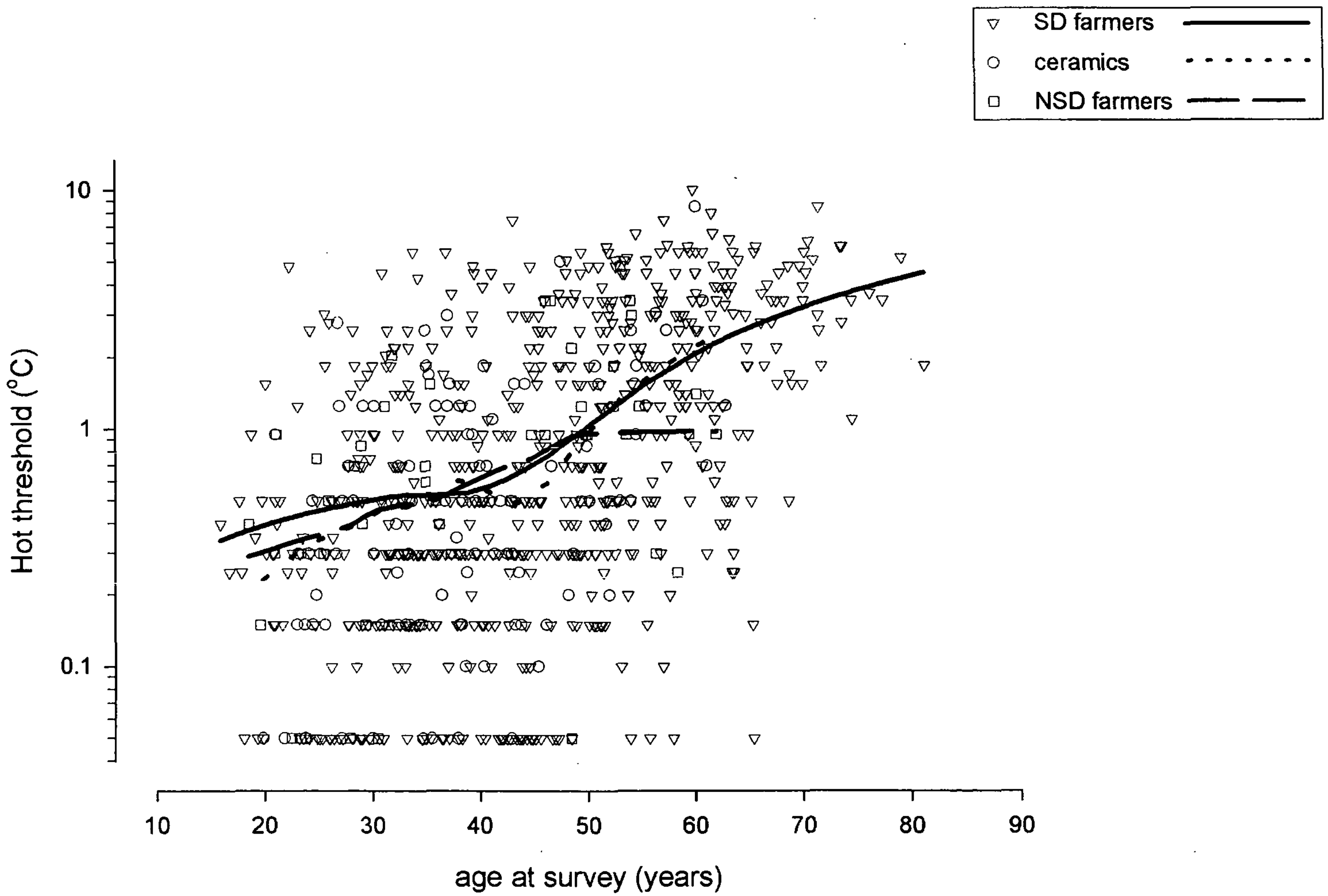


Figure 8.1 Hot thresholds against age at survey

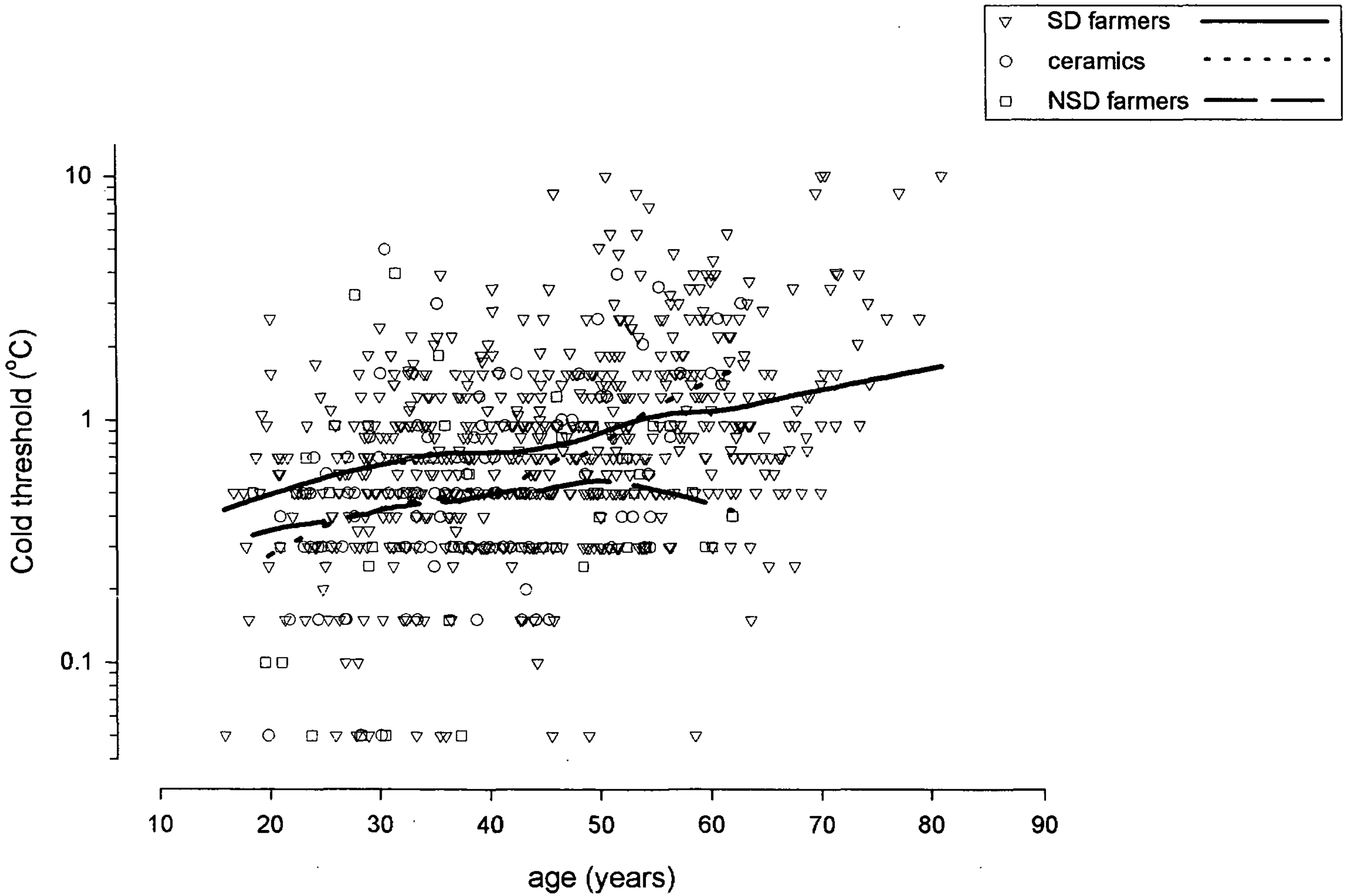


Figure 8.2 Cold thresholds against age at survey

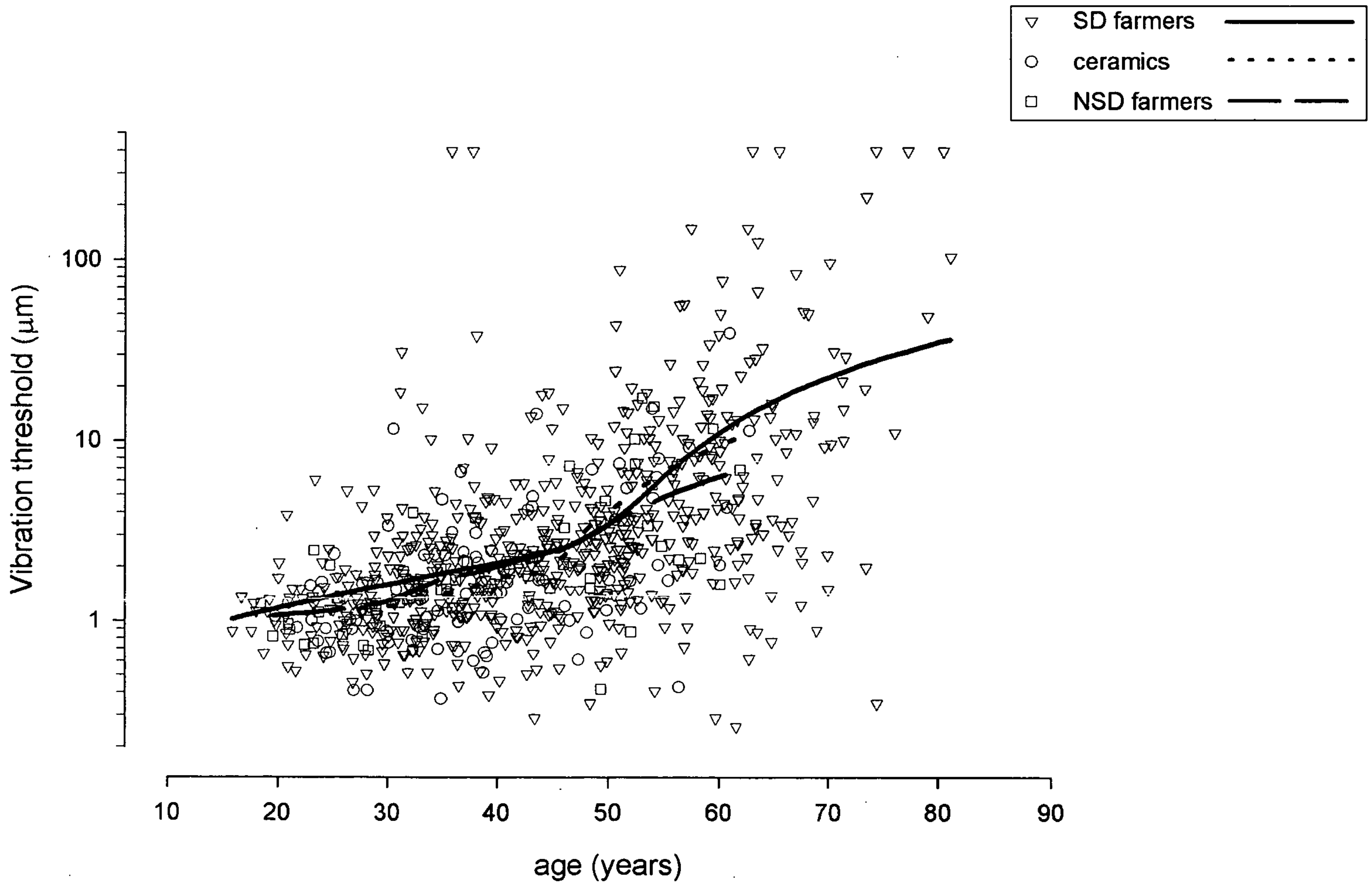


Figure 8.3 Vibration thresholds against age at survey

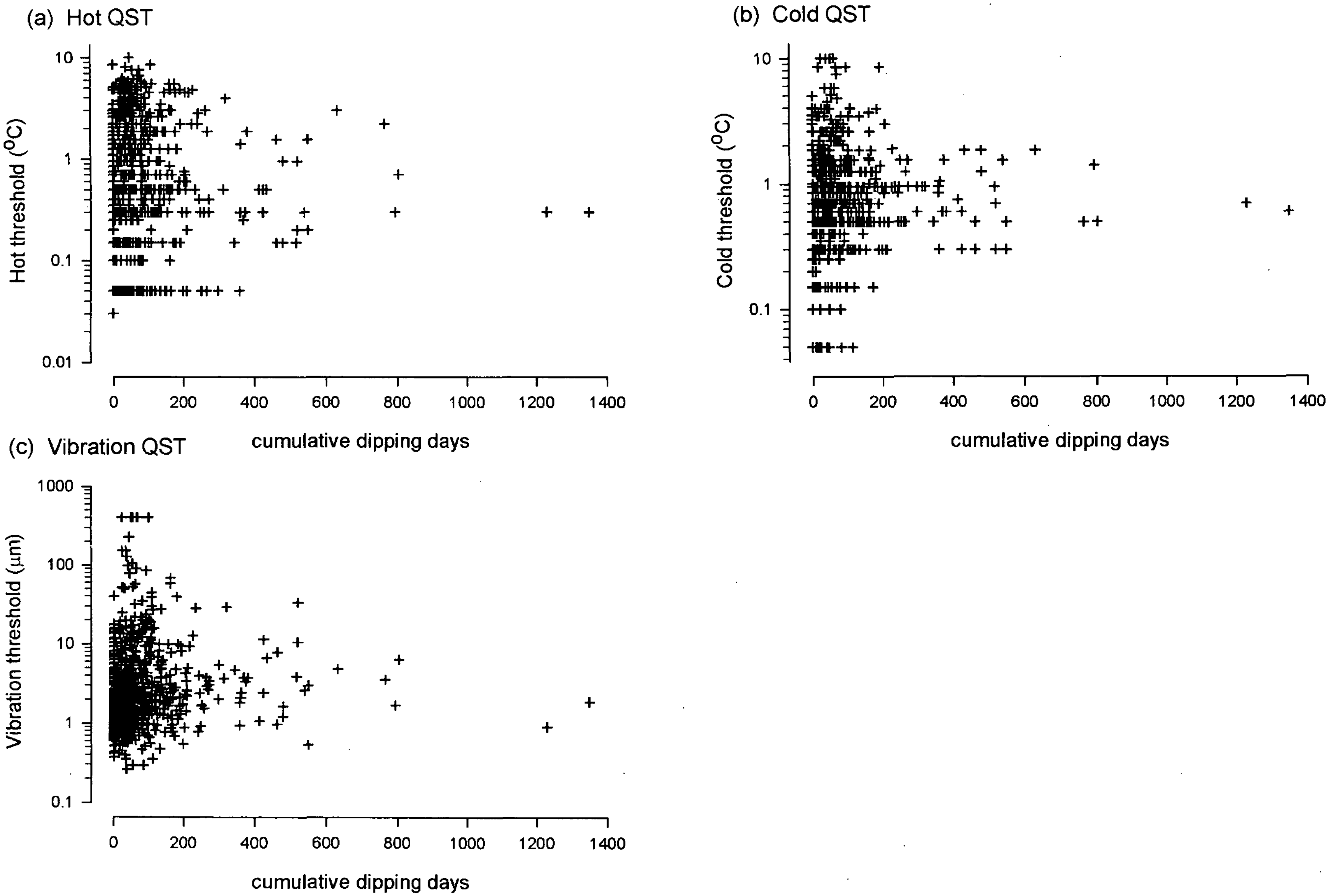


Figure 8.4 Sensory test thresholds for all subjects against cumulative days dipped.

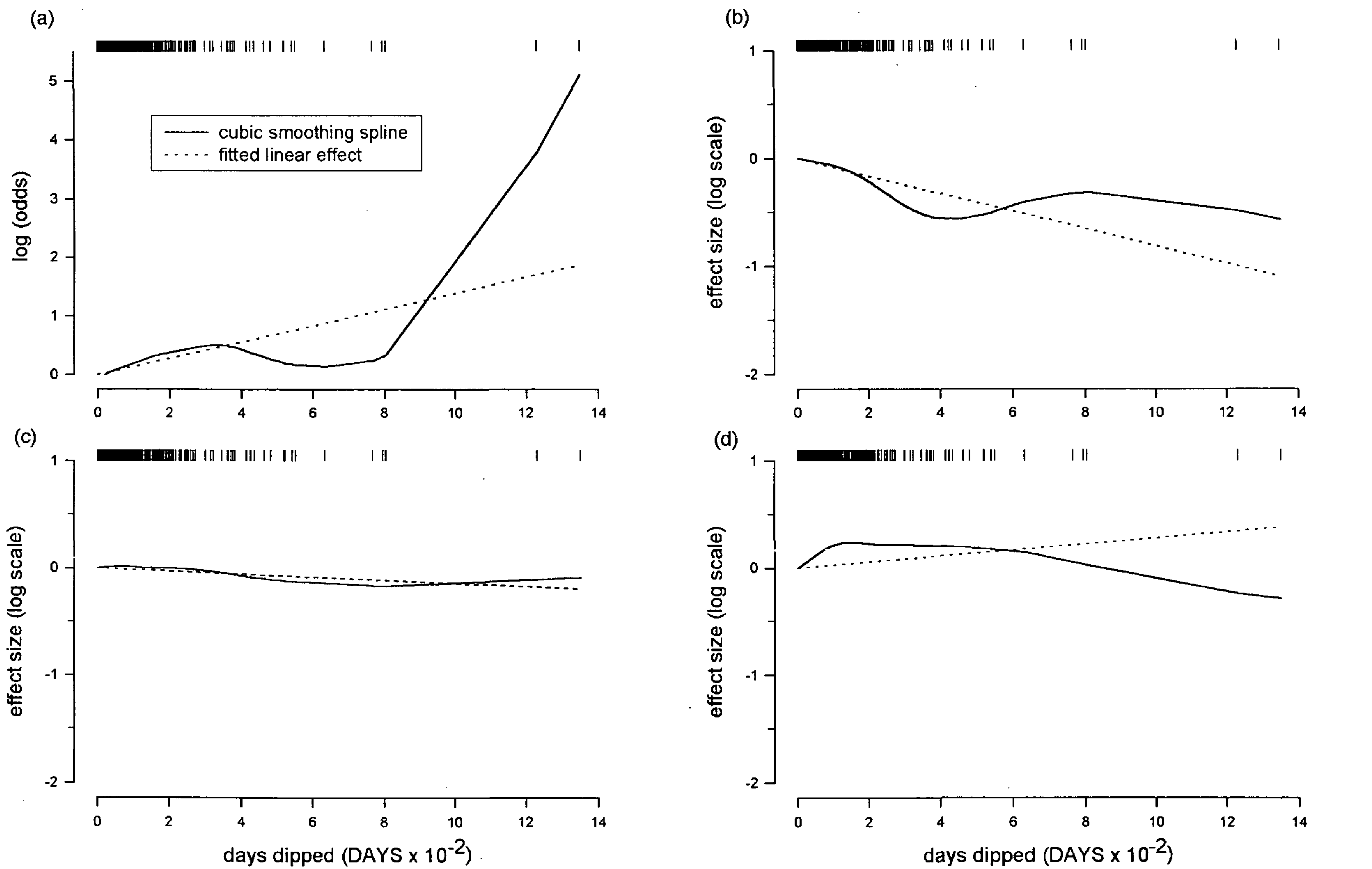


Figure 8.5 Comparison of nonparameteric and linear effects of cumulative exposure, adjusted for confounders, on (a) symptoms, (b) hot, (c) cold and (d) vibration thresholds, relative to zero exposure. Tick marks show distribution of days dipped.

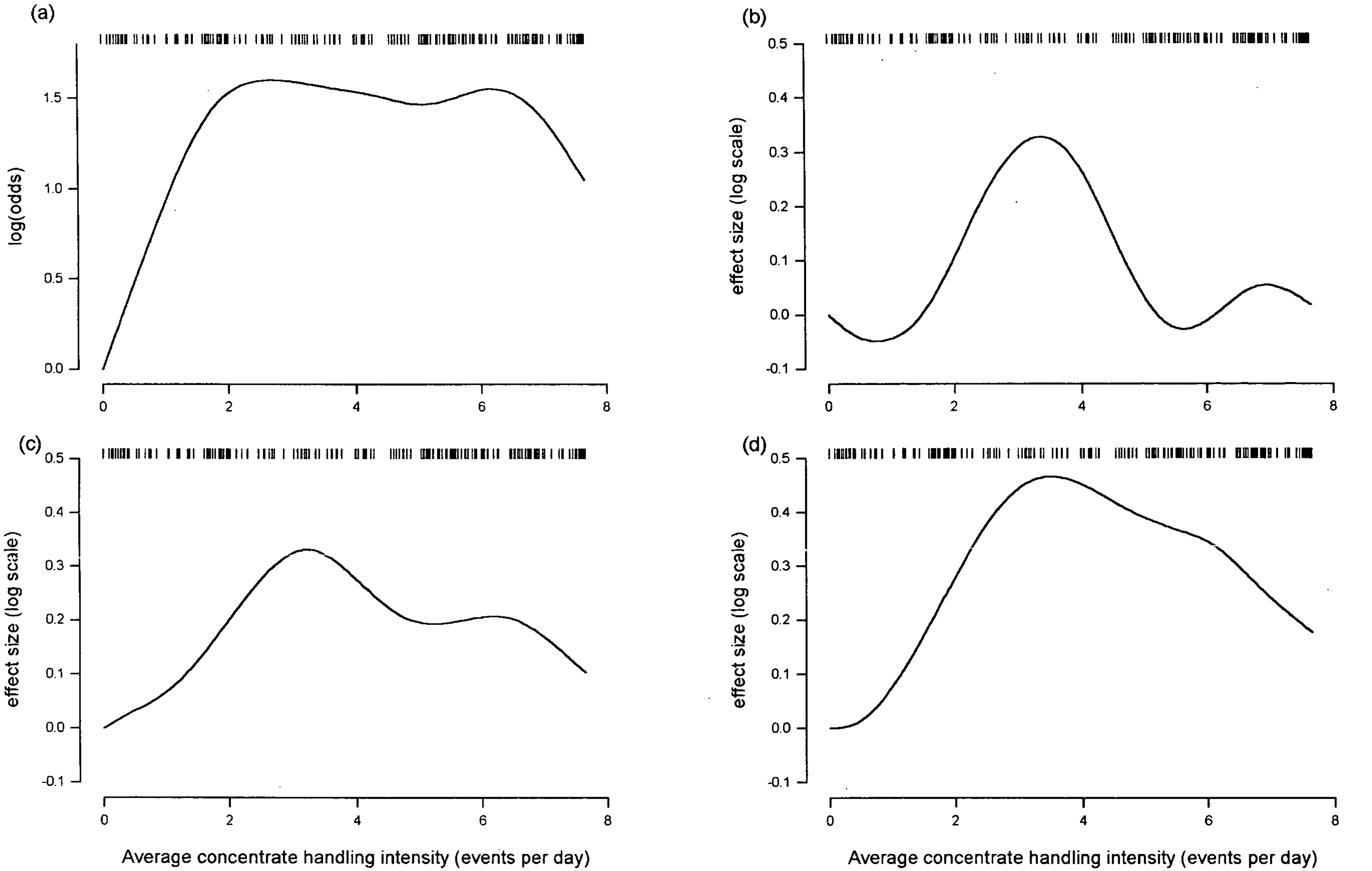


Figure 8.6 Effect of average concentrate handling exposure intensity, relative to zero exposure, and adjusted for confounders, using a cubic smoothing spline for (a) symptoms, (b) hot, (c) cold and (d) vibration thresholds. Tick marks show distribution of exposure intensity.

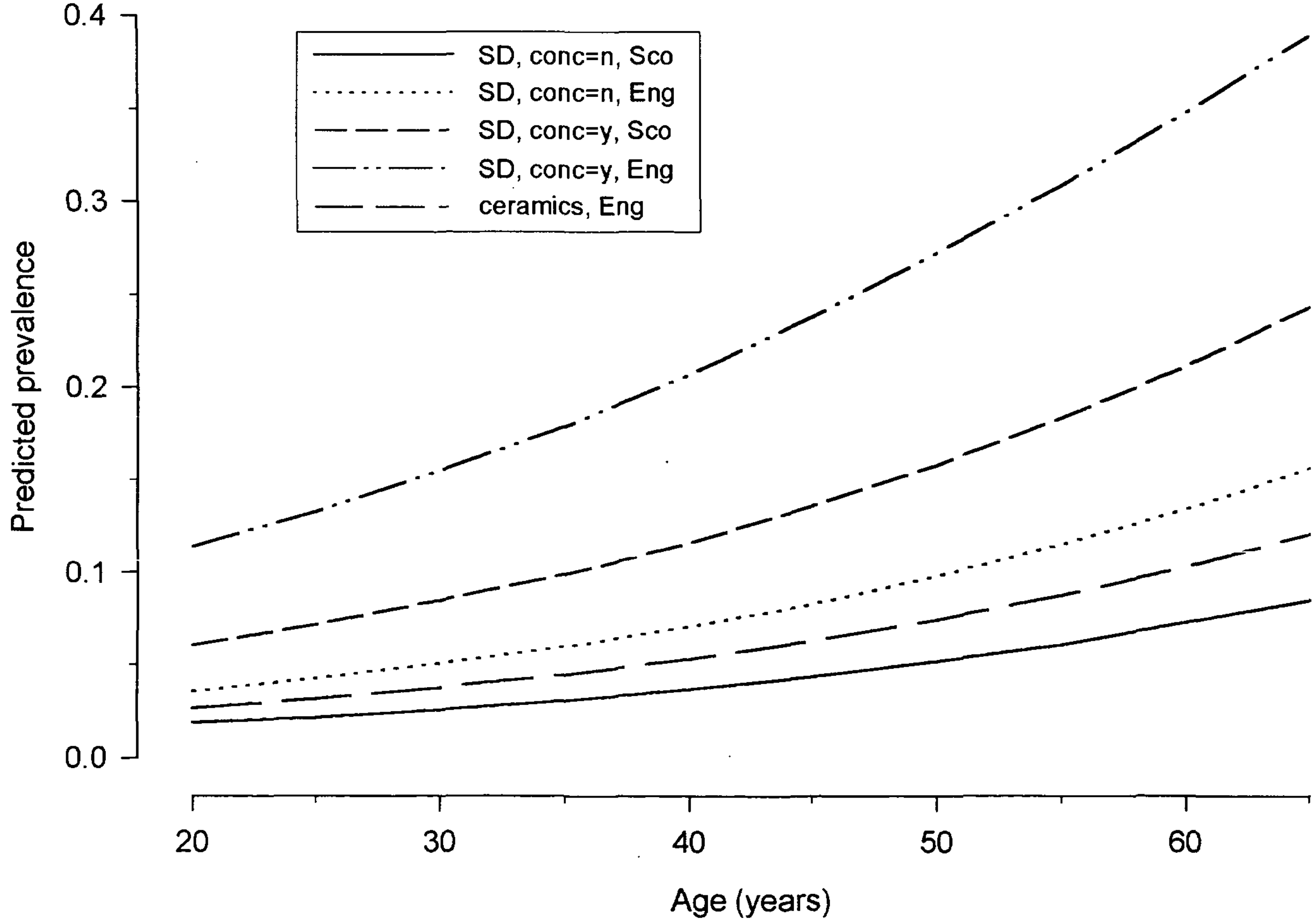


Figure 8.7(a) Predicted prevalence of symptoms among male sheep dippers (SD) and ceramics workers by concentrate handling (conc) and country.

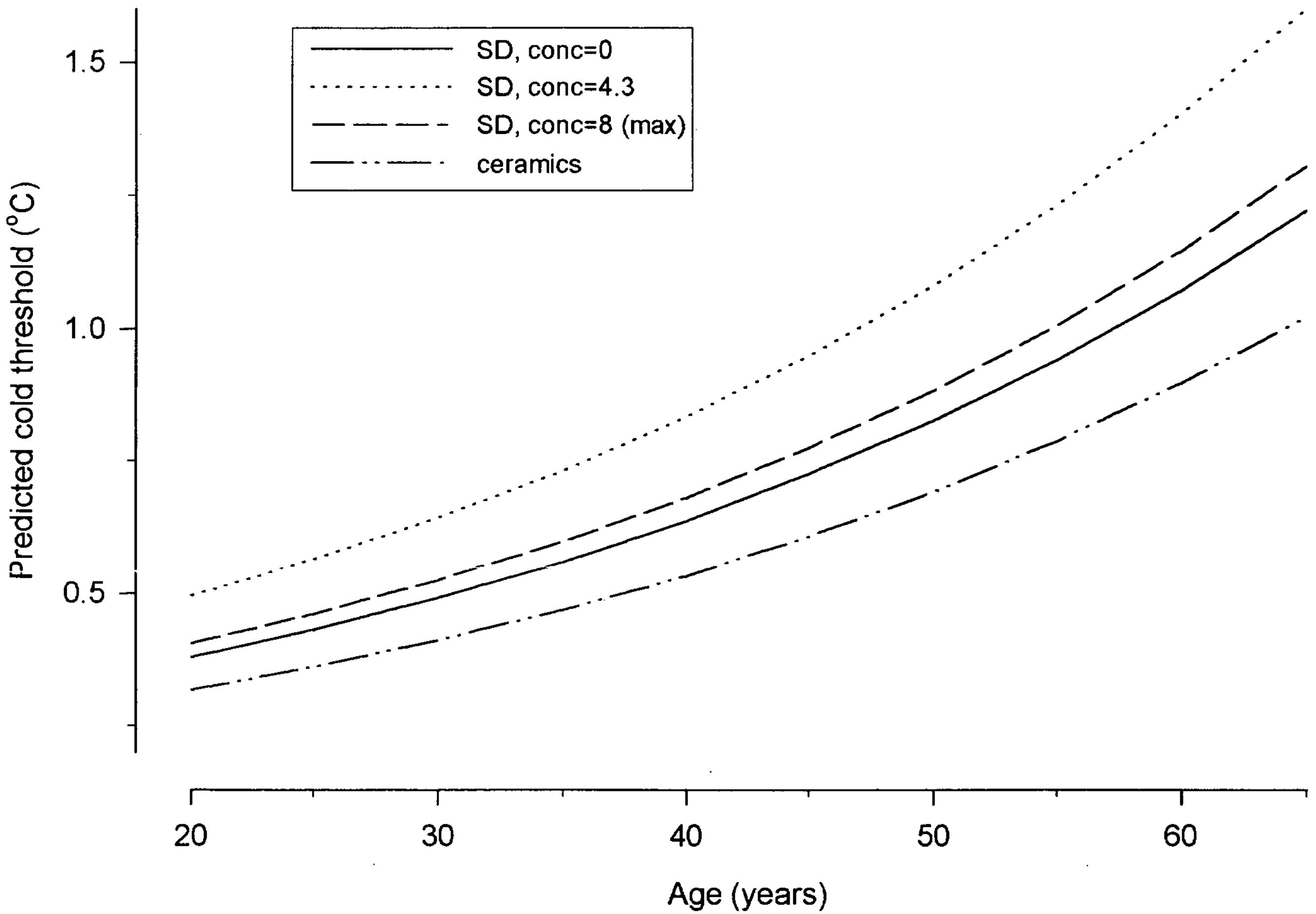


Figure 8.7(b) Predicted cold thresholds among male sheep dippers (SD) and ceramics workers by concentrate handling intensity (conc).

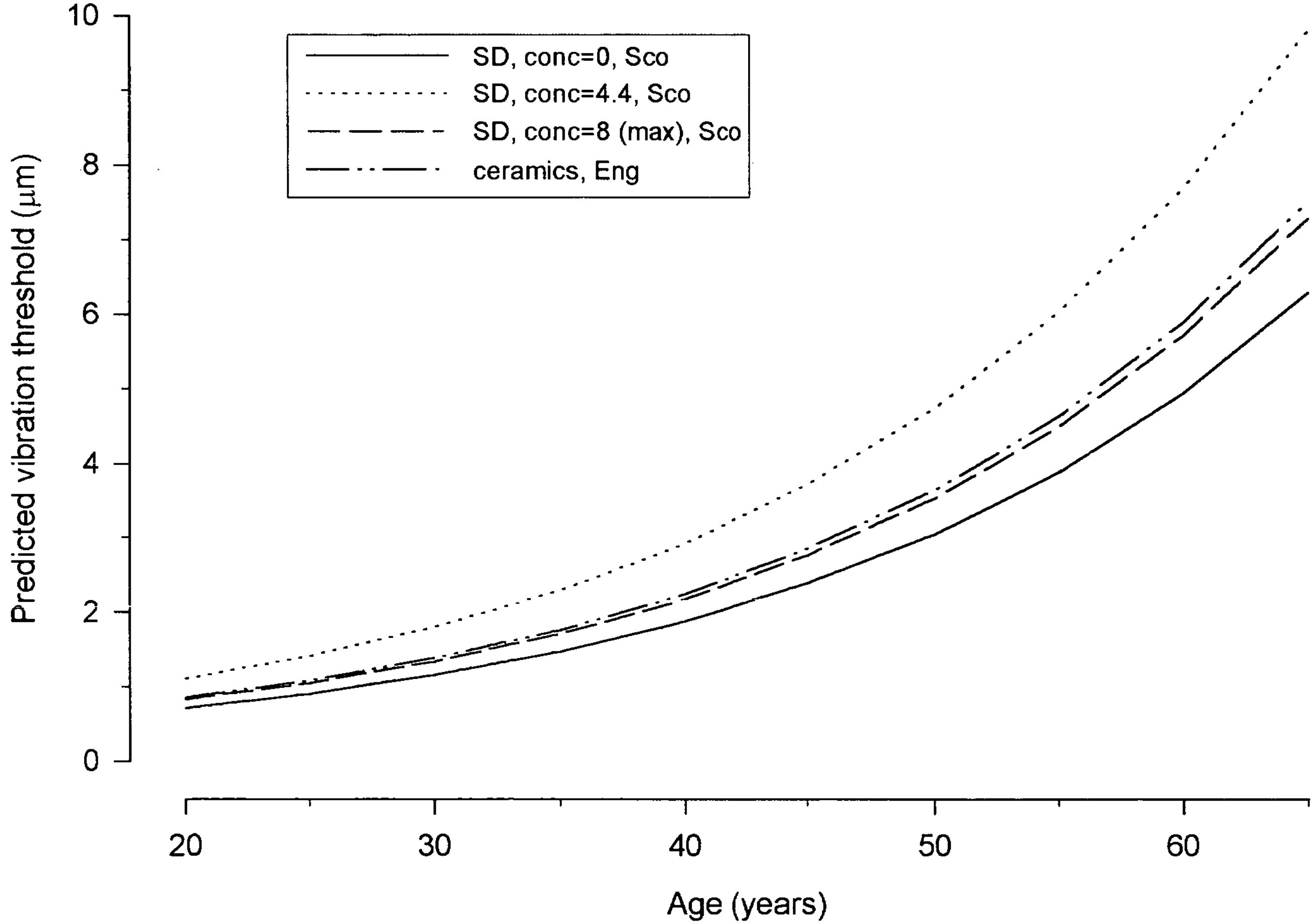


Figure 8.7(c) Predicted vibration thresholds among male sheep dippers (SD) and ceramics workers by concentrate handling intensity (conc) and country.

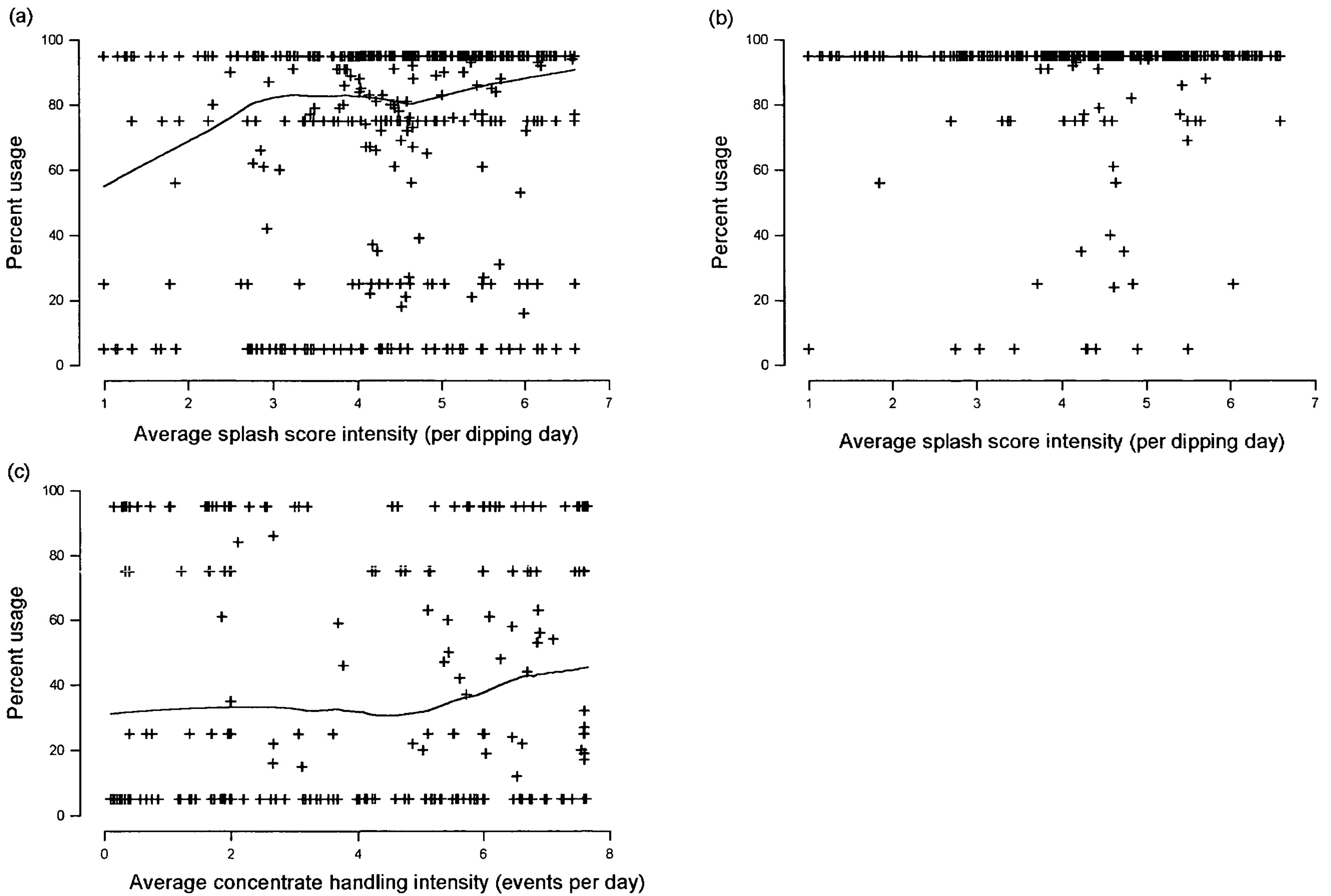


Figure 8.8 Estimated average percent use of PPE by average exposure intensity showing a), waterproof trousers, b), waterproof footwear and c), gloves (specific to concentrate handling).

APPENDIX 1

Exposure history questionnaire and protocol
- Sheep farm personnel

Protocol for the completion of the exposure history questionnaire
Sheep farm personnel

INTRODUCTION

This questionnaire has been designed for use in the second phase of the project, the epidemiological field survey, and will be used in conjunction with a neurological symptom questionnaire. The purpose of the questionnaire is to obtain exposure history information based on those groups of factors from the revised OP uptake model, which are thought to influence uptake of OPs. These factors include: job history; work with dip wash and work with concentrate; and also use of OPs in non-dipping activities.

GENERAL INSTRUCTIONS

The subject's personal details should be recorded prior to administering the questionnaire. Farm and subject code as defined by the survey planner should be entered initially. After the personal details have been recorded and before starting to ask questions, the interviewer should instruct the subject that the majority of questions offer a number of specific answer options. The actual printed wording should be used for each question, and the alternative answer options offered to the subject. The option chosen will be recorded in the format provided on the questionnaire. Repeating the question can be helpful where the subject appears unsure about the response required. In certain cases additional explanatory information is provided within the protocol.

Part 1
The interviewer should ask about each job in the subject's working life starting with their current job and going back through time. Part time jobs should be included. Each job should be allocated a number in sequence, which is recorded in the box marked `sequence'. Consecutive casual jobs may be summarised under a single entry of `various casual'.

In addition each section of the questionnaire also includes a pre-amble to introduce the subject to the type of topic which will be covered in that section.

A Part 2 should be completed for every job which has involved more than 3 days total sheep dipping. Only a single part 3 should be completed for the whole of working life.

The questionnaire has been designed to facilitate transfer of data to a computer. Where a number of answer options are available the appropriate answer should be circled or ticked as indicated.

COMMENTS ON INDIVIDUAL QUESTIONS

General information

a. Farm number Insert the number that has been assigned to this farm. Each box should be filled e.g. farm 342 should be recorded as 0342.
b. Individual's name and code Insert the individual's name and corresponding code number. At some sites father and son may have the same name, under these circumstances record senior and junior as appropriate.
c. Male or female Insert M or F in space provided.
d. Date of Birth Each box should be filled e.g. 7 August 1952 should be recorded as 070852.
e. Date of Survey Each box should be filled as described above.

Section 1 - Occupational history

Jobs held for 3 months or less can be regarded as casual, and consecutive casual jobs may be summarised under a single entry of `various casual'.

Following the preamble, the interviewer should start with the current or most recent job first, then proceeding back in time to obtain details of previous jobs.

Ask the following questions, and record answers on the form. Use as many continuation sheets for Part 1 as are required.

1.1 When did you stat your current job? (OR When did you start that job?)
Where possible record information as `month and year', or accept year only if the subject is unable to remember the exact month.

1.2 When did you leave the job?
Omit the question if current job. Record month and year.

1.3 Who was your employer?
Employers may include non-farming organisations. For farming jobs the employer may be the farm owner or tenant.

1.4 What was your employers business?
Record the main activity or type of production carried out by the employer.

1.5 What was your job title?
Record the main activity or job title of the subject during this period of employment.

1.6 In this job did you dip sheep?
Ask whether the individual was involved in sheep dipping during this job, include herding sheep ready to go into the bath, and gathering sheep into draining pens. Include time spent helping on neighbours farms. Circle answer `yes' or `no'.

Any jobs which did not involve sheep dipping do not require completion of a Part 2.

1.7 Did you work with any of the following during this job?

Vibrating equipment	e.g.	driving tractors, use of chain saws, pneumatic drills
Lead	e.g.	chipping/burning lead-painted surfaces, pigments, battery manufacture
Solvents	e.g.	thinners, degreasers, varnishes
Insecticides	e.g.	any job where organophosphates may have been used for pest control

Enter Y or N in the appropriate box.

1.8 Sequence
Record the jobs in number sequence, starting with number 1. this number will be used in Part 2 to trace the relevant data to the jobs listed in part 1.

1.9 Did you have a previous full time job?
If `Yes' return to question 1.1, and record details of previous job.

Part 2
Record the farm and the individuals code number at the start of Part 2.
Record the job sequence number from Part 1, which relates to this job, in the box provided.

Section 2.1 - Job summary

Question 2.1b - Total days dipping in the job
Ask the subject how many days they dipped sheep in this job. In order to help them make this calculation a box is provided, which allows the interviewer to tally the number of days over specific periods within the job, thus allowing for periods where no dipping had been performed.
If the subject has less than 3 days total dipping in the job, do not continue with the rest of the questions on this job. Instead start a new Part 2 for the next job in sequence.
If the subject has done more than 3 days dipping in this job, continue with the rest of Part 2.

Question 2.1c - Consecutive days dipping
Ask the subject what was the most number of days in a row that they dipped sheep in this job. If the answer is more than 5 days, ask whether the dipping continued over weekends. If there is less than a 2 day break over weekends, then this can be considered as consecutive days. Otherwise record the maximum number as 5 days. Record the number in the box provided.

Question 2.1d - Size of flock
Ask what was the average size of the flock dipped during this job. Farmers have to return figures on flock size at the 1st June each year to the Ministry of Agriculture for the purpose of Census data, and this might be used as a prompt. Alternatively, if the flock has varied significantly during the job, record a range from maximum to minimum and take an average. Record the average in the box provided.

Question 2.2a - Tasks performed

Plunger (paddler/dipper)	The worker who actually plunges the sheep under the dip
Chucker	The worker who feeds the sheep into the dipping bath
Helper	The worker who herds the sheep ready to go into the bath

Ask about the proportion or percentage of time spent in each task. If the subject requires prompting, suggest the following as a guide:

nearly always	(90-100% of the time)
more than half of the time	(>50-90% of the time)
less than half the time	(>10-50% of the time)
hardly ever	(less than 10% of the time)

If no time has been spent as plunger/dipper proceed to section `2.2c', otherwise continue.

Question 2.2b - Submerging sheep
Record whether an implement, hands or feet were used to submerge sheep.

Question 2.2c - Type of dipping bath
The types of bath which may be identified are as follows:
Straight swim A rectangular bath, plunge or swim-through. May be variable in length. There may be a pit at the side for the operator. The operator may put the sheep in, or there may be a walk through entry. Occasionally the bath may have a slide entry, located at the side of the bath. Sheep usually walk out of the bath to an adjacent draining area which should drain back into the bath.

Circular A round or hexagonal bath made of glass reinforced plastic or concrete. they usually have slide entries and ramps out to draining areas.

Other Enquire about mobile dips used by contractors, or any other system used which is not covered by the above definitions. In addition to circling this option, please describe the bath type in the box provided.

Question 2.2d - Protective clothing
Ask the subject about how much time protective clothing was worn on feet and legs.

Question 2.2d,e and subsequent questions in section 2.3 offer the following options (suggested interpretations are also given as an additional prompt if required) :

nearly always	(90-100% of the time)
more than half of the time	(>50-90% of the time)
less than half the time	(>10-50% of the time)
hardly ever	(less than 10% of the time)

Question 2.2e - Soaking with dip wash
Further explanation if required, `soaking' in the case of dip wash may occur as the result of a large splash from sheep entering or leaving the bath which could saturate skin or clothing.

Question 2.2f - Falls into dipping bath
Ask whether subject has ever fallen into dipping bath, and circle the appropriate answer option in terms of number of incidents.

Section 2.3 - Work with concentrate dip
Define concentrate as sheep dip when it is not diluted by water.

Question 2.3a - Pouring or adding concentrate to bath
Ask how often the subject was the person who poured out the concentrate or added it to the bath. Present the range of answer options, and circle the appropriate option.

If the subject answers `never' to 2.3a, proceed to next job in sequence, otherwise continue to the end of section 2.3.

Question 2.3b - Use of gloves
Ask the subject how often they wore gloves when pouring out concentrate or adding it to the bath. Present the range of answer options, and circle the appropriate option.

Question 2.3c - Spill of concentrate on skin or clothes
If necessary explain that getting concentrate on the skin could occur from a spill whilst handling containers or metered pumps. Getting concentrate on own clothing may occur as the result of a spill or when concentrate has got inside protective clothing.
Circle the appropriate answer option, in terms of number of incidents.

Part 3
Section 3.1 - Compounds used for dipping

Ask which sheep dips the subject remembers working with. Please refer to the list of products provided to check the names given against actual product names. If there is a choice of winter and summer dip for the product, ask the subject if they can remember which of the types they used. If the subject cannot remember, record `don't know'.

Question 3.2 - Other use of sheep dips
Ask whether sheep dips have been used for any purpose other than dipping, for example direct application to infested sheep.Record the frequency of this event, by circling the appropriate answer option.

The following questions cover other possible situations where individuals may have been exposed to organophosphate pesticides and include:

Question 3.3a - Treatment of warble fly on cattle
Question 3.3b - Treatment of arable, fodder crops or grass-land
question 3.3c - Treatment of stored grain or grain storage buildings
Question 3.3d - Any other work on farms which involved the use of pesticides
Question 3.4 - Use of pesticides in your garden

For each of questions record the frequency of the event, by circling the appropriate answer option.

Question 3.5 - Pesticide use in the home
Ask whether pesticides have been use by anyone else in the home, for example timber treatment. Circle the appropriate answer as `yes' or `no'.

Exposure History Questionnaire
Part 1

IOM (18/11/96)

1. Occupational History

Farm code number	
Individual's name and code	
Sex	*M/F*
Date of Birth	*DDMMYY*
Date of Survey	*DDMMYY*

Interviewer's Introduction

This questionnaire has been designed to gather information about your experience of sheep dipping. In particular, how much dipping you have done in the past and how you went about it. Please answer the questions as best you can. If you cannot remember a piece of information just say so.

I am going to ask you some questions about the kind of jobs you have held, starting with your present job and going back through time. Please tell me about all jobs including casual or part-time work.

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	(*circle one*) Y N	Sequence	1

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	(*circle one*) Y N	Sequence	

Farm and Individuals code numbers | | | | |

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	*(circle one)* Y N	Sequence	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	*(circle one)* Y N	Sequence	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	*(circle one)* Y N	Sequence	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	*(circle one)* Y N	Sequence	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	
In this job did you dip sheep?	*(circle one)* Y N	Sequence	

Exposure History Questionnaire Part 2
IOM (18/11/96)

Farm and Individuals code numbers

2.1 Job Summary

2.1a Job sequence number

All of the following questions refer only to dipping sheep with Organo-phosphate dips

2.1b How many days in total did you dip sheep in this job?

Start MMYY	End MMYY	Dip days in year
	TOTAL	

☞ *If less than 3 days total dipping start another part 2 for next job, otherwise continue*

2.1c What was the most number of days in a row that you dipped sheep?

2.1d On average how many sheep did you have at the 1st June Census?

2.2 Work with the Dip Wash

The next set of questions are about work with dip wash, by which we mean the sheep dip once it has been diluted by water in the dipping bath.

2.2a What proportion of the time did you perform the following tasks? *(record as %)*

	%
plunger *(dipper)*	
chucker	
helper	

☞ *If no time spent as plunger/dipper go on to question 2.2c, otherwise continue*

2.2b When you were the plunger/dipper what did you use most often to submerge the sheep ?
(circle one option)

implement	1
hands	2
feet	3

Farm and Individuals code numbers

2.2c What type of dipping bath did you use most often? *(circle one option)*

straight swim	1
circular	2
other (specify)	3

2.2d How much of the time did you wear protective clothing on your feet and legs? *(Tick one box in each row)*

	nearly always	more than half the time	less than half the time	hardly ever
waterproof trousers				
waterproof footwear				

2.2e How often did you get soaked to the skin with dip wash on any part of your body? *(circle one option)*

nearly always	1
more than half the time	2
less than half the time	3
hardly ever	4

2.2f Did you ever fall into the dipping bath? *(circle one option*

no	1
once	2
more than once	3

(record number of times).

2.3 Work with Concentrate

The next questions are about work with concentrate, by which we mean the sheep dip when it is not diluted by water.

2.3a How often were you the person who poured out the concentrate or added it to the bath? *(circle one option)*

nearly always	1
more than half the time	2
less than half the time	3
hardly ever	4
never	5

☞ *If 'never' go on to next job, otherwise continue*

2.3b How often did you wear gloves whilst pouring out the concentrate or adding it to the bath? *(circle one option)*

nearly always	1
more than half the time	2
less than half the time	3
hardly ever	4

2.3c Did you ever spill concentrate on yourself? *(circle one option)*

no	1
once	2
two or three times	3
more than three times	4

Exposure History Questionnaire Part 3
IOM (18/11/96)

Farm and Individuals code numbers | | | | | |

3.1 Compounds used for dipping

Which sheep dips do you remember working with? *record name(s) or "don't know"*

Name given by subject	Code

3.2 Over your working life have you ever used sheep dips for anything other than dipping? eg. Direct application to infested sheep, in sheep showers, etc.

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.3 Over your **working life** how often did you carry out the following:

3.3a Treatment of warble fly on cattle? *(circle one option)*

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.3b Application of insecticides to arable, fodder crops or grassland? *(circle one option)*

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.3c Treatment of stored grain or grain storage buildings? *(circle one option)*

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.3d Any other work with insecticides on farms?

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.4 Have you used insecticides in your garden? *(circle one option)*

at least twice a year on average 1
less than twice a year on average 2
did not carry out this task 3

3.5 Have insecticides been used within your home by anyone eg timber treatment, lice or insect infestation, or pet care? *(circle one option)*

Yes 1
No 2

APPENDIX 2

Exposure history questionnaire and protocol - Low exposure groups

Exposure history questionnaire - Instructions for interviewers
Non-Sheep farm personnel

INTRODUCTION

This questionnaire has been designed for use in the second phase of the project, the epidemiological field survey, and will be used in conjunction with a neurological symptom questionnaire. The purpose of the questionnaire is to obtain exposure history information from groups of workers who are considered to have low exposure to organophosphate pesticides. The groups chosen, to act as a comparison for sheep farm personnel, will be ceramics workers, pig and chicken farmers.

GENERAL INSTRUCTIONS

The subject's personal details should be recorded prior to administering the questionnaire. Factory or farm code and subject code as defined by the survey planner should be entered initially. After the personal details have been recorded and before starting to ask questions, the interviewer should instruct the subject that the majority of questions offer a number of specific answer options. The actual printed wording should be used for each question, and the alternative answer options offered to the subject. The option chosen will be recorded in the format provided on the questionnaire. Repeating the question can be helpful where the subject appears unsure about the response required. In certain cases additional explanatory information is provided within the protocol.

Part 1
Part 1 should be completed for all subjects. This section is used to confirm low-exposure status.
If a subject has done more than 3 days sheep dipping in a working life, do not proceed with parts 1 or 2. Otherwise continue.

Part 2
The interviewer should ask about each job in the subject's working life starting with their current job and going back through time. Part time jobs should be included. Each job should be allocated a number in sequence, which is recorded in the box marked `sequence'. Consecutive casual jobs may be summarised under a single entry of `various casual'.

Only a single part 3 should be completed for the whole of working life.

The questionnaire has been designed to facilitate transfer of data to a computer. Where a number of answer options are available the appropriate answer should be circled or ticked as indicated.

COMMENTS ON INDIVIDUAL QUESTIONS

Part 1
0. Identifying the subject

a. Factory or farm code Insert the number that has been assigned. Each box should be filled e.g. code 342 should be recorded as 0342.
b. Individual's name and code Insert the individual's name and corresponding code number. At some sites father and son may have the same name, under these circumstances record senior and junior as appropriate.
c. Male or female Insert M or F in space provided.
d. Date of Birth Each box should be filled e.g. 7 August 1952 should be recorded as 070852.
e. Date of Survey Each box should be filled as described above.

1. Confirmation of low-exposure status

1.1 Have you ever been involved in sheep dipping during your working life?
Include time helping on neighbours farms. Enter Y or N in appropriate box.
If `No' go onto Part 2, if `Yes' continue.

1.2 How many days in total did you dip sheep?
In order to help the subject make this calculation a box is provided, which allows the interviewer to tally the number of days over the subject's working life.
If the subject has more than 3 days dipping in working life, **terminate interview**. Otherwise continue.

Part 2 - Occupational history

Write down the factory or farm code, and the sequence number assigned to the individual.
Following the preamble, the interviewer should start with the current or most recent job first, then proceeding back in time to obtain details of previous jobs.

Ask the following questions, and record answers on the form. Use as many continuation sheets for Part 2 as are required.

2.1 When did you start your current job? (OR When did you start that job?)
Where possible record information as `month and year', or accept year only if the subject is unable to remember the exact month.

2.2 When did you leave the job?
Omit the question if current job. Record month and year.

2.3 Who was your employer?
Employers may include both non-farming and farming organisations. For farming jobs the employer may be the farm owner or tenant.

2.4 What was your employers business?
Record the main activity or type of production carried out by the employer.

2.5 What was your job title?
Record the main activity or job title of the subject during this period of employment.

2.6 Did you work with any of the following during this job?

Vibrating equipment	e.g.	driving tractors, use of chain saws, pneumatic drills
Lead	e.g.	chipping/burning lead-painted surfaces, pigments, battery manufacture
Solvents	e.g.	thinners, degreasers, varnishes
Insecticides	e.g.	any job where organophosphates may have been used for pest control

Enter Y or N in the appropriate box.

2.7 Did you have a previous full time job?
If `Yes' return to question 2.1 and record details of previous job.

Part 3 - Pesticides other than sheep dip

The following questions cover other possible situations where individuals may have been exposed to organophosphate pesticides and include:

Question 3.1a - Treatment of warble fly on cattle
Question 3.1b - Treatment of arable, fodder crops or grass-land
Question 3.1c - Treatment of stored grain or grain storage buildings
Question 3.1d - Any other work on farms which involved the use of pesticides
Question 3.2 - Use of pesticides in your garden
For each of questions record the frequency of the event, by circling the appropriate answer option.

Question 3.3 - Pesticide use in the home
Ask whether pesticides have been use by anyone else in the home, for example timber treatment. Circle the appropriate answer as `yes' or `no'.

Exposure History Questionnaire

Ceramics Workers

Part 1

IOM (18/10/96)

0. Identification

Factory code number — CF [|]

Individual's name and code [ ] [| |]

Sex — *M/F* [ ]

Date of Birth — *DDMMYY* [| |]

Date of Survey — *DDMMYY* [| |]

1. Confirmation of low-exposure status

<u>Interviewer's Introduction</u>

This questionnaire has been designed to gather information about the jobs you have done. In particular, whether you have done any work with animals. Please answer the questions as best you can. If you cannot remember a piece of information just say so.

1.1 Have you ever been involved in sheep dipping during your working life?
Please include any time you helped out on a friend or relatives farm. *(Y/N)* [ ]

If no go on to Part 2, if yes continue.

1.2 How many days in total did you dip sheep?

Start MMYY	End MMYY	Dip days in year

TOTAL [ ]

If more than 3 days dipping in working life then ***terminate interview****, otherwise continue.*

Exposure History Questionnaire Part 2
Ceramics Workers
IOM (17/10/96)

Factory and Individuals code numbers | CF | |

I am going to ask you some questions about the kind of jobs you have held, starting with your present job and going back through time.

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	

Job Start MMYY	Job End MMYY	Vibration	
Employers Name	Employers Business	Lead	
		Solvents	
Job Title		Insecticides	

Exposure History Questionnaire Part 3
Ceramics Workers
IOM (18/10/96)

Factory and Individuals code numbers | C F | | | | |

3.1 Over your **working life** how often did you carry out the following:

3.1a Treatment of warble fly on cattle? *(circle one option)*

at least twice a year on average	1
less than twice a year on average	2
did not carry out this task	3

3.1b Application of insecticides to arable, fodder crops or grassland? *(circle one option)*

at least twice a year on average	1
less than twice a year on average	2
did not carry out this task	3

3.1c Treatment of stored grain or grain storage buildings? *(circle one option)*

at least twice a year on average	1
less than twice a year on average	2
did not carry out this task	3

3.1d Any other work with insecticides on farms?

at least twice a year on average	1
less than twice a year on average	2
did not carry out this task	3

3.2 Have you used insecticides in your garden? *(circle one option)*

at least twice a year on average	1
less than twice a year on average	2
did not carry out this task	3

3.3 Have insecticides been used within your home by anyone eg timber treatment, lice or insect infestation, or pet care? *(circle one option)*

Yes	1
No	2

Appendix 3

Neuropathy questionnaire

Neuropathy Symptoms Questionnaire

Preliminary Information

0.1 Site number.

0.2 Date of survey (ddmmyy)

0.3 Subject's Name and Code

Surname	Forenames	Code

0.4 Other Information

Date of Birth

Gender M / F

Height m

Weight kg

Are you right or left handed ? *(which hand do you write with)* R/L

Do you eat meat, poultry or fish? Y/N

Use of vibrating equipment

0.5 Does your work regularly involve the use of the following equipment?

	Hours/day	Years in job
Chain saws/ wood work machines		
Power hammers/percussive drills		
Grinding and rotary tools		
Riveting tools		
Fork lift driving		
Tractor/ quad bike driving		

Hobbies:

0.6 Do you take part in any of the following at least once per week?

	Hours/week
Motorcycling or Mountain biking	
Wood working	
Vehicle maintenance	

Highest level of education

0.7 What was the highest qualification you obtained at school or college? (*tick one box*)

No certificates	
O-level/standard grade	
A-level/Highers	
College/University	

Scored symptoms

Muscle weakness

I am going to ask you questions about any weakness in your muscles. Weakness means loss of power or strength right from the beginning of attempting to do something. It should not be confused with fatigue or tiredness. (*Fatigue is used to describe inability to sustain muscle activity which initially was of normal strength*).

Hands:

		Yes	No
1a	**Do you have a muscle weakness in the hands?**	☐	☐
	(*Have you noticed any difficulty with the strength of your hand grip?*)		
1b	Do you have difficulty unscrewing tops of jars due to finger or hand weakness?	☐	☐
1c	Do you have difficulty buttoning or unbuttoning shirts/clothes?	☐	☐
	If yes to any above:		
1d	Do you have difficulty with weakness in both hands?	☐	☐
1e	Have the problems been there for the last month?	☐	☐
1f	How long have you had this weakness? [in months]	____	
1g	Do you have pain in the hands?	☐	☐
	If yes,		
1h	Do you think your weakness is caused by the pain alone?	☐	☐

Shoulders:

		Yes	No
2a	**Do you have a muscle weakness in the upper arms or shoulders?**	☐	☐
2b	Do you have difficulty lifting your arms to reach objects on high shelves?	☐	☐
2c	Do you have difficulty brushing your hair?	☐	☐
2d	Do you have difficulty putting on your jacket?	☐	☐
	If yes to any above:		
2e	Do you have difficulty with weakness on both sides?	☐	☐
2f	Have the problems been there for the last month?	☐	☐
2g	How long have you had this weakness? [in months]	____	
2h	Do you have pain in the arms or shoulders?	☐	☐
	If yes,		
2i	Do you think your weakness is caused by the pain alone?	☐	☐

Feet:

		Yes	No
3a	**Do you have muscle weakness in the toes or feet?**	☐	☐
3b	Are you unable to walk on tiptoes ?	☐	☐
3c	Are you unable to walk on your heels ?	☐	☐
	If yes to any above:		
3d	Do you have difficulty with weakness in both feet?	☐	☐
3e	Have the problems been there for the last month?	☐	☐
3f	How long have you had this weakness? [in months]	____	
3g	Do you have pain in the feet?	☐	☐
	If yes,		
3h	Do you think your weakness is caused by the pain alone?	☐	☐

Legs/hips:

		Yes	No
4a	**Do you have a muscle weakness in the legs or hips?**	☐	☐
4b	Do you have difficulty in climbing stairs?	☐	☐
4c	Do you have difficulty in rising from a low chair?	☐	☐
4d	Do you have difficulty in getting into or out of a bath without help because of muscle weakness (not because of loss of balance or pain) ?	☐	☐
	If yes to any above:		
4e	Do you have difficulty with weakness on both sides?	☐	☐
4f	Have the problems been there for the last month?	☐	☐
4g	How long have you had this weakness? [in months]	____	
4h	Do you have pain in the legs or hips?	☐	☐
	If yes,		
4i	Do you think your weakness is caused by the pain alone?	☐	☐

Negative sensory symptoms

I am going to ask you about numbness which you might call loss of feeling, insensitivity or deadness. I will start with the hands.

Hands:

		Yes	No
5a	**Do you have numbness of the hands?**	☐	☐
5b	**Do have you difficulty feeling objects with your hands?**	☐	☐
5c	**Are you unable to distinguish hot from cold water with your hands?**	☐	☐
	If yes to any above:		
5d	Do any of these occur only occasionally and only last a few minutes?	☐	☐
5e	Do you have this problem in both hands?	☐	☐
5f	Have the problems been there for the last month?	☐	☐
5g	How long have you had this abnormal sensation? [in months]	____	
5h	Are any of the problems associated with discomfort or pain?	☐	☐
5i	Do any of the problems extend up the forearm?	☐	☐

I am now going to ask you about numbness or what you might call loss of feeling, insensitivity or deadness affecting your feet.

	Feet:	Yes	No
6a	**Do you have numbness of the feet?**	☐	☐
6b	**Are you unable to feel your feet or the ground when walking?**	☐	☐
6c	**Are you unable to distinguish hot from cold when taking a bath?**	☐	☐
	If yes to any above:		
6d	Do any of these occur only occasionally and only last a few minutes ?	☐	☐
6e	Do you have this problem in both feet?	☐	☐
6f	Have the problems been there for the last month?	☐	☐
6g	How long have you had this abnormal sensation? [in months]	____	
6h	Are any of the problems associated with discomfort or pain?	☐	☐
6i	Do any of the problems extend up the leg?	☐	☐

Positive sensory symptoms

I am going to ask you about any pain or other peculiar or unusual sensations you might have. I will start with the hands.

	Hands:	Yes	No
7a	**Do you have "burning discomfort" in the hands?**	☐	☐
7b	**Do you have prickling sensation in the hands?**	☐	☐
7c	**Do you have pins and needles or tingling in the hands?**	☐	☐
7d	**Do you have spontaneous pain in the hands (jabbing, stabbing, burning, dull, sharp,toothache-like)?**	☐	☐
7e	**Do you have painful unpleasant sensations in the hands for example when touching nonpainful things?**	☐	☐
7f	*if yes*, is the pain continuous rather than occurring intermittently?	☐	☐
7g	*if intermittent*, how long do the attacks last? [in hours]	____	
7h	**I am going to read out a list of types of pain or other strange sensations you may have in your hands: Please say yes to any that apply to you.**	☐	☐

(Operator: Please circle the symptoms present)

jabbing or stabbing pain	tingling/prickling	aching or hurting
burning/excessively warm	excessively cold	tight/tightly wrapped
too sensitive	pain	

If yes to any of the above (a-h) :

		Yes	No
7i	Do any of these problems occur only occasionally and only last a few minutes ?	☐	☐
7j	Do you have the problems in both hands?	☐	☐
7k	Have the problems been there for the last month?	☐	☐
7l	How long have you had this type of discomfort [in months]?	____	

Feet:

		Yes	No
8a	**Do you have "burning discomfort" in the feet?**	☐	☐
8b	**Do you have prickling sensation in the feet?**	☐	☐
8c	**Do you have pins and needles or tingling in the feet?**	☐	☐
8d	**Do you have spontaneous pain in the feet (jabbing, stabbing, burning, dull, sharp,toothache-like)?**	☐	☐
8e	**Do you have painful unpleasant sensations in the feet for example when touching nonpainful things?**	☐	☐
8f	*if yes*, is the pain continuous rather than occuring in attacks?	☐	☐
8g	*if attacks*, how long do they last? [in hours]	______	

8h **I am going to read out a list of types of pain or other strange sensations you may have in your feet: Please say yes to any that apply to you.** ☐ ☐

(Operator: Please circle the symptoms present)

jabbing or stabbing pain	tingling/prickling	aching or hurting
burning/excessively warm	excessively cold	tight/tightly wrapped
too sensitive	pain	

If yes to any of the above (8a-h) :

		Yes	No
8i	Do any of these problems occur only occasionally and only last a few minutes at a time?	☐	☐
8j	Do you have the problems in both legs?	☐	☐
8k	Have the problems been there for the last month?	☐	☐
8l	How long have you had this type of discomfort [in months]?	______	

Autonomic

I am going to ask you a number of questions; some may be difficult or embarassing to answer. They include questions about bowel, bladder and sexual function. They are important and I would be grateful if you can answer them. If you feel some are too private then you can say that you prefer not to answer.

Postural hypotension/fainting:

First some questions about fainting or light headedness.

		Yes	No
9a	**Do you feel light headed when you suddenly change your position** (from lying to sitting position or from lying/sitting position to standing)	☐	☐
9b	**Do you faint when you suddenly change your position** (from lying to sitting position or from lying/sitting position to standing)	☐	☐
	If yes to any of the above:		
9c	Has the problem been there for the last month?	☐	☐
9d	Have you fainted/felt light headed more than once during the last year?	☐	☐
9e	Often while standing?	☐	☐
9f	Often while seated?	☐	☐
9g	Often while lying?	☐	☐
9h	How often [number of times per week]?	______	
9i	How long have you had these attacks of fainting/light headedness [in months] ______		

Night diarrhoea

Now some questions about diarrhoea (passing watery or loose stool).

		Yes	No
10a	**Do you have night diarrhoea?**	☐	☐
	If yes to the above:		
10b	Has the problem been there for the last month?	☐	☐
10c	Does this occur frequently (every night)?	☐	☐
10d	How many nights during the week?	____	
10e	How long have you had this problem? [in months]	____	

Loss of urinary control

Now some questions about water works/bladder function.

		Yes	No
11a	**Do you have loss of control of bladder function?** (Alternative question: Do you have a problem with your water works?)	☐	☐
	If yes to the above:		
11b	Has the problem been there for the last month?	☐	☐
11c	*(For females)* Does the problem only occur when you cough, sneeze, strain or push?	☐	☐
11d	How long have you had this problem [in months]	____	
11e	Can you feel yourself passing urine?	☐	☐
11f	Can you feel when wiping yourself?	☐	☐
11g	Do you leak without knowing it?	☐	☐
11h	Do you feel your bladder is empty after you have passed urine?	☐	☐
11i	Do you have difficulty starting to pass urine?	☐	☐
11j	Do you wet the bed at night?	☐	☐
11k	Can you pass or hold urine when you want to ?	☐	☐

Impotence

Now some questions about sexual function. If you find these too embarassing, you can fill in the answers yourself on the questionnaire.

		Yes	No
12a	***(For males)* Are you unable to have an erection of the penis?**	☐	☐
12b	***(For males)* Are you unable to ejaculate or come** (emission of fluid with sexual climax)?	☐	☐
12c	**Do you have loss of sexual desire?**	☐	☐
	If yes to any of the above:		
12d	Has the problem been there for the last month?	☐	☐
12e	How long have you had this problem [in months]	____	

Sweating

Now some question about sweating.

		Yes	No
13a	**Have you noticed lack of sweating in your hands?**	☐	☐
13b	**Have you noticed lack of sweating in your feet?**	☐	☐
13c	**Do you feel you overheat because you sweat insufficiently?**	☐	☐
13d	**Do you sweat too much in your hands?**	☐	☐
13e	**Do you sweat too much in your feet?**	☐	☐
	If yes to any of the above:		
13f	Do you have this problem on both sides	☐	☐
13g	Has the problem been there for the last month?	☐	☐
13h	How long have you had this problem [in months]	____	

Other information

		Yes	No
14.	**Do you have to stop for breath when walking at your own pace on level ground ?**	☐	☐
15a.	**Do you smoke?**	☐	☐
	If yes,		
	How many manufactured cigarettes/cigars do you smoke each day?	____	
	How many ounces of tobbaco do you smoke each week? *Pipe/ roll-ups*	____	
	If no,		
15b.	**Have you ever smoked?**	☐	☐
	If yes, in what year did you stop	____	
16.	**Do you drink alcohol?**	☐	☐
	If yes, number of pints beer or lager /week	____	
	number of glasses wine or spirits / week	____	

		Yes	No
17.	**Are you on medication?**	☐	☐

If yes, please complete below

name of medication	*size of tablet (mg)*	*number of tablets/day*	*since which date*
____	____	____	____
____	____	____	____
____	____	____	____
____	____	____	____

	Yes	No
18. Does anyone in your family have muscle weakness or sensory loss?	☐	☐

19. Do any of your relatives have excessively high arches of the feet with or without curled toes? ☐ ☐

If yes, which of the following are affected? (Operator: please circle)

grandparents, uncles or aunts, parents, brothers or sisters, children, nephews or nieces, grandchildren

	Yes	No
20. Has a Doctor ever told you that you have a neurological disease?	☐	☐

If yes, please complete:
Name of disease: ______________________
Duration: ______________________

	Hospital	GP
21. Who diagnosed the condition?	☐	☐

	Yes	No
22. Do you have any other disease?	☐	☐

If yes, please complete:

	Type	Duration
Diabetes	______	______
Thyroid	______	______
Other	______	______

	Yes	No
23.a Have you ever been unable to carry out your work activities because you felt unwell after dipping?	☐	☐
b Have you ever been admitted to hospital as a result of work with organophosphate sheep dips?	☐	☐

Appendix 4

Protocol for neuropathy questionnaire

Protocol for the completion of the neuropathy symptoms questionnaire and for performing the thermal and vibration sensory tests.

INTRODUCTION

The diagnosis of neuropathy is based on symptoms and other features of clinical history, together with quantitative neurophysiological tests.. The purpose of the questionnaire is to obtain information about the presence or absence of a neuropathy. Since the nervous system is complex and has many different functions, a number of different sites and functions are investigated.

This questionnaire has been designed to be administered in the field by a non-neurologist after training and is based on a questionnaire developed at the Mayo Clinic in Rochester, Minnesota, USA. The sensory tests have been chosen for their high sensitivity and specificity and their suitability of use by a non-clinician after training. They are also portable and are therefore easily performed outside the hospital clinic. The neuropathy symptoms questionnaire and the sensory tests will be used in the second phase of the project, the epidemiological field survey.

GENERAL INSTRUCTIONS

The surface temperature of the subject's foot should be measured at the start of the assessment. If the temperature is below 31°C, the foot must be heated (e.g. in warm water) whilst completing the questionnaire. This will ensure reliable results for the sensory tests, and avoid unnecessary delays between subjects.

The subject's personal details together with details of his/her use of vibrating equipment, participation in certain hobbies and education should be recorded prior to administering the questionnaire. The subject should be informed that the majority of questions require a simple "yes" or "no" answer. The actual printed words should be used for each question. The questionnaire is divided into sections, each with a preamble to introduce the subject to the kind of questions that will be asked.

Questions about a specific symptom at a specific site consist of a main question followed by explanations or one or more subsidiary questions giving a different manifestation of the same symptom. If the answer to all of these questions is "no" go on to the next site/symptom. If the answer to any of these questions is "yes", further questions are asked to exclude :

1) temporary disabilities from which most people suffer some time or other during their life without having neuropathy (e.g. pin and needles in the hand after lying on the arm) or,
2) asymmetrical symptoms which are unlikely in a toxic neuropathy, of the type which may be associated with exposure to organo-phosphates.

When after repetition of a question or a brief explanation, doubt remains whether the answer is "yes" or "no", the answer should be recorded as "no".

After completion of the questionnaire the sensory tests are performed. The tests should take place in a quiet, warm room with subject seated in a comfortable chair. The right foot should rest on a low stool or similar with padded surface. The surface temperature of the foot should be measured and if below 31 °C, the foot must he heated (e.g. in warm water). The thermal sensation test is then performed followed by the vibration sensation test according to instructions given later in this protocol.

RECORDING THE REPLIES TO THE QUESTIONS

The questionnaire has been set out to facilitate transfer of data to computer. Most questions are of the yes/no type and replies to these question should be recorded as ticks in the appropriate box. Where the answer to the question is a number, e.g. How long have you had this weakness? [in months] the number should be recorded directly in the boxes provided. Where the question are of a more open type e.g. name of medication, the reply should be recorded in full and coding will be assigned later.

The results of the sensory test should be entered on the special *Sensory Test Record Sheet.*

General information

Site number Insert the number that has been assigned to this site. Each box should be filled e.g. code 342 should be recorded as 0342.

Date of survey Each box should be filled e.g. 1st November 1996 should be recorded as 011196.

Subject's name and code number insert the subject's name and corresponding code number. At some sites father and son may have the same name, under these circumstances record senior and junior as appropriate.

Date of birth Each box should be filled e.g. 7 August 1952 should be recorded as 070852.

Gender Insert M or F in the space provided.

Height/weight Record height in metres and weight in kilogrammes.

Handedness Record which hand they write with.

Dietary information This is recorded as certain types of vitamin deficiency may result in neuropathy. Vegetarian refers to someone who refrains from eating red meat.
Please tick the relevant option.

Use of vibrating equipment Regular exposure to vibration may result in nerve damage, the symptoms of which may be confused with symptoms occurring as a result of neuropathy.

Regular use of vibrating equipment involves the use of the type of equipment listed for periods greater than one hour on most working days. If possible, record the average number of hours per day in their current job that the equipment is used, and the number of years they have spent in that job.

Hobbies The hobbies listed may expose individuals to vibration. Where individuals take part in these hobbies, please write down the average number of hours per week spent on the hobby.

Educational attainment This information may be useful when interpreting results of the questionnaire. Please place a tick against the relevant category.

COMMENTS ON SECTIONS OR INDIVIDUAL QUESTIONS

N.B. For all relevant sections, if the reply to "How long have you had this ....?" is less than one full month, record a zero.
The notes in the 'general instructions' section should be referred to when completing the 'scored symptoms' section of the questionnaire.
If after repetition of a question or brief explanation, doubt remains whether the answer is 'yes' or 'no', the answer should be recorded as 'no'.

Muscle weakness (sections 1, 2, 3 & 4)

The preamble is used to make sure that the subject understands what is meant by weakness.
The questions are designed to consider weakness occurring in both upper and lower limbs, to establish how long the weakness has been present and to distinguish weakness associated with neuropathy caused by painful conditions, such as arthritis.

The two or three additional questions following question (a) in each section give examples of the type of problem which might be noticed due to weakness in that specific part of the body, and help the subject to understand the information which is being sought.

Section 3a: muscle weakness in toes or feet Examples of this problem are given in questions 3b and c. In question 3c 'walking on heels' may be something that the subject has not tried before, and it is reasonable for them to test this ability at the time of the assessment.

Negative sensory symptoms (sections 5 & 6)

This covers loss of sensation and the preamble explains the different terms that may be used to describe these symptoms.

Section 5b: difficulty feeling objects This includes being able to tell for example whether an object has sharp edges or is cold. It should be distinguished from being able to recognise what an object is by its size and shape, without looking at the object. (This ability is covered later in the questionnaire).

Section 5i: do any of the problems extend up the forearm
This question aims to identify whether subjects with 'yes' answers to questions 5a to 5c, experience similar symptoms of numbness in the forearm.

Section 6b: ability to feel your feet or the ground when walking This question seeks the same type of information as 5b. Again subjects may consciously have to think about whether they are aware of their feet being in contact with the ground when walking. People who lack this ability often describe themselves as 'walking on cotton wool'.

Positive sensory symptoms (sections 7 & 8)
This section is used to record the presence of unusual sensations.

Section 7a-c: Only record a "yes" if the subject has the specific symptom mentioned in the question. Further explanation should not be offered at this stage. Other similar symptoms may be covered in Section 7h.

Section 7d:spontaneous pain in the hands This refers to pain which is not associated with any activity, and can vary in nature from sharp to dull or burning.

Section 7e: asks about painful sensations occurring either spontaneously or when the subject performs tasks with his/her hands that should not normally be painful, for example picking up a coin or a pillow.

Section 7f and 7g: are used to characterise further a painful sensation reported by the subject in 7e.

Section 7h: Read the list of sensations to the subject, and circle only those symptoms to which the subject gives a "yes" answer. **Further explanation should not be offered for this question.**

Section 8: As section 7, but for feet.

Section 8e: An example might be touching bedclothes or a soft carpet.

Autonomic (sections 9, 10, 11, 12 & 13)

This covers the part of the nerve system that control "automatic" functions of the body over which we exert little or no voluntary control. The preamble prepares the subject for some questions which may be embarrassing. Stress the importance of obtaining answers to all questions. If the subject declines to answer, offer him/her that page of the questionnaire for self completion there and then. When page is returned insert it into the folder without scrutinising the replies. Later, the relevant sections should be marked subject-completed or reply declined as appropriate.

Section 9: Postural hypotension

This is a fall in blood pressure associated with a change in position , for example, from lying to standing or standing to sitting. Individuals may experience lightheadedness, or may faint.

If the subject answers "yes" to 9a or 9b, the subsequent questions explore how often these symptoms occur, and how long they have been present. You may offer as examples the changes in position listed.

Section 10: Night diarrhoea This is the passage of a loose or watery motion during the night, at least once a week. Any pattern associated with dietary intake or alcohol should be excluded.

Section 11a: Loss of urinary control
Ask the alternative question "Do you have problem with your water works" if the subject has difficulty understanding the information which is being sought.

Section 11c: The purpose of this question is to exclude stress incontinence which may occur in women after child birth.

Section 11e to k These questions consider specific problems associated with autonomic bladder dysfunction, and seek to exclude other conditions resulting in loss of urinary control.
Possible additional explanations are as follows:
11e. Being aware of the sensation of passing urine , not just the sound
11f. Can you feel the toilet paper moving over your skin
11g. Do you sometimes wet yourself and not know that it has happened
11h. After passing urine do you feel comfortable, as though your bladder is empty
11i. Do you have any difficulty getting started
11k. Can you wait a while or do you need to pass urine quickly when you feel you want to go.

Section 12: Sexual function The questions in this section should be handled discreetly.
Self completion by the subject is acceptable as outlined above.
Section 12a and 12b are applicable to men only.

Section 13: Sweating
These questions ask about unusual patterns of sweating, either too little or too much both in hands and feet.

Other information

Breathlessness
Section 14: The pace at which the subjects normally walks is their own walking pace.

Smoking and alcohol consumption
Section 15 and 16: Enter the average values for cigarette and alcohol consumption on a daily and weekly basis respectively.

Medication
Section 17: The subject should have had prior warning that information about medication will be asked. Please record details given by subject or from medicine containers the subject might bring along. If any detail is not known, leave the corresponding section blank.

Family history
Section 18: Record "don't know "responses as "no". If necessary repeat the explanations: muscle weakness means loss of power or strength right from the beginning of attempting to do something. Sensory loss refers to numbness, loss of feeling or deadness.

Section 19: This question seeks information about a specific neurological condition which may be associated with neuropathy. If the answer is "yes" to main question read the categories of relatives to the subject.

Relevant medical history
Section 20: Multiple Sclerosis (MS) and epilepsy are examples of neurological diseases.

Section21:
Ask whether the condition was diagnosed at a hospital or by the GP (family doctor).Place a tick in the appropriate box

Section 22: Enquire specifically about diabetes and thyroid disease as these may be associated with neuropathy. Make a note of other diseases for which the subject is receiving treatment.

Section 23:
These questions relate to illness which may have occurred as a result of sheep dipping.
Part (a) relates to illness occurring immediately after or within a few hours of dipping.
Part (b) relates to illness which may have occurred immediately or several weeks after dipping, but resulted in hospital admission.

SENSORY TEST

Preparation

The tests should take place in a quiet, warm room with subject seated in a comfortable chair. The right foot, after removal of sock and shoe/boot, should rest on a low stool or similar with padded surface. The dorsum (top) of the foot should be kept in a horizontal plane by supporting the foot with a bag filled with rice or sand. The surface temperature of the foot should be measured and if below 31°C, the foot must he heated (e.g. in warm water).

Please follow the summary instructions below. Text in *[italics]* indicates explanations and instructions to the subject.

Thermal sensation test

Explaining the test to the patient is absolutely crucial. The patient must fully understand the test and what is required from him/her. Otherwise the result will be unreliable.
Please take great care of the thermode. It is easily damaged if dropped onto a hard surface.

1. Make sure all connections to **Triple T** are secure. Switch on.

["I am going to test how well you are able to feel small changes in temperature using this machine. The test takes a few minutes, is completely harmless and painless but we need your constant concentration.]

2. Apply the thermode to the top of the foot
   - Thermode surface must be as horizontal as possible
   - The foot should be in a relaxed position

3. Apply the elasticated Velcro strap round thermode and foot
   1. Hold the strap tight without stretching elastic (negligible tension in strap)
   2. Pull the top part of strap so that elastic stretches by 1cm
   3. Press Velcro straps together to fasten (this procedure allows thermode to be applied with a constant and reproducible force).

4. Input patients data (while this takes place thermal equilibrium will develop between thermode and skin)

With display showing: START OR PROGRAM ? Press **P** to enter program mode
Press ← four times until display shows:
UP-DOWN TRANSFORM
2 CHANGES ↑ / ↓
Press ↑ so that 4 changes is indicated
Press **P** to exit program mode.

5. Hand the 'Patient Control Unit' to the subject.

[I am giving you this Control Unit to hold and look at during the test. There are three lights and I will explain how they are used as we go along. First you will see all three lights come on and you may feel the skin under the probe getting warm]

6. Start (press start button) which begins the test with calibration. (Before starting, make sure of thermode application and position, step 3).

   If calibration is done inappropriately, then the whole test is unreliable and excessively prolonged.
   Calibration uses a temperature change of about 2 °C. This may give an idea about whether the threshold is below or above this value.

7. Press ← button to start manual Test : The idea is to bracket the threshold between two large values.

[This time you will see light 1 come on alone] Ask subject after the light disappears if he/she could feel the probe becoming warm for a brief period.

   Spend as much time as necessary on this. Repeat several times and at least 2 - 3 times at the level that you decide to start the test at. This will be the lowest level which the subject reliably can feel.
   Level of manual stimulation can be altered by using the ↑ and ↓ keys.
   Please note that the **UDTR** (Up and Down Transform Rule) test will start at the last manual stimulation value.

[From now on the test will be slightly different. The green light will come on first to alert you to that a test is about to start. Next light 1 will go on and stay on for a short time and then go off again. After a short pause, light 2 will come on and then go out again. Last, the green light will disappear. During one of these two periods indicated by light 1 and 2 - and only during one of them - you may feel a little warmth. I would like you to tell me, when all the lights have gone off, with which one, 1 or 2, you felt this warmth. You may sometimes find difficulty in deciding because some of the temperature changes are small, but you still have to indicate a number to the best of your judgement.

You will have several such trials and at the end of each we would like you to tell us one of the two numbers you think you felt the warmth with. Please keep concentrating on the unit in your hand all the time.]

8. Press start button to proceed with the UDTR test.
   - Subject *must* answer 1 or 2
   - Subject 's reply *must* be keyed in by the OPERATOR through the keyboard
     (and not by the subject through the Patient Control Unit)

- Subject should be watched during the test and be encouraged to concentrate.

9. The test usually takes 5 - 7 minutes and if done appropriately it should NOT take more than 10 minutes.

10. The machine bleeps when the threshold is available. Write down the hot threshold value in the Sensory Test Record Sheet. You are now ready to continue with the cold threshold test.

[I will repeat the whole test but now you will feel the probe going cold instead of warm. First all three lights come on]

11. Start (press start button) which begins the cold test with calibration. (Before starting, make sure of thermode application and position, step 3).
    If calibration is done inappropriately, then the whole test is unreliable and excessively prolonged.
    Calibration uses a temperature change of about 2 °C. This may give an idea about whether the threshold is below or above this value.

12. Press ← button to start manual Test : The idea is to bracket the threshold between two large values.

[This time you will see light one come on alone] Ask subject after the light disappears if he/she could feel the probe going colder.
Spend as much time as necessary on this. Repeat several times and at least 2 - 3 times at the level that you decide to start the test at. This will be the lowest level which the subject reliably can feel.
Level of manual stimulation can be altered by using the ↑ and ↓ keys.
Please note that the UDTR test will start at the last manual stimulation value.

[Now we go back to light 1 and 2 coming on in sequence while the green light is on. Please tell me, after all the lights are off, with which one, 1 or 2, you felt the cold. Please keep concentrating on the unit in your hand all the time.]

13. Press start button to proceed with the UDTR test.
    - Subject ***must*** answer 1 or 2
    - Subject 's reply ***must*** be keyed in by the OPERATOR through the keyboard
    (and not by the subject through the Patient Control Unit)
    - Subject should be watched during the test and be encouraged to concentrate.

14. The machine bleeps when the threshold is available. Write down the cold threshold value in the Sensory Test Record Sheet.

15. Press the print key to obtain a printout. Examine the print out. Fluctuations of more than 3 levels in the proper UDTR indicate inconsistency (lack of concentration or diverted attention) and the reliability of the test may be questioned. Repeat the test if time allows.

16. Remove the thermode and **return it to a safe storage place** e.g. the instrument case

Vibration sensation test

1. Make sure all connections to the VIBRAMETER are secure. Switch the power switch at the back of the control unit to ON. On the front panel press the button marked **I** and the digital display will be illuminated.

2. Hold the vibrator in your right hand and let the probe rest on a flat surface. Press with your left hand simultaneously the two buttons marked **C** and **W** . Note that the red dot on the pressure indicator (slit display) moves to the centre. After this happens release buttons **C** and **W**.

["I am going to test how well you are able to feel small levels of vibration using this machine. The test takes a few minutes, is completely harmless and painless but we need your constant concentration.]

3. The vibration amplitude of the probe is controlled using the push buttons marked with arrows or with the thumbwheel. The ↑ button indicates increase and the ↓ button indicates decrease. A fat arrow indicates a rapid change in vibration amplitude while a thin arrow means a slower rate of change. Pressing the **H** button will hold the measured value for reading later. The **R** button toggles the full scale display range of VIBRAMETER between 39.99μm and 399.9μm.

4. As examiner, you should sit in strain free position with comfortable access to, and visual contact with both the test site and VIBRAMETER. During measurements place the probe perpendicular to the test site to provide smooth, painless contact. The test site is 1st metatarsal bone (on top of the foot in line with the big toe) of the right foot. There should be no tendons between the probe and the bone. This placement should be checked during measurement to verify that the vibrator stays in the correct position.

5. Adjust the pressure for centre indication on the VIBRAMETER pressure indicator

6. Start with no vibration and tell the subject that *[this is the feeling of the pressure from the vibrator]*. Then increase the vibration amplitude until the patient clearly feels a vibration. When these two initial sensation are defined (repeat if thought necessary) you have a coarse indication of the subjects threshold and the subject starts to be come familiar with the measurement procedure.

7. Reduce the vibration amplitude so that the subject cannot feel the vibration. Ask the subject *[please say "yes" when you feel the vibration again]* and increase the vibration amplitude at the slower rate (using the thin ↑ button). Remember the meter reading at which the subject said "yes". Now ask the subject *[please say "off" as soon as you no longer feel the vibration]* Decrease the amplitude (at the slower rate) until the subject reports "off" and remember the meter reading. Write the "yes" and "off" values into the appropriate columns on the Sensory Test Record Sheet and calculate the average of these two value and enter it in the third column.

8. Repeat the procedure in point 6 until three consecutive mean values with less than 10% variation are obtained

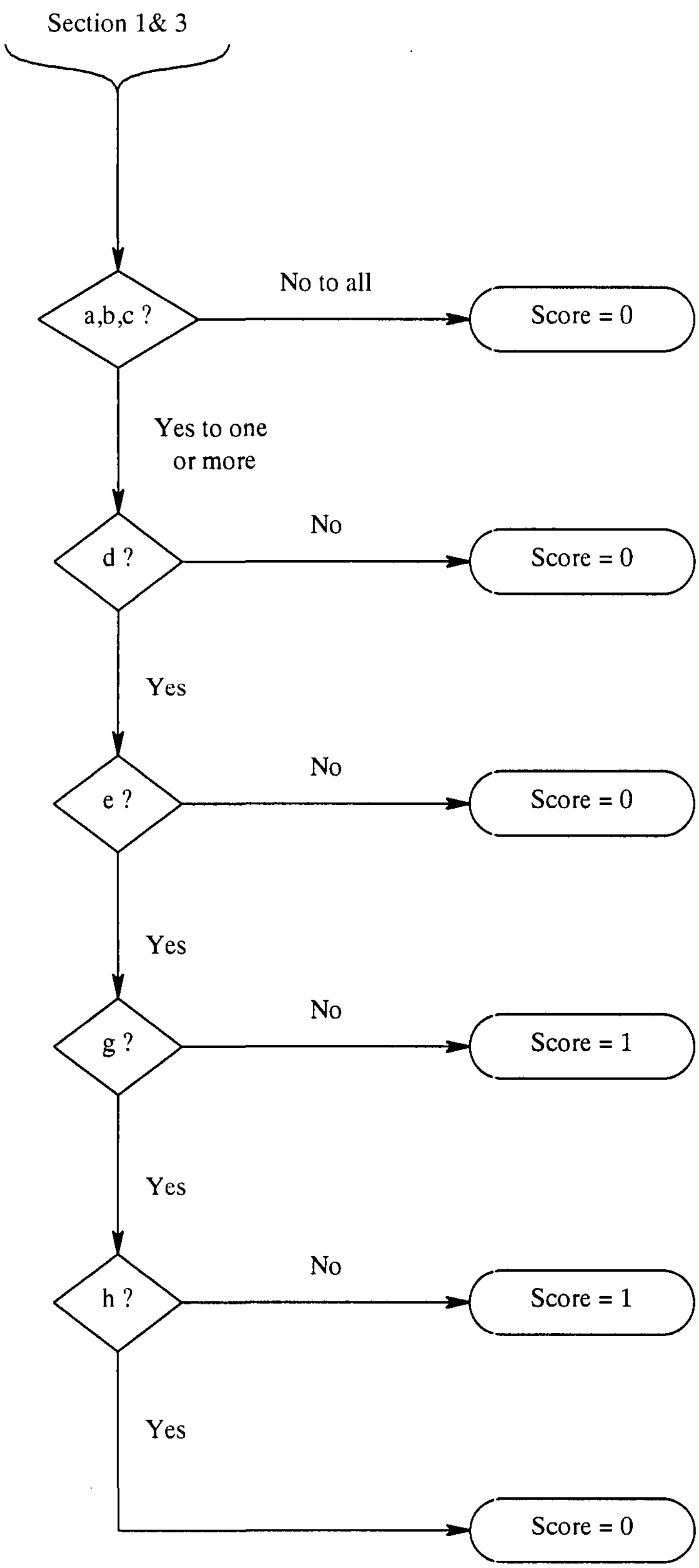
9. Enter the mean of last three mean threshold values as the Vibration Threshold on the Sensory Test Record Sheet.

Appendix 5

Neuropathy scoring system

Rules for scoring Neuropathy Questionnaire

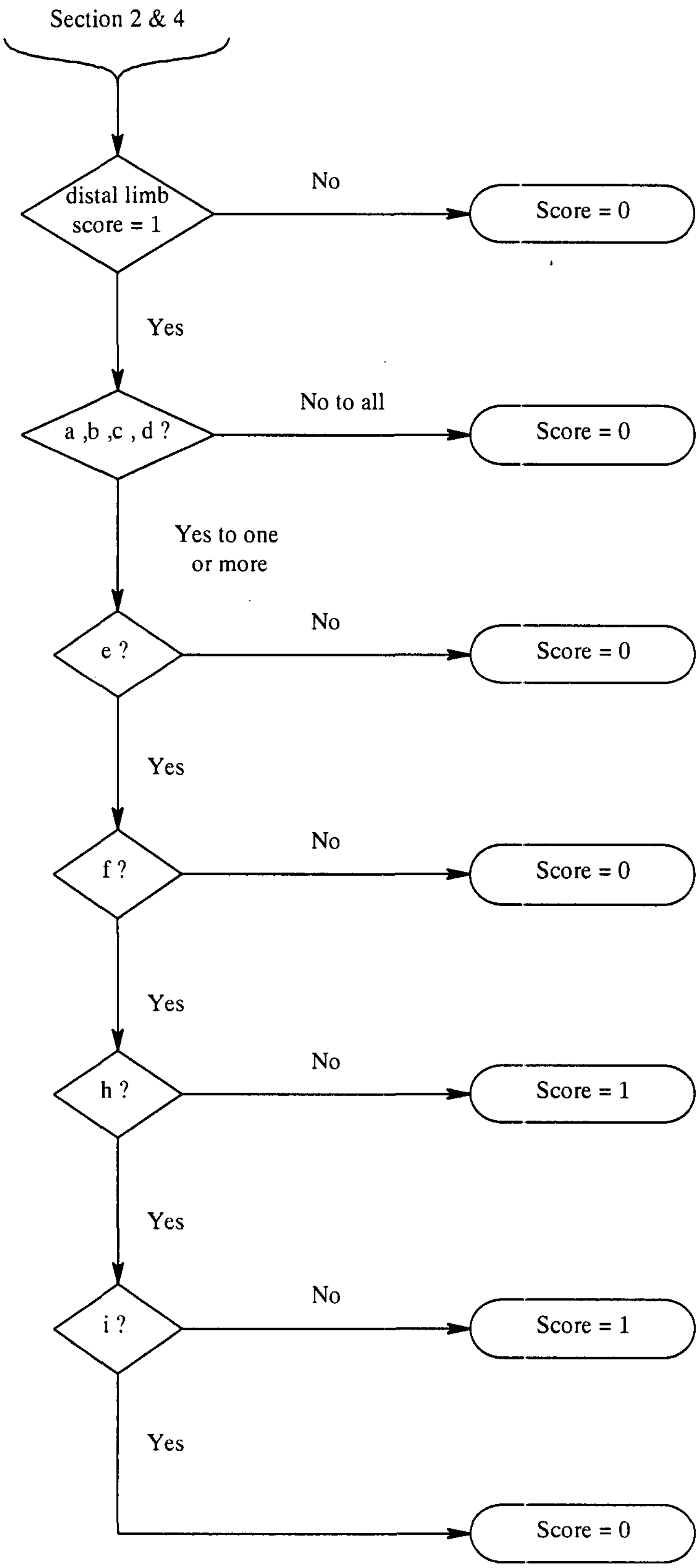
The two sections on *muscle weakness* in hands and in feet, are each scored as follows:



Question f is used for profile

Rules for scoring Neuropathy Questionnaire

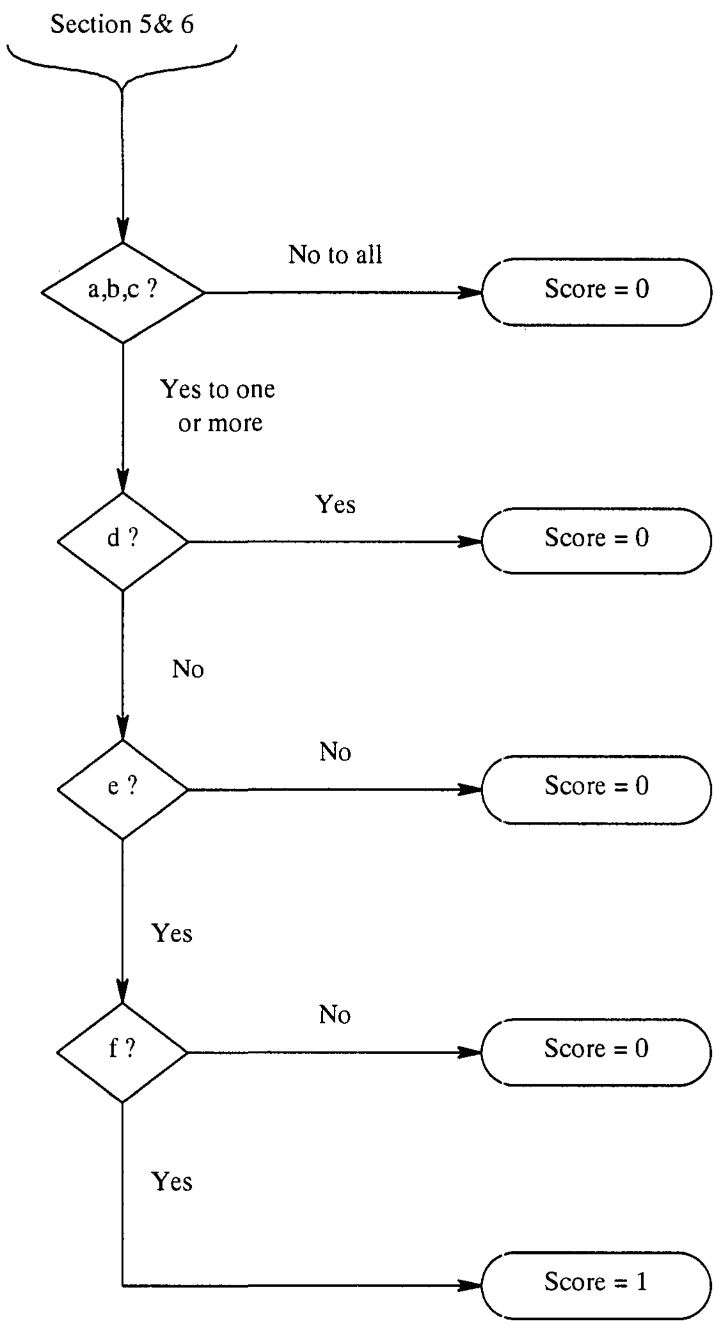
The two sections on *muscle weakness* in shoulders and in legs / hips, are each scored as follows:



Question g is used for profile

Rules for scoring Neuropathy Questionnaire

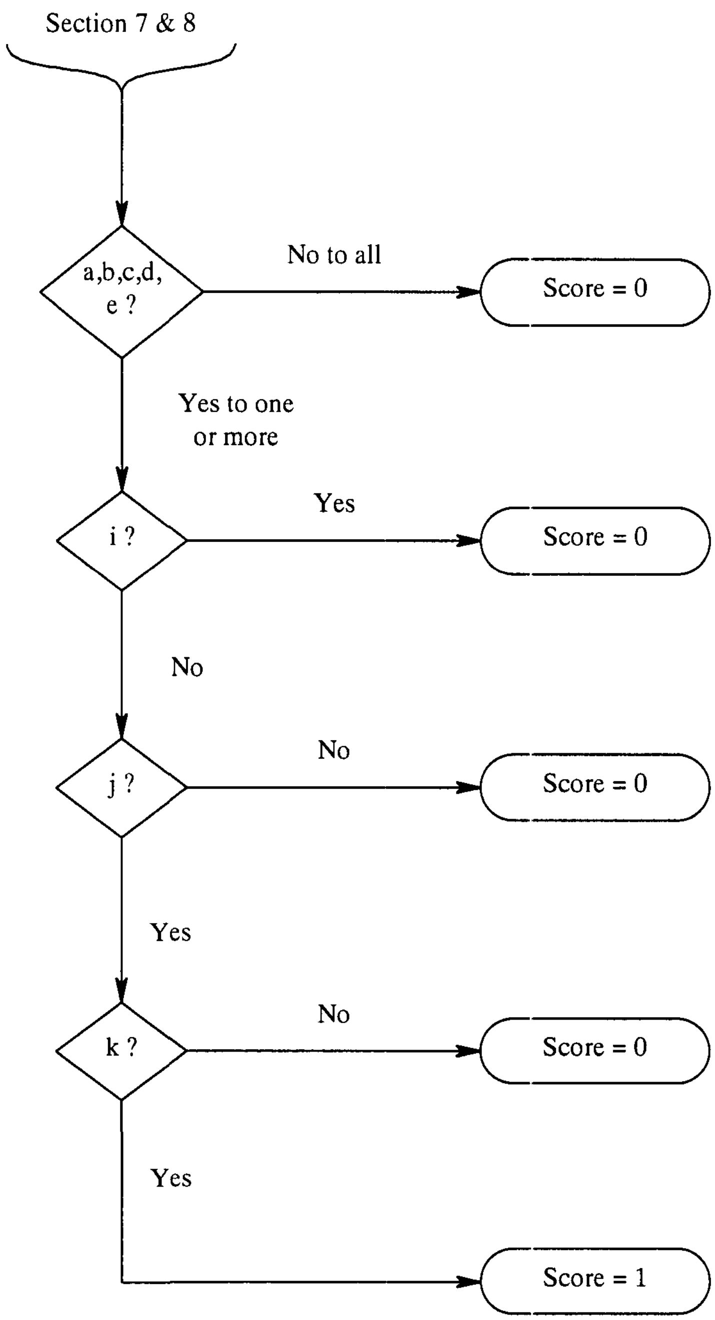
The two sections on *negative sensory symptoms* are each scored as follows:



Question g, h and I are used for profile

Rules for scoring Neuropathy Questionnaire

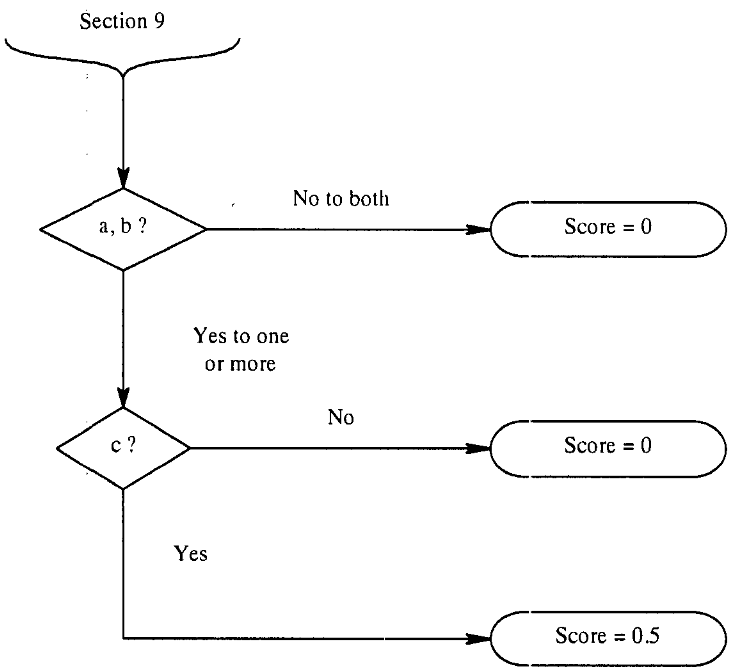
The two sections on *positive sensory symptoms* are each scored as follows:



Questions f, g, h and l are used for profile

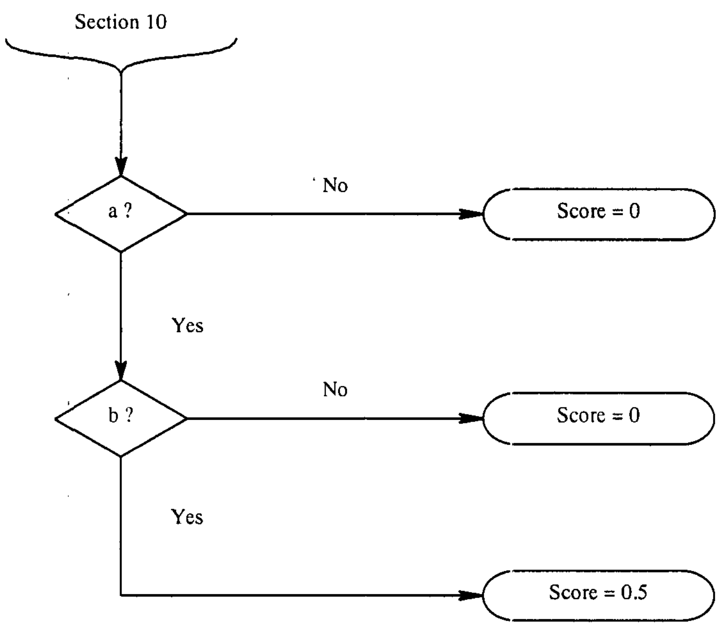
Rules for scoring Neuropathy Questionnaire

The section on *postural hypertensive / fainting* is each scored as follows:



Questions d, e, f, g, h and I are used for profile

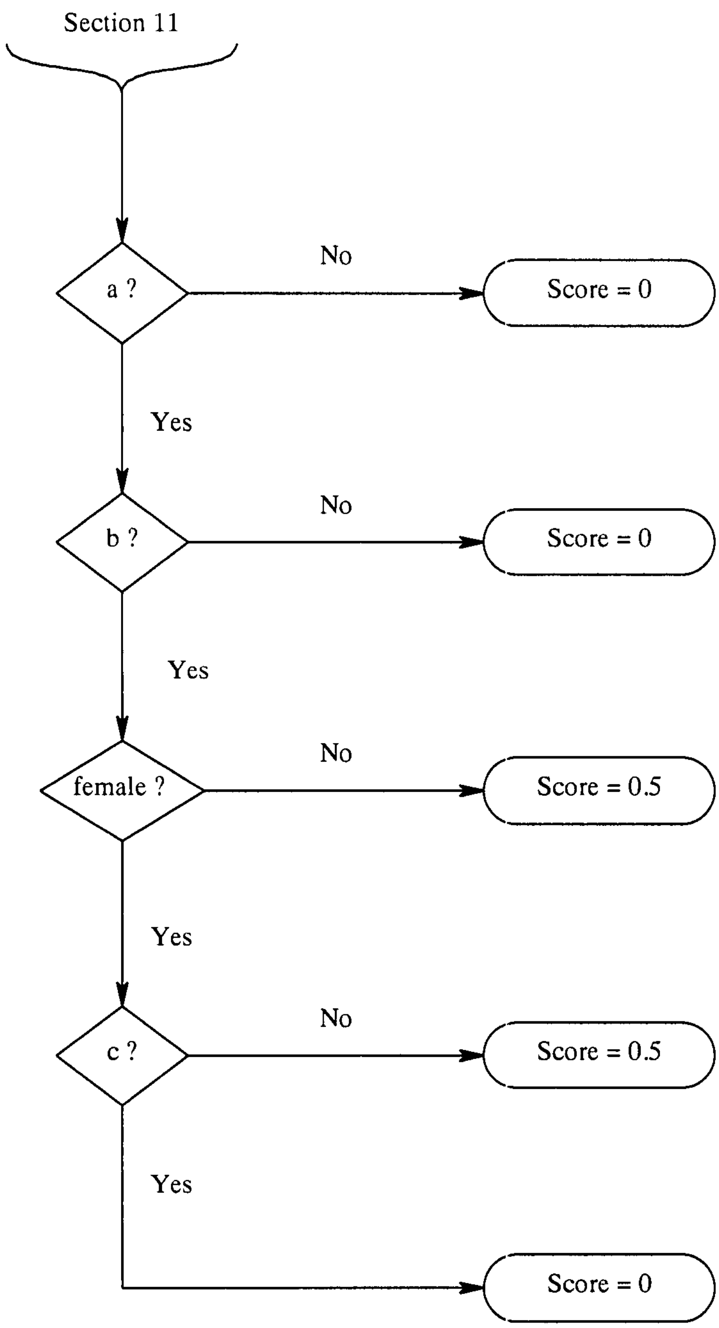
The section on *night diarrhoea* is each scored as follows:



Questions c, d and e are used for profile

Rules for scoring Neuropathy Questionnaire

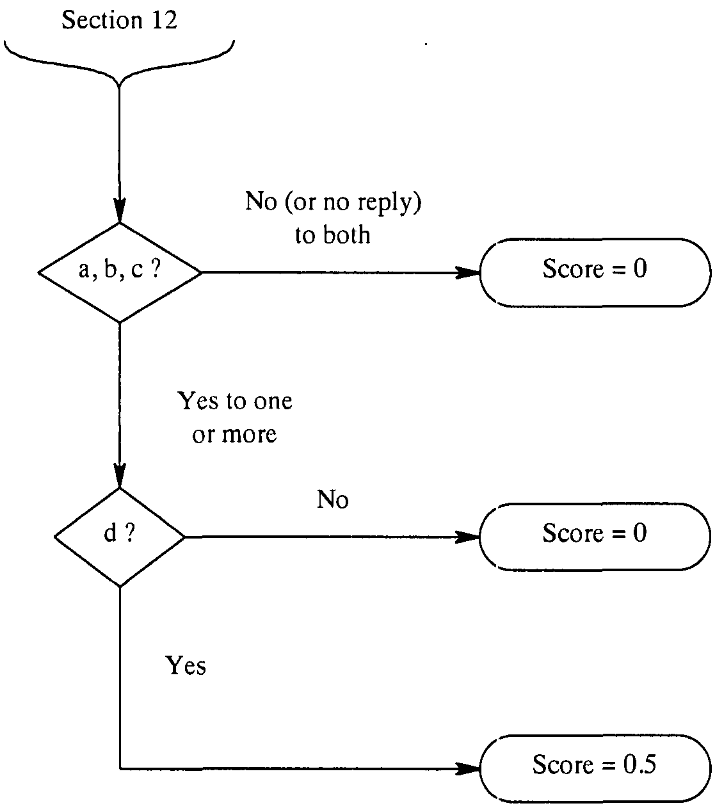
The section on *loss of urinary control* is each scored as follows:



Questions d, e, f, g, h, I, j and k are used for profile

Rules for scoring Neuropathy Questionnaire

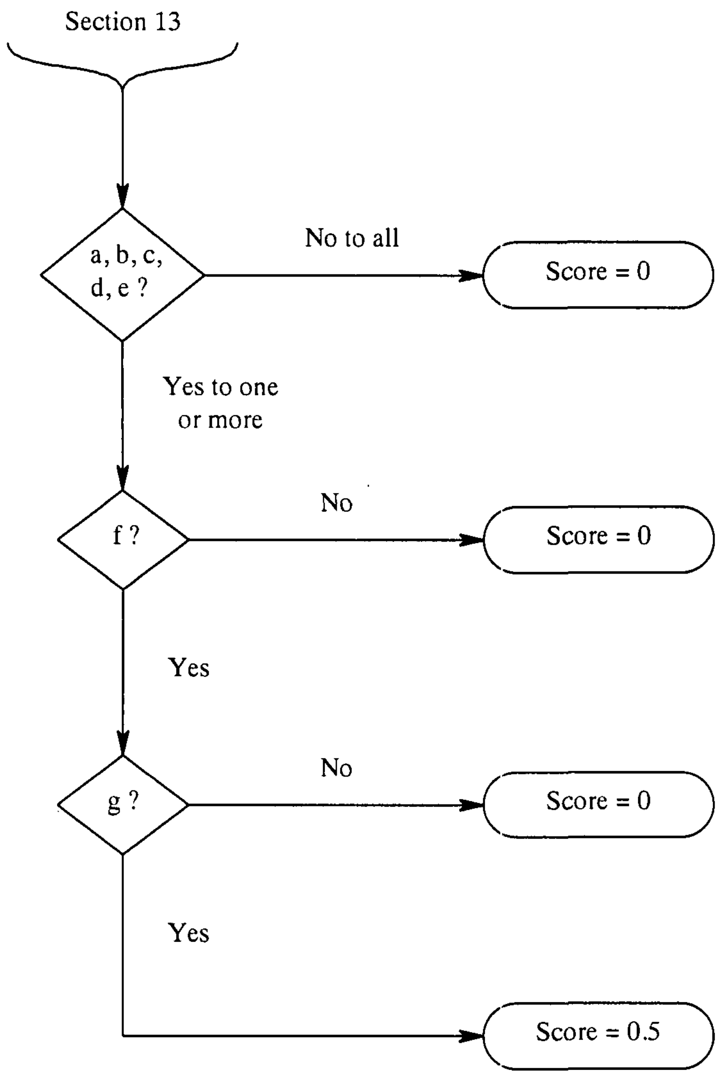
The section on *impotence* is each scored as follows:



Question e used for profile

Rules for scoring Neuropathy Questionnaire

The section on *sweating* is each scored as follows:



Question h is used for profile

Neuropathy Symptoms Scoring Sheet

0.1 Site number. [| | |]

0.2 Subject's Name and Code

Surname	Forenames	Code

Score 1, 2, & 3 by the rules in attached diagrams **SCORE**

		SCORE
1. Muscle Weakness	Hands	___
	Upper arm / shoulder	___
	Feet	___
	Legs / hips	___
2. Sensory	Negative symptoms Hand	___
	Negative symptoms Foot	___
	Positive symptoms Hand	___
	Positive symptoms Foot	___
3. Autonomic	Postural fainting / lightheadedness	___
	Nocturnal diarrhoea	___
	Loss of urinary control	___
	Impotence	___
	Sweating	___
		====
Overall Symptom Score	Sum of above scores	___

---

4. Sensory thresholds		Measured	Limit	**SCORE**
	Vibration µm	___	___	___
	Cold °C	___	___	___
	Heat °C	___	___	___
				====
Overall QST Score	Sum of above scores			___

Neuropathy Outcome

Classification	Criteria	**Outcome**
Definite neuropathy	Symptom score ≥ 2 AND QST score ≥ 1	
Probable neuropathy	Symptom score ≥ 1 AND QST score ≥ 1	
Possible neuropathy	Symptom score ≥ 1 OR QST score ≥ 1	
No neuropathy	Symptom score < 1 AND QST score = 0	

Tick highest applicable outcome

Sensory Test Record Sheet

Site Number

Subject's Name and Code

Surname / Forenames / Code

Date of Survey (ddmmyy)

Technician's Initials

Thermal Sensation Test

Instrument Serial Number

Dorsum Right Foot

Foot temperature ___ °C

Heat threshold ___ °C

Cold threshold ___ °C

Vibration Sensation Test

Instrument Serial Number

1st Metatarsal Bone, Right Foot

"Yes" Level	"off" level	test mean

Vibration threshold (*average of last three test means showing < 10% variation*) ___ µm

Appendix 6

Sensory tests - validation, choice of percentiles and graphs of threshold limits

Choice of percentiles defining abnormal tests

In all three sensory tests, a cut-off point is needed above or below which is then defined as 'abnormal'. All three tests give thresholds estimates on continuous scales, and the cut-off point chosen will determine the sensitivity and specificity of each tests.

Sensitivity in this case is defined as the probability of being `abnormal' on the test out of all those who truly have peripheral neuropathy (defined clinically), in other words, true positives. Similarly, specificity is the probability of being negative (or 'normal') out of all those who are truly not clinical cases, that is, true negative.

In the table below sensitivity = a/(a + b) x 100; while
specificity = d/(c + d) x 100.

Note that 100 - sensitivity = false negative percentage and
100 - specificity = false positive percentage.

	Test Abnormal	Test Normal	Total
Clinically a case	**a**	b	a + b
Clinically <u>not</u> a case	c	**d**	c + d

A high cut-off point will give good specificity and lower sensitivity, while a low cut-off point will give good sensitivity but reduce specificity. The cut-off point should be based on the general or 'normal' population to avoid bias.

If the prevalence of probable neuropathy is around 0.5% to 1% then it seems logical to go for a 99th percentile (this will be at the lower or upper end of the distribution depending on which side abnormality lies). However, this may be too high giving very poor specificity, so that the 95th percentile may be better.

The threshold values for all three tests increase with age so that the cut-off point will also increase with age. Figures 1 and 2 show plots of data from a sample of 68 healthy men and women aged 16 to 76 years from Glasgow for the hot and cold thermal tests. The regression line was obtained from regressing the natural logarithm of the thresholds on age, as a log linear relationship was found to be a better fit to the data than a simple linear model. The sample was composed of 47% females and 53% males, and although males had significantly higher thresholds than females, the slopes of the regression line did not differ significantly between males and females, and so only one line is presented in figures 1 and 2 (Appendix 4). The residuals from the regression model were obtained (observed values minus the fitted values) and the 95th percentile value was calculated. This constant value was added to the expected value for each age based on the regression model. Finally, the 95th percentile line and fitted line were converted back to the original scale by exponentiating these lines to give figures 1 and 2. This procedure corresponds to that given by Dyck et al (1985) to obtain percentile lines. For use in the field, tables will also be produced giving the mean threshold value for each age and the associated 95th percentile.

Normal values of the vibrameter threshold have been obtained from a sample of 110 healthy male volunteers, aged from 10 to 74 years, with no signs or symptoms of neurological diseases (Goldberg and Lindblom 1979), which is included in the vibrameter manual (Somedic IV). The plot of vibration threshold against age is shown in figure 3 and the 95th percentile inserted. A table showing the mean at each age with the associated 95 percentile limit will also be available when carrying out this test in the field.

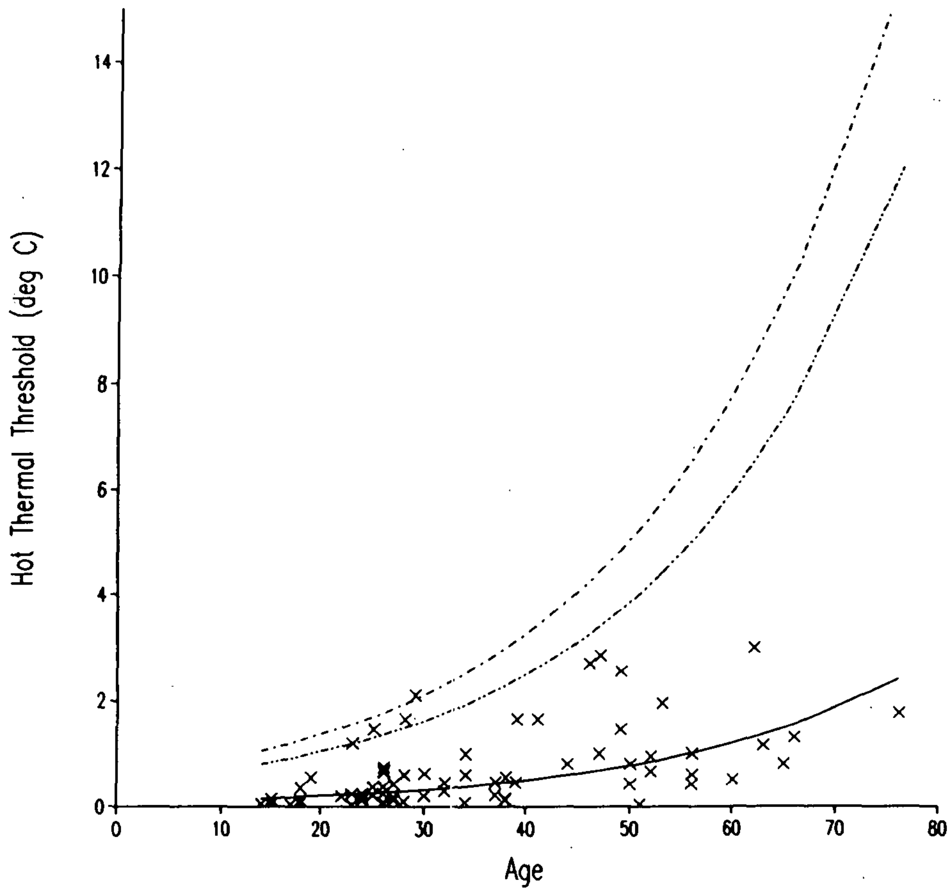


Figure 1 Regression of hot thermal threshold (log transformed) against age and line based on the 95th percentile of the residuals from the regression model (n = 68) and upper line is the upper 95% confidence limit of threshold for a given age.

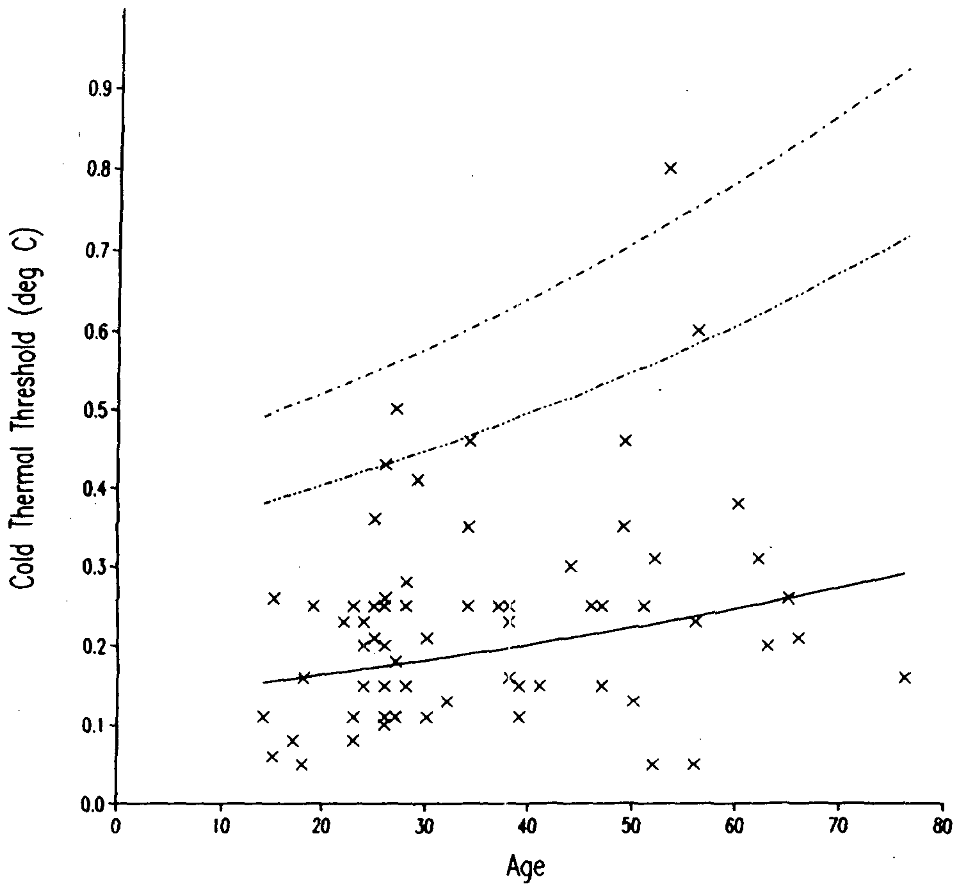


Figure 2 Regression of Cold Thermal Threshold (log transformed) against age and line based on he 95th percentile of the residuals from the regression model (n = 68), and upper line is the upper 95% confidence limit for threshold for a given age.

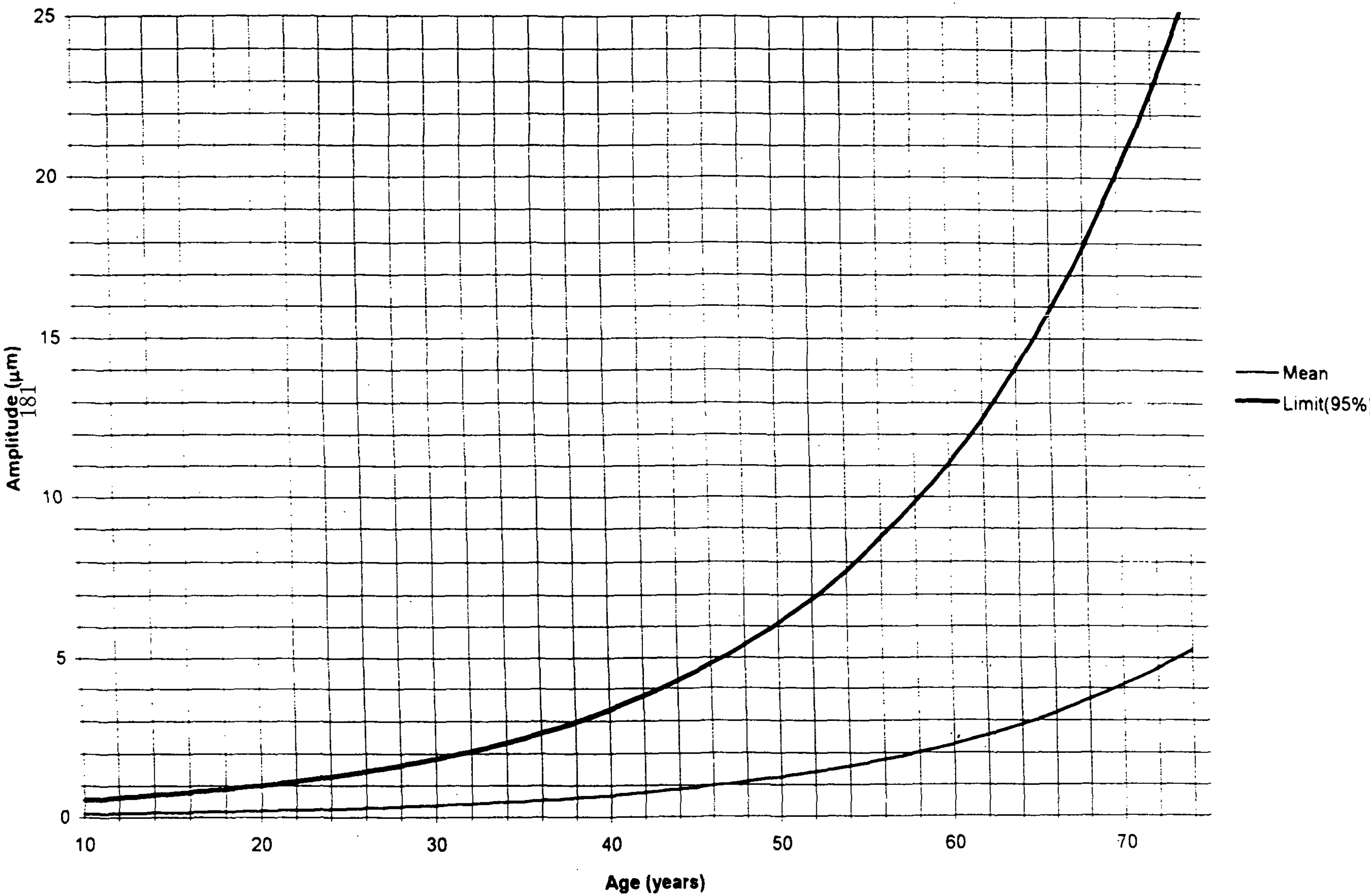


Figure 3

Regression of vibration threshold (log transformed) against age and line based on the 95th percentile of the residuals from the regression model (n = 10) and upper line is the upper 95% confidence limit of threshold for a given age.

Validation of the thermal and vibration sensory test.

Vibration Threshold. We use the Somedic Vibrameter™ for measurement of Vibration Threshold (VT) [1]. This equipment follows physiological principle by indicating the stimulus strength as the amplitude of vibration and not the voltage input to the vibration transducer [2]. The physiological stimulus to the mechanoreceptors is the amplitude of displacement of the receptor membrane. The output from devices like the Bio-Thesiometer or Neurothesiometer at a given voltage setting will vary due to difference in soft tissue damping[1].

The Somedic Vibrameter is applied videly in numerous centres and Departments of Neurology [3,4], and has been used in several clinical trials. The INS has more than 8 years experience with this technique.

Sensitivity: In a study with 279 diabetic patients, VT measurement provided more than twice the detection rate of peripheral nerve dysfunction compared with the most careful clinical examination [5]. None of the patients with clinically overt neuropathy had a normal VT.

Thermal Threshold. The method has been developed at the INS, Glasgow and the repeatability evaluated using a group of 320 normal individuals [6,7]. The method is used in many centres [8,9] and separate validation and repeatability studies have been carried out [10]. The high sensitivity of the technique is supported by a study of 143 patients with neuropathies of diverse aetiologies. Ninety-nine percent of the patients had one or more abnormal thermal threshold while 89% showed abnormalities in their conventional nerve conduction studies [11]. Thirty-nine out of 40 patients with normal sensory conduction studies had abnormal thermal thresholds. Futhermore, the specificity was tested in a study of 25 patients with clinical symptoms and signs of small fibre neuropathy but normal conventional electrophysiological indices. All 25 patients had abnormal thermal thresholds [12]. Further studies showed that patients with selective large fibre involvement (Friedreich's Ataxia) had no abnormality of their thermal thresholds [13].

We have more than 10 years clinical experience with the technique which has been used on around 5000 patients. It is used in two major multi centre clinical trials of diabetic neuropathy [14, Second study completed and report in preparation]. A consensus report of the International Panel of the Peripheral Neuropathy Association has endorsed the principle of the technique [15]. Approximately 40 original publications by our group at the INS and others confirms the reproducibility of the results and the usefulness of the technique. The equipment is commercially produced by a leading medical equipment manufacturer.

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Appendix 7

Letters of invitation

(Letter to other groups of farmers)

Dear

Study of Sheep Dippers Health

I would very much appreciate your help with a survey of the health of sheep dippers which is due to take place between October 1996 and May 1997. The study, which is of benefit to farmers and farm workers, is being carried out by the Institute of Occupational Medicine, an independent research organisation based in Edinburgh, in conjunction with the Institute of Neurological Sciences (INS) in Glasgow. The work is supported by the Health and Safety Executive (HSE), the Ministry of Agriculture Fisheries and Food (MAFF), and the Department of Health.

It is hoped to include other groups of farmers in the survey to provide a comparison group of workers who are not involved in sheep dipping. The survey will also consider exposure to pesticides from other sources.

You may know that there is concern whether exposure of farm personnel to pesticides may affect health. The study would involve a health survey of all people at selected farms. Our medical survey team would visit farms on the basis of pre-arranged appointments. Each person would be asked about symptoms in the arms and legs, general health, and jobs held. Two quick and comfortable tests of sensation in the hands and feet will be conducted. The examination is expected to take 30 to 40 minutes for each individual.

On the completion of this survey, a small number of individuals will be invited for an examination in a hospital outpatient department in Glasgow for a day, and a shift payment and expenses will be paid.

You will receive a brief medical report, and we would like, with your permission, to send information on anything unusual to your family doctor. All the information you give us will be held by us in strictest confidence, will not be released to any employer, and will only be used for medical research. Participation in the survey is voluntary, but each person is important to the success of the study and I would be most grateful if you would agree to take part.

If you would like more information about the survey, or are willing to participate please complete the appropriate section on the enclosed form, and return it to the IOM in the pre-paid envelope provided. A member of the IOM team will then contact you in due course to explain the survey in more detail. Even if you do not wish to take part we would be grateful if you could indicate this on the form, returning it to the IOM in the envelope provided.

We also wish to invite any members of your family who work on the farm, and farm workers to participate in the survey. If you agree to be contacted, a member of the IOM team will ask you for the names and addresses of all who have worked on your farm within the past twelve months. They would all be sent a similar letter and invitation to participate.

I thank you in advance for your cooperation,

Yours sincerely,

Dr Adele Pilkington
Occupational Physician

(Letter to other groups of farm workers)

Dear

Study of Sheep Dippers Health

I would very much appreciate your help with a survey of the health of sheep farmers and farm workers which is due to take place between October 1996 and May 1997. The study, which is of benefit to farmers and farm workers, is being carried out by the Institute of Occupational Medicine, an independent research charity based in Edinburgh, in conjunction with the Institute of Neurological Sciences (INS) in Glasgow. The work is supported by the Health and Safety Executive (HSE), the Ministry of Agriculture Fisheries and Food (MAFF), and the Department of Health.

We have invited other groups of farmers in the area to participate, and asked those who have agreed for the names and addresses of their farm workers. It is hoped to include other farmers in the survey to provide a comparison group of workers who are not involved in sheep dipping. The survey will also consider exposure to pesticides from other sources.

You may know that there is concern whether exposure of farm personnel to pesticides may affect health. The study would involve a health survey of all people at selected farms. Our medical survey team would visit farms on the basis of pre-arranged appointments. Each person would be asked about symptoms in the arms and legs, general health, and jobs held. Two quick and comfortable tests of sensation in the hands and feet will be conducted. The examination is expected to take 30 to 40 minutes for each individual.

On the completion of this survey, a small number of individuals will be invited for an examination in a hospital outpatient department in Glasgow for a day, and a shift payment and expenses will be paid.

You will receive a brief medical report, and we would like, with your permission to send information on anything unusual to your family doctor. All the information you give us will be held by us in strictest confidence, will not be released to any employer, and will only be used for medical research.
Participation in the survey is voluntary, but each person is important to the success of the study and I would be most grateful if you would agree to take part.

If you would like more information about the survey, or are willing to participate please complete the appropriate section on the form, and return it to the IOM in the envelope provided. A member of the IOM team will then contact you in due course to explain the survey in more detail. Even if you do not wish to take part we would be grateful if you could indicate this on the form, returning it to the IOM in the envelope provided.

I thank you in advance for your cooperation,

Yours sincerely,

Dr Adele Pilkington
Occupational Physician

SURVEY OF SHEEP DIPPERS HEALTH

INVITATION TO PARTICIPATE

NAME: .... **DATE OF BIRTH:** ....

ADDRESS: ....

....

TELEPHONE CONTACT NUMBER: ....

TIMES/DAYS WHEN YOU CAN BE CONTACTED ....

PLEASE COMPLETE THE APPROPRIATE SECTION AND RETURN THE FORM IN THE ENVELOPE PROVIDED

(i) **I am willing to participate in the survey** of the health of sheep farmers and farm workers. I understand that this will include confidential questionnaires on general health and occupational history, and two simple tests of sensation.

SIGNATURE: .... **DATE:** ....

(ii) **I would like more information about the survey** and understand that I will be contacted by a member of the IOM team.

SIGNATURE: .... **DATE:** ....

(iii) **I do not wish to participate in the survey**

SIGNATURE: .... **DATE:** ....

SURVEY OF SHEEP DIPPERS HEALTH

CONSENT FORM

PLEASE READ PARTS A AND B

PART A

I am willing to participate in the survey of the health of sheep farmers and farm workers. I understand that this will include confidential questionnaires on general health and occupational history, and two simple tests of sensation.

NAME: .... **DATE OF BIRTH:** ....

ADDRESS: ....

SIGNATURE: .... **DATE:** ....

PART B
PLEASE COMPLETE THE APPROPRIATE SECTION

(i) I understand that I will receive a brief medical report, and I wish my GP to be informed of unusual test results

NAME OF GP: ....

ADDRESS: ....

....

SIGNATURE: .... **DATE:**.........

(ii) I wish to receive a brief medical report, but do not wish my GP to be informed of any unusual test results

SIGNATURE: .... **DATE:**.........

Appendix 8

Farm details recording forms

Farm Number:

SUBJECT RECRUITMENT TO EPIDEMIOLOGICAL STUDY OF SHEEP DIPPING

Letter:	Subject's Reply: **INF NO YES**	Recruited? **NO YES**

Subject's Name	
Subject's Address	
Phone Number	

Summary of Phone Conversations:

Date	Contact	Summary	Initials

Appendix 9

Statistical regression models used in exposure-response analyses

Statistical regression models used in exposure-response analyses

Statistical analysis methods are summarised in section 6.2. This appendix explains on that summary and explains in more detail the regression models used in the exposure-response analyses. There were basically two types of regression model used: logistic regression to model the prevalence of symptoms, and multiple linear regression to model the differences in sensory test thresholds. However, both regression models can be viewed as particular forms of the family of generalised linear models (GLMs).

1. Logistic regression model for symptoms

Each individual in the study group was labelled as either showing symptoms (symptoms score ≥1) or not (symptoms score < 1). This binary response variable cannot be modelled using standard linear regression but requires an appropriate model for the probability of symptoms. One such model is the logistic regression model. An example of the form of the logistic regression model used to describe the probability, or prevalence, p, of symptoms is:

$$\log\left(\frac{p}{1-p}\right) = a + bx_1 + cx_2 \qquad (1)$$

where x_1 and x_2 are two explanatory variables, and a, b and c corresponding parameters. The left-hand side of (1) is the log of the odds, $p/(1-p)$, of symptoms. As a regression model, it is not intended to fit the observed data perfectly and the parameters are optimised (using maximum likelihood) assuming a probability distribution (in this case the binomial) for the unexplained variation. The model then predicts the probability of each individual reporting symptoms, given the corresponding values of the explanatory variables. The constant parameter a, corresponds to the log odds of symptoms when all explanatory variables are zero. With two or more explanatory variables in the model, each variable is said to be *adjusted* for all other included variables.

In the above the interpretation of parameter b depends on whether the variable represents a continuous measurement (e.g. age), or a different levels of a factor (e.g. sex). If a continuous measurement, then exp(b) is the increase in odds of symptoms per unit increase in x_1. If x_1 distinguishes two levels of a factor, then exp(b) is the odds ratio (OR) of reporting symptoms given one level of the factor (x_1=1) relative to the other level of the factor (x_1=0). This can be written:

$$OR = \frac{p_1/(1-p_1)}{p_0/(1-p_0)} = \frac{p_1}{p_0} \times \frac{(1-p_0)}{(1-p_1)} \qquad (2)$$

where p_1 is the probability of symptoms when x_1=1, and p_0, when x_1=0. Therefore, OR = 1 when there is no difference in prevalence between the two levels. In fact, the OR is approximately equal to the relative risk (p_1/p_0) when, overall, the probability of symptoms (both p_0 and p_1) are small. If this is not the case, then the OR will overestimate the relative risk when OR > 1, and underestimate it when OR < 1.

2. Multiple regression model for sensory thresholds

Measurement of thresholds for the three sensory tests were also made for each individual. Since thresholds were continuous variables, standard linear regression models were used. An example of the form of the regression models used describe the sensory threshold y is:

$$\log(y) = a + bx_1 + cx_2 \qquad (3)$$

given values for two explanatory variables x_1 and x_2 and parameters a, b and c. The thresholds were log-transformed to ensure that the unexplained random variation, an additional component on the right hand side of equation (3), followed a normal distribution. This is a necessary assumption for making statistical inference using the fitted regression model. When x_1 corresponds to a continuous measurement (e.g. age), then exp(b) corresponds to a multiplicative effect per unit of x_1. When x_1 distinguishes between two levels of a factor (e.g. sex), then exp(b) corresponds to the multiplicative difference between the mean thresholds in level x_1=1 relative to mean thresholds in level x_1=0.

Appendix 10

Farmers recollection of OP sheep dip products

OP sheep dip products recalled

The exposure history questionnaire (Appendix 1) included, in part 3, a question asking interviewees to list any OP sheep dip products that they remembered working that could be checked against a list held by the interviewer of known products used during the research period. Table 1 summarises the number of individuals who could recall at least one OP product. Against each product name is a code (OP) denoting the OP compound as follows:

P	Propetamphos
D	Diazinon
Cf	Chlorfenvinphos
CD	Chlorfenvinphos Diazinon
Ca	Carbophenothion
Cm	Coumaphos
Cp	Chorpyrifos
B	Bromophos
I	Iodofenphos

Exactly 50% of sheep-dipping farmers could remember at least one product and this proportion was approximately the same among Scottish and English subjects. The table shows, ranked by the number of times quoted by subjects, each product quoted at least once and the number of times it was quoted, split by English and Scottish farmers. There products quoted most often among Scottish farmers were also generally most often quoted among English farmers, and this informal comparison did not suggest that there were a particular set of products that were selectively used in either English or Scottish.

Table 1 OP products recalled by sheep dipping farmers

OP product	OP	Sco	Eng	All
At least one product remembered	-	157	149	306
Not identifiable	-	70	54	124
Topclip Gold Shield (Scab) Approved	D	20	39	43
Youngs Summer Dip	P	28	15	59
Coopers Summer Dip 400	Cf	29	14	43
Coopers Border Winter Dip Scab Approved	P	21	17	38
Coopers Powerpack Summer Dip	CD	13	21	34
Youngs Scab Apprvd Ectomort Sheep Dip	P	18	16	34
Coopers Powerpack Winter Dip	D	14	18	32
Coopers Winter Dip 200	D	21	7	28
Ectomort Centenary	P	19	1	20
Youngs Scab Approved Jason Winter Dip	P	7	9	16
Seraphos Scab Approved	P	4	12	16
Diazadip All Seasons Sheep Dip	D	13	1	14
Coopers All Seasons Fly And Scab Dip	D	10	3	13
Asuntol Sheep Dip	Cm	12	0	12
Coopers Scab Approved Dip (Border Type)	P	7	4	11
Youngs Jason Green Label Liquid Dip	Ca	8	2	10
Osmonds Gold Fleece Sheep Dip	D	2	6	8
Youngs Scab Apprvd Diazinon Winter Dip	D	5	1	6
Golden Fleece Sheep Dip	D	3	2	5
Downland Seraphos Scab Approved	P	0	5	5
Coopers Winter Dip (With Phenols)	P	3	2	5
Ovidip R Scab Approved Sheep Dip	P	3	2	5
Prodip	P	0	4	4
Diazadip Scab Approved All Purpose	D	3	1	4
Youngs Summer Mycotic Dip	B	0	3	3
Deosan Diazinon Sheep Dip	D	2	1	3
Flyte 1250	P	2	1	3
Youngs Defly Liquid Dip	Ca	2	1	3
Youngs Killtick Liquid Tick Dip	Cp	2	0	2
Supona Sheep Dip	Cf	1	1	2
Rodgers No.10 Neu Fly And Tick Dip	Cp	2	0	2
Paracide Fly And Scab Dip	D	0	2	2
Youngs Powder Fly Dip	B	1	1	2
Deosan Fly Dip	Cf	1	1	2
Deosan Traditional Dip	CD	2	0	2
Downland Scab Approved Fly Dip	D	0	2	2
Osmonds Superfleece Scab Approved Fly Dip	CD	2	0	2
Osmonds Northern Fly Dip	Cf	0	2	2
Youngs Carbonphenothion Powder Fly Dip	Ca	1	0	1
Youngs Dursban Winter Dip	Cp	0	1	1
Youngs Mycotic Dip	I	0	1	1
Youngs 200 Liquid Tick Dip	Cp	0	1	1
Viper Winter Dip	Cf	0	1	1
Deosan Regional Dip	CD	1	0	1
Neocidol Winter Dip	D	1	0	1
Youngs Iodophefos Scab Approved Wntr Dip	I	1	0	1
Battles Op Fluid Dip	Cf	1	0	1

Appendix 11

Tables showing prevalence of individual symptoms among the occupational groups.

Table 1 Prevalence of individual symptoms by occupational group.

	Ceramics		NSD farmers		SD farmers	
Symptom	%	*n*	%	*n*	%	*n*
Muscle weakness						
hands	0.0	*0*	1.9	*1*	6.4	*39*
shoulders	0.0	*0*	0.0	*0*	2.0	*12*
feet	0.0	*0*	0.0	*0*	2.3	*14*
legs	0.0	*0*	0.0	*2*	0.8	*5*
Negative sensory						
feet	0.0	*0*	3.8	*2*	5.2	*32*
hands	0.0	*0*	0.0	*0*	2.1	*13*
Positive sensory						
feet	1.9	*2*	5.7	*3*	10	*61*
hands	0.9	*1*	3.8	*2*	5.4	*33*
Autonomic						
fainting	3.7	*4*	15	*8*	14	*87*
diarrhoea	0.0	*0*	0.0	*0*	0.7	*4*
bladder	0.0	*0*	0.0	*0*	1.8	*11*
impotence	0.0	*0*	1.9	*1*	5.6	*34*
sweating	7.5	*8*	5.7	*3*	8.2	*50*
group size		*107*		*53*		*612*

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