BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018212
Article Type:	Cohort profile
Date Submitted by the Author:	13-Jun-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	PESTICIDE, OCCUPATIONAL HEALTH, PROSPECTIVE COHORT STUDY

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The Prospective Investigation of Pesticide Applicators' Health (PIPAH) Study, a cohort study of professional pesticide users in Great Britain

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Purpose

The purpose of the study is to monitor the exposure and health of workers in Great Britain (GB) who use pesticides as a part of their job, and to gain a better understanding of the relationship between long-term exposure to pesticides and health.

Participants

Study participants are professional pesticide users who are certified in the safe use of pesticides or who were born before 1965 and apply pesticides under 'grandfather rights'. Overall response rate was 20 %; participants are mostly male (98 %) and the average age is 54 years, ranging from 17 to over 80 years.

Findings to date

Participants have completed a baseline general questionnaire and three follow-up questionnaires on the use of pesticides. These data will enable investigations into the relationship between occupational pesticide exposure and health outcomes taking into account non-occupational confounding factors.

Future plans

There is no set end date for data collection. Recruitment into the cohort will continue, and for the foreseeable future there will be annual pesticide use questionnaires and five-yearly follow-up general questionnaires.

The intention is to validate the pesticide use questionnaire, and to develop a crop/ job exposure matrix (C/JEM) which can be updated regularly. This C/JEM will be able to look at general categories

of pesticide, such as insecticides, structurally related pesticides, such as organochlorines, or individual active ingredients. Data collected on use of personal protective equipment and method of application will provide information on how potential exposure to pesticide during application may have been modified. The study will be able to estimate changes in individual pesticide use over time, and to examine the associations between pesticide use and both baseline and long-term health outcomes.

The cohort members will be linked to national databases for notification of hospital episode statistics, cancer incidence, and mortality for follow-up of health outcomes.

Strengths and limitations of this study

Key strengths include:

- Breadth of data collected comprising comprehensive demographic, lifestyle and socioeconomic data, general history of pesticide use and detailed prospective information on pesticide use
- Objective assessment of health by flagging the cohort for notification of hospital admissions, and cancer and death registrations
- Repeat assessments of pesticide use, potential confounding factors, and self-reported health outcomes planned

Main limitations include:

- The lack of objective exposure measurement which may result in exposure misclassification
- There may be some participation bias but this is unlikely to be large

Introduction

Pesticides and biocides are designed and developed to be toxic to specific plant or animal pests. There is a long history of their use; compared to the simple treatments used in earlier times, such as arsenic, the pesticides developed for use today have active ingredients which are usually highly effective against particular pests[1]. Pesticides are almost as diverse as the pests they target, but they should have all been tested for their efficacy and for their effect on the environment and on non-target organisms, including humans. In Great Britain (GB), all pesticide products must be authorised by the Chemicals Regulation Division (CRD), of the Health and Safety Executive, before they can be sold, distributed, stored or used (https://www.gov.uk/pesticide-approval). Despite their potential for harm, pesticides are widely used because of the important role they play in improving public health and protecting food supplies[2].

Many epidemiological studies have investigated the association between the use of pesticides and adverse long-term health effects. However, ascertaining the causes of disease within pesticide-exposed populations is complex because of the multifactorial nature of many diseases and the presence of other potential risk factors[3]. Genetic susceptibility, lifestyle factors and environmental exposures may all affect risk of disease, either independently or through interactions with one another. In addition, the term pesticide covers a wide range and diverse group of chemicals or products. When investigating the health risks associated with pesticide exposure, identifying the cause of disease is complicated by the fact that individuals are often exposed to several types of pesticide, which may have different modes of action, and they may also be exposed to other potential risk factors, such as fuel and exhaust fumes, solvents, ultraviolet radiation, organic and inorganic dusts, and animal pathogens.

Many epidemiological studies have researched occupational groups who use or are exposed to pesticides as part of their daily activities[3]. Workers for these studies were recruited from the agricultural, horticultural, forestry, amenity or pesticide manufacturing sectors, because they are likely to regularly handle one or more types of pesticide during the course of their work. The body of evidence on the association between exposure to pesticides and disease provides a mixed picture, and the meta-analyses undertaken often report significant heterogeneity between studies[3-5]. This heterogeneity may be attributable to a variety of factors, including differences in exposure assessment, disease status ascertainment and study design, and to confounding.

A recent systematic review of epidemiological studies linking pesticide exposure to health effects was commissioned by the European Food Safety Authority (EFSA)[3] and published in 2013. They reviewed over 600 articles published between 2006 and 2012, which included nearly 6500 different analyses of the association between pesticide exposure and health outcomes. The majority of studies (55 %) investigated occupational exposures. The health outcomes identified in the review were assigned to 23 major disease categories; the commonest outcomes reported in the studies reviewed were cancer (29 %), child health (15 %), reproductive diseases (11 %) and neurological conditions (11 %). However despite the very large amount of data available, encompassing all adverse health outcomes identified in the literature review, the authors report that findings were inconclusive for the majority of health outcomes studied. Some of the strongest evidence linking pesticide exposure to disease was found for certain cancers, particularly childhood cancers, and neurological conditions. Other health effects, including asthma, allergies, obesity and endocrine disorders, also showed an increased risk[3].

Mostafalou and Abdollahi[2] also published a review of pesticides and chronic diseases in 2013. Their comprehensive review covered publications between 1975 and 2013, and it included a wide range of diseases. However, the review was not systematic and the authors did not focus on epidemiological studies, but instead they gave an insight into possible causal molecular mechanisms. The major disease categories included in this review were cancer, cardiovascular disease, diabetes, developmental and reproductive disorders, kidney disease, neurological conditions, respiratory disease, and autoimmune disease. Pesticide exposure has been linked with genetic damage and epigenetic changes, both of which are associated with cancer. Epigenetic changes have also been implicated in neurological conditions, diabetes, aging, chronic kidney disease and atherosclerosis. Whether the epigenetic changes in these diseases are related to pesticide exposure or are markers of exposure[6], has not been established. Some pesticides have been shown to impair mitochondrial function, increase oxidative and endoplasmic reticular stress, affect the unfolded protein response and protein degradation, or to be endocrine disruptors[2]. These mechanisms have all been implicated in the development of chronic disease but further research is needed to confirm whether exposure to particular pesticides is on the causal pathway.

The body of evidence reporting on the association between pesticides and ill health is largely inconclusive, and despite the large number of studies in this area, more information is needed on the potential adverse effects of pesticide exposure on chronic disease risk. In 1998 the GB Health and Safety Executive (HSE) established the Pesticide Users' Health Study (PUHS), a prospective study of nearly 67,000 professional pesticide users[7]. Their aim was to monitor the long-term health of pesticide users who are potentially exposed to low levels of pesticide. Individuals obtaining certificates of competence in the safe use of pesticides were invited to take part in the study, and the cohort was followed-up for long-term health outcomes through national registers for notification of cancer and death registrations. Cancer incidence overall was lower, and standardised mortality ratios for all causes and all cancers were significantly lower in these pesticide users than in the general population. Incidence of multiple myeloma, cancer of the testes, and non-melanoma skin cancer were higher than expected in men, and in women non-melanoma skin cancer was higher. None of the standardised mortality ratios for specific causes of death, including respiratory and neurological diseases, was higher than expected. However, being certified for the safe use of pesticides may not necessarily indicate using pesticides regularly and there is no active follow up of the study participants to monitor the changes in their pesticide use. Furthermore, only basic demographic information was available for this cohort so interpretation of the findings in terms of causal relationships is not possible.

In 2013, HSE established the Prospective Investigation of Pesticide Applicators' Health (PIPAH) study. Professional pesticide users were enrolled into the PIPAH study, and baseline data were collected on self-reported health and potential risk factors. The PIPAH study is smaller than the PUHS, but it is collecting the detailed information which is lacking in the PUHS, such as information on pesticide exposure at product level and potential confounding factors. The PIPAH study's aims are similar to those of the PUHS: the overall aims are to monitor the long-term health of workers in GB who use pesticides as a part of their job, and to gain a better understanding of the relationship between long-term exposure to pesticides and health.

Cohort description

Study design

The study is a prospective cohort study, which includes a baseline cross-sectional survey at recruitment and ongoing follow-up of study participants' pesticide use and health outcomes. Data will be collected by conducting periodical surveys and through linkage to administrative health records.

Target population and sampling frame

The target population for the PIPAH study is men and women in GB who apply pesticides as a part of their job. Individuals belonging to this population were identified through a number of registers. Until November 2015, individuals applying pesticides on a professional basis in GB were required to be certified in the safe use of pesticides, unless they were born before 1965 in which case they could apply pesticides under 'grandfather rights'. From November 2015, 'grandfather rights' were revoked and everyone wishing to apply a professional pesticide must now be certified. City & Guilds (http://www.cityandguilds.com/) offer the necessary training and keep a register of all individuals who hold certificates of competence. Members of the PUHS were recruited from this training register. In addition to this register, City & Guilds maintain the National Register of Sprayer Operators (NRoSO, https://www.nroso.org.uk/) and previously also the National Amenity Sprayer Operators' Register (NAsOR). These are central registers of sprayer operators in GB who use continuing professional development as a means of ensuring ongoing training. The relationship between the registers, the PUHS and the target population is shown in Figure 1. The members of NRoSO and NAsOR, and the sub-group of the PUHS who responded to a study questionnaire in 2004-2006, were invited to take part in the PIPAH study.

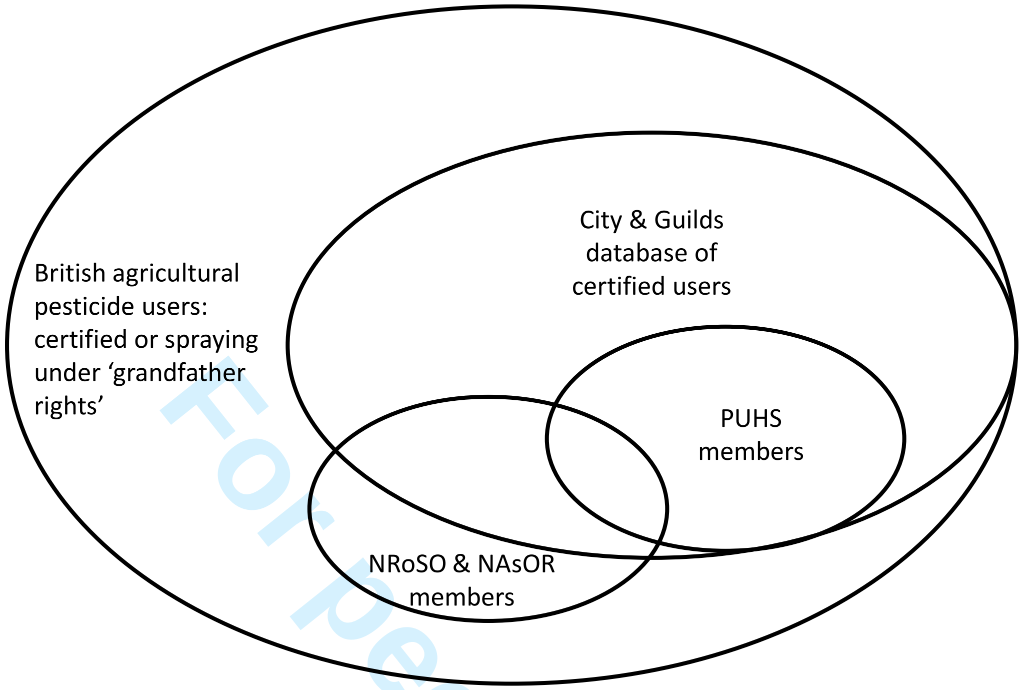

Figure 1 The relationship between the registers of pesticide users, the PUHS and the target population

Recruitment and response rates

Enrolment in the baseline phase of the PIPAH study was carried out in two stages: NRoSO and NAsOR members were recruited during the first half of 2013, and the subset of PUHS members were recruited in early 2014. Approximately 21 000 members of NRoSO and NAsOR, and around 7500 PUHS members were sent a survey pack inviting them to participate in the PIPAH study. The packs contained an information leaflet, consent form, questionnaire and a postage paid envelope for the return of completed questionnaires. During the first stage, when recruiting members of NRoSO and NAsOR, a reminder postcard was sent to everyone a week after the first invitation pack. During the second stage, when recruiting members of the PUHS, a full survey pack was sent to everyone who had not responded four weeks after the first invitation. In addition to the baseline phase, all new members of NRoSO are invited to take part in the PIPAH study in an on-going rolling recruitment programme. Recruitment activities have resulted in the collection of baseline data from 5731 GB based pesticide users by March 2014. Recruitment data and response rates are described in Table 1. Response rates for men and women were similar at around 20 %.

Table 1 Recruitment data and overall response rates

	Responders		Non-responders		All		Response rate
	Number	Percent	Number	Percent	Number	Percent	Percent
Recruitment phase							
NRoSO/NAsOR	3948	68.9	17103	74.3	21051	73.5	18.8
PUHS	1676	29.2	5921	25.7	7597	26.5	22.1
Sub-total	**5624**		**23024**	**100.0**	**28648**	**100.0**	**19.6**[a]
Rolling recruitment	107	1.9					
Total	**5731**	**100.0**					

a, Overall response rate

Data collection and follow-up

A baseline general questionnaire was developed. Where possible, questions were based on validated questions used in other cohort studies. The questionnaire was tested in face-to-face interviews with professional pesticide users before being included in the study invitation pack. On joining the study participants completed the baseline general questionnaire which included sections on demographic, diet, lifestyle, and socioeconomic factors, job history and history of pesticide use, family medical history, and self-reported ill health. It was unrealistic to gather accurate detailed lifetime pesticide use information retrospectively using a self-completion questionnaire. So the history of pesticide use questions concentrated on pesticide groups and crops which could be refined using a Crop/Job Exposure Matrix. Follow-up general questionnaires will be sent to study participants every five years (Figure 2). This will provide updated information on self-reported ill health and potential risk factors. The follow-up general questionnaires will incorporate additional disease-specific question sets, for example on respiratory health, which are relevant to this occupational cohort.

Information on pesticide exposure is collected on an annual basis. Pilot pesticide use questionnaires were sent to age-stratified random samples of 400 participants in early 2014, 2015 and 2016. The remaining participants were sent a short postcard questionnaire which requested information on the main areas of their pesticide work. The postcard questions are included in the full pilot questionnaires. After validating the pilot questionnaire, the detailed pesticide use questionnaire was sent to all study members in 2017.

The data collected in the general questionnaire and the pesticide use questionnaires are summarised in Table 2.

Study participants will be linked with GB central registers for notification of hospital episode statistics, and cancer and death registrations. This is an efficient and effective method of following-up on participants' health outcomes in the long-term.

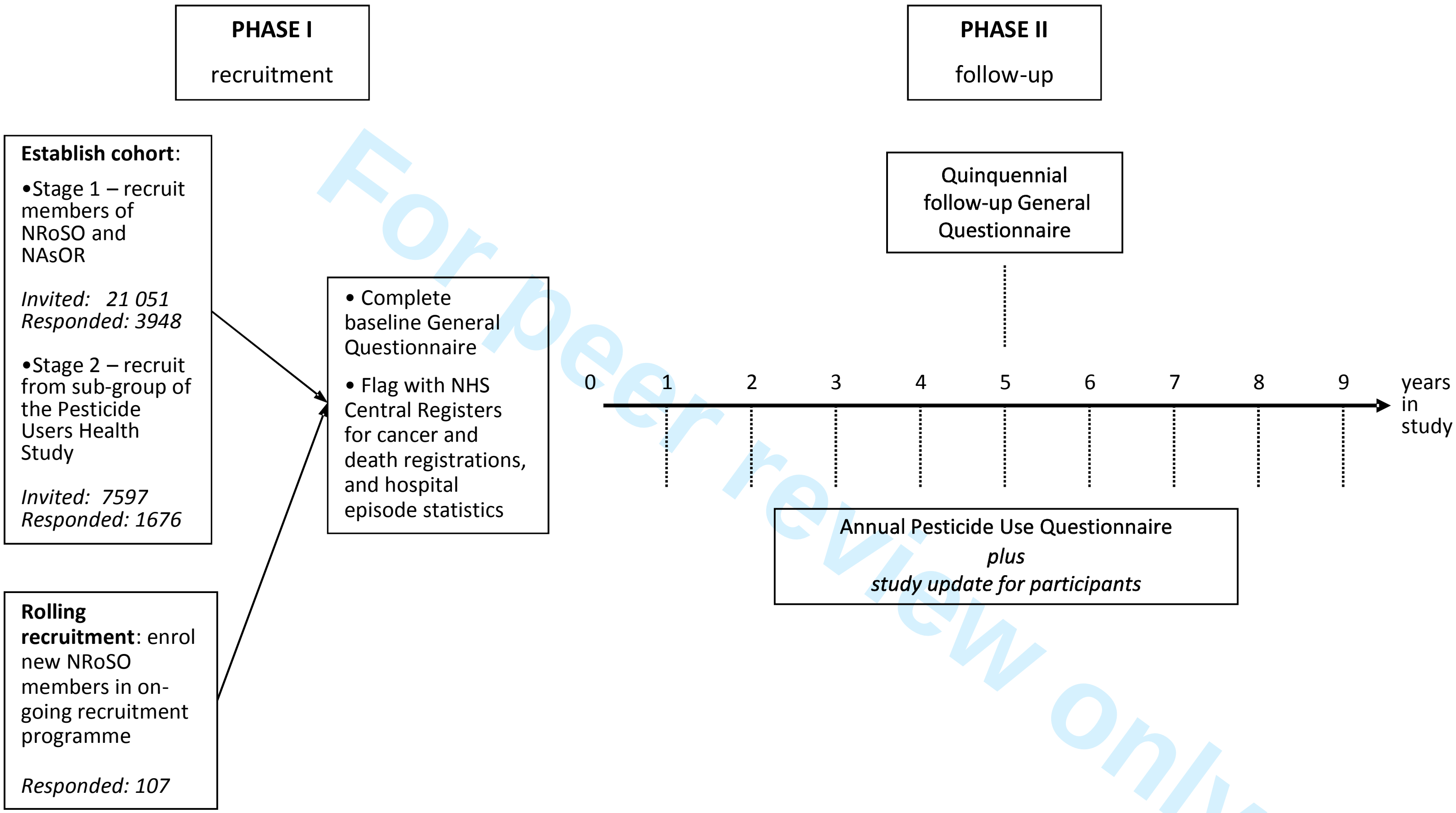

Figure 2 The PIPAH study flow chart

Table 2 Data collected by the General Questionnaire and the Pesticide Use Questionnaire

Baseline General Questionnaire
Age
Time lived on a farm and farm type
Work History
Crops where pesticides have been used (current and past)
Number of years applying specific types of pesticides (e.g. herbicides)
Number of days spent applying specific types of pesticides in a typical year
Decade when a specific type of pesticide was first used
Use of personal protective equipment
Use of pesticide concentrate
Application methods
Repair and maintenance of application/mixing equipment
General health
Ever been doctor diagnosed with a range of specified health conditions
Self-report of a range of ill health symptoms
Family medical history
Lifestyle
Physical activity
Time spent outdoors and use of sun protection measures
Diet
Tobacco and alcohol consumption
Circumstances
Marital status
Home ownership
Qualifications
Employment status
Follow-up Pesticide Use Questionnaire
Work history during the last year
Pesticide products used in last year
The number of days each pesticide product was used in last year
The typical number of hours per day each pesticide product was used in last year
Whether each pesticide product was liquid, dry or a gas (added in 2016)
Application method
Use of personal protective equipment

Baseline characteristics of the study participants

The mean age for the cohort overall was 54 years. The mean age of the NRoSO (52 years) and NAsOR (53 years) participants was similar, while the PUHS members were older (mean age 60 years). Study participants are predominantly male (98 %) which reflects the male-female proportion in the sampling frame.

The highest level of education achieved is shown in Table 3. The proportion of cohort members who reported that their highest level of education was GCSE or equivalent was similar to the general population of England and Wales (28 %)[8]. A smaller proportion of study participants had A-levels (or equivalent), or a degree/higher degree than the general population (12 % and 27 % respectively[8]), but 25 % of the cohort had vocational qualifications and a substantial proportion had other (most likely vocationally based) qualifications. Almost three quarters of the cohort reported being married, which is substantially higher than the 47 % who reported being married in the general population[8]. The proportion of study participants who were divorced or separated was approximately half that in the general population (12 %)[8]. The majority of the cohort (52 %) described themselves as self-employed compared with nearly 15 % in the population of the UK[9]. Approximately 36 % of the cohort reported that they were employed compared with almost 75 % for England and Wales[8]. These differences are likely to be attributable to the high proportion of farmers in the cohort, many of whom are self-employed. The educational, marital and employment profiles of the cohort differ from those of the general population in a number of respects but these comparisons are not adjusted for the differences in age and gender between the study participants and the general population.

Table 3 Education, marital, and employment status

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Education status						
GCSE, O-level or equivalent	1339	24.8	15	12.4	1361	24.5
A-level or equivalent	415	7.7	13	10.7	428	7.7
Vocational	1379	25.6	13	10.7	1406	25.3
Degree or higher degree	897	16.6	66	54.5	972	17.5
No formal or Other[b]	1363	25.3	14	11.6	1383	24.9
Sub-total	**5393**	**100.0**	**121**	**100.0**	**5550**	**100.0**
Missing	154		5		181	
Total	**5547**		**126**		**5731**	
Marital status						
Never married	509	9.5	18	15.0	529	9.6
Married	4069	75.7	64	53.3	4161	75.3

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Living together	404	7.5	17	14.2	424	7.7
Widowed	104	1.9	8	6.7	112	2.0
Divorced/separated	288	5.4	13	10.8	303	5.5
Sub-total	**5374**	**100.0**	**120**	**100.0**	**5529**	**100.0**
Missing or Other [c]	173		6		202	
Total	**5547**		**126**		**5731**	
Employment status						
Employed	1968	36.2	59	48.8	2031	36.3
Self employed	2867	52.7	42	34.7	2932	52.4
Other	607	11.2	20	16.5	637	11.4
Sub-total	**5442**	**100.0**	**121**	**100.0**	**5600**	**100.0**
Missing	105		5		131	
Total	**5547**		**126**		**5731**	

a, includes 58 people missing response for sex; b, No formal category includes small numbers; c, Other category includes small numbers

Lifestyle characteristics at baseline

Table 4 summarises the status of the cohort with regard to alcohol consumption and smoking status. The majority of the cohort (94 %) reported that they currently drink alcohol, which is just over nine percentage points higher than GB based comparator statistics[10]. The reported proportion of current smokers in the cohort at 9 % is around half of the estimated 19 % smoking rate in England[11], although about 28 % report that they have smoked in the past. These comparisons between the cohort and population wide statistics are not adjusted for age or sex, but the statistics suggest that the study participants differ from the general population, particularly with respect to their smoking status.

Some of the important components of diet are summarised in Figure 3. Altogether 9.5 % (n = 290) reported eating five or more portions of fruit and vegetables per day, compared with 30 % of adults aged 19 to 64 years in GB who meet the government minimum target of five portions of fruit and vegetables per day[12]. Overall 94 % (n = 4962) of the cohort reported eating one portion of red or processed meat less than once a day and 62 % (n = 3508) reported eating oily fish at least once a week. The GB nutritional guidelines recommend that adults do not eat more than one portion of red or processed meat per day, and that they should eat two portions of fish per week. The latter should include one portion of oily fish.

Table 4 Alcohol consumption and smoking status

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Alcohol consumption status						
Never drinker	118	2.2	4	3.3	122	2.2
Former drinker	189	3.6	7	5.9	196	3.6
Current drinker	4988	94.2	108	90.8	5132	94.2
Sub-total	**5295**	**100.0**	**119**	**100.0**	**5450**	**100.0**
Missing	252		7		281	
Total	**5547**		**126**		**5731**	
Smoking status						
Never smoked	3216	63.4	77	67.5	3311	63.4
Former smoker	1403	27.7	25	21.9	1439	27.6
Current smoker	454	8.9	12	10.5	471	9.0
Sub-total	**5073**	**100.0**	**114**	**100.0**	**5221**	**100.0**
Missing	474		12		510	
Total	**5547**		**126**		**5731**	

a, includes 58 people missing response for sex

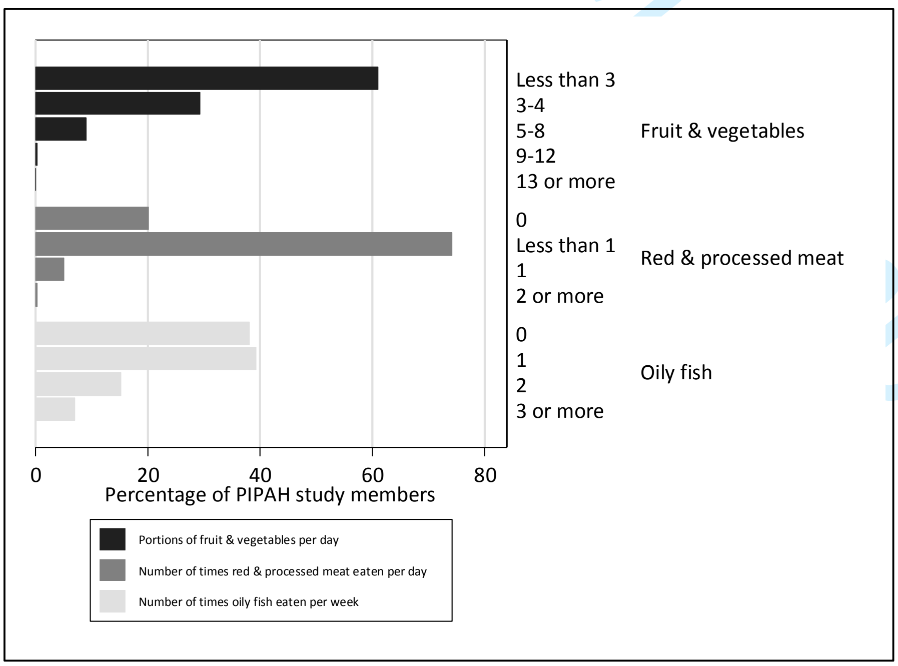

Figure 3 Frequency of fruit and vegetable, red and processed meat, and oily fish consumption

Main areas of pesticide work

The men and women who enrolled in the PIPAH study applied pesticides in a wide range of work areas. Cereals, oilseeds and grassland/fodder crops currently involve the highest proportions of cohort members (65 %, 48 % and 40 % respectively) all of which belong to the agricultural sector (Figure 4). Smaller proportions of participants were involved in other areas of pesticide work such as the amenity sector (9.6 %), forestry (3.4 %), and orchard crops (2.8 %). There were substantial increases in the proportions working in cereals, oilseeds and grassland/fodder crops compared to their past areas of work and there was a notable reduction in the proportion of the cohort reporting involvement in potato related pesticide work.

History of working with pesticides

Table 5 summarises the participants' history of working with pesticides before joining the study. The large majority of participants (over 80%) have worked with herbicides, plant growth regulators, fungicides, insecticides and treated seed, while smaller percentages have worked with poultry, livestock and animal house area insecticides, fumigants and wood preservatives. The largest proportion of participants began working with pesticides during the 1970s, 1980s and 1990s, and across all of the pesticide groups most participants had worked with pesticides for more than 10 years. This distribution reflects the age structure of the cohort. The majority of participants have handled pesticide concentrate, which has previously been observed to increase the risk of reporting 'ill health'[13]. Except when working with herbicides, most participants used personal protective equipment when mixing, handling or applying pesticides; only 12% reported using personal protective equipment when working with herbicides.

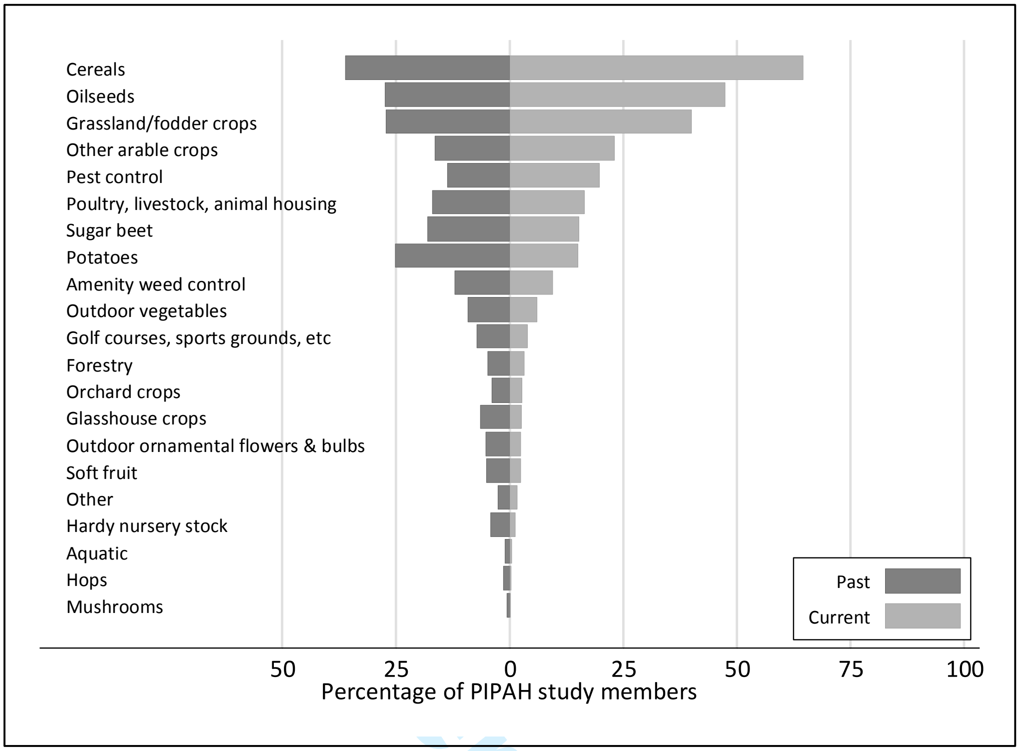

Figure 4 Past and current areas of pesticide work

Table 5 History of working with each type of pesticide: summary statistics

	Herbicides	Plant growth regulators	Fungicides	Insecticides	Poultry, livestock, or animal house area insecticides	Fumigants	Wood preservatives	Treated seed
Ever mixed or applied pesticide								
No	120 (2.2 %)	1078 (19.2%)	500 (8.9 %)	495 (8.8 %)	3868 (70.1 %)	3660 (66.1 %)	2462 (44.7 %)	1042 (18.5 %)
Yes	5410 (97.8 %)	4537 (80.8 %)	5105 (91.1 %)	5114 (91.2 %)	1653 (29.9 %)	1874 (33.9 %)	3047 (55.3 %)	4595 (81.5 %)
Missing	201	116	126	122	210	197	222	94
First used pesticide								
In the 2010s	130 (2.4 %)	151 (3.3 %)	152 (3.0 %)	147 (2.9 %)	34 (2.0 %)	30 (1.6 %)	35 (1.4 %)	94 (2.0 %)
In the 2000s	436 (8.0 %)	500 (11.0 %)	449 (8.8 %)	467 (9.1 %)	149 (8.9 %)	245 (12.9 %)	135 (5.5 %)	368 (8.0 %)
In the 1990s	853 (15.7 %)	953 (21.0 %)	873 (17.1 %)	915 (17.9 %)	252 (15.1 %)	447 (23.5 %)	364 (14.8 %)	738 (16.1 %)
In the 1980s	1596 (29.4 %)	1679 (37.0 %)	1704 (33.4 %)	1715 (33.5 %)	493 (29.5 %)	633 (33.3 %)	719 (29.2 %)	1379 (30.0 %)
In the 1970s	1413 (26.1 %)	1021 (22.5 %)	1393 (27.3 %)	1271 (24.8 %)	481 (28.8 %)	368 (19.4 %)	680 (27.6 %)	1234 (26.9 %)
In the 1960s	790 (14.6 %)	211 (4.6 %)	456 (8.9 %)	499 (9.7 %)	211 (12.6 %)	149 (7.8 %)	397 (16.1 %)	614 (13.4 %)
Before 1960	206 (3.8 %)	26 (0.6 %)	80 (1.6 %)	104 (2.0 %)	50 (3.0 %)	28 (1.5 %)	135 (5.5 %)	165 (3.6 %)
Missing	307	1190	624	613	4061	3831	3266	1139
Years used pesticide								
More than 20	3739 (69.2 %)	2632 (57.9 %)	3304 (64.8 %)	3185 (62.4 %)	716 (42.9 %)	631 (33.3 %)	1098 (44.6 %)	3081 (67.2 %)
11-20	906 (16.8 %)	927 (20.4 %)	912 (17.9 %)	982 (19.3 %)	400 (24.0 %)	441 (23.3 %)	431 (17.5 %)	786 (17.1 %)
6-10	338 (6.3 %)	395 (8.7 %)	389 (7.6 %)	396 (7.8 %)	247 (14.8 %)	317 (16.7 %)	314 (12.8 %)	325 (7.1 %)
2-5	333 (6.2 %)	447 (9.8 %)	392 (7.7 %)	427 (8.4 %)	247 (14.8 %)	369 (19.5 %)	424 (17.2 %)	297 (6.5 %)
1 year or less	85 (1.6 %)	141 (3.1 %)	102 (2.0 %)	112 (2.2 %)	58 (3.5 %)	135 (7.1 %)	193 (7.8 %)	97 (2.1 %)
Missing	330	1189	632	629	4063	3838	3271	1145

	Herbicides	Plant growth regulators	Fungicides	Insecticides	Poultry, livestock, or animal house area insecticides	Fumigants	Wood preservatives	Treated seed
Ever handled pesticide concentrate								
No	241 (4.5 %)	230 (5.1 %)	236 (4.6 %)	255 (5.0 %)	139 (8.4 %)	397 (21.1 %)[a]	454 (18.5 %)	-
Yes, sometimes	1139 (21.1 %)	1304 (28.7 %)	1178 (23.1 %)	1360 (26.6 %)	715 (43.2 %)	884 (47.1 %)	1160 (47.2 %)	-
Yes, often	4019 (74.4 %)	3002 (66.2 %)	3693 (72.3 %)	3491 (68.4 %)	800 (48.4 %)	597 (31.8 %)	846 (34.4 %)	-
Missing	332	1195	624	625	4077	3853	3271	-
Repair or maintain application or mixing equipment								
No	225 (4.1 %)	147 (3.2 %)	201 (3.9 %)	204 (4.0 %)	302 (18.3 %)	1248 (68.7 %)	1321 (54.9 %)	-
Yes	5206 (95.9 %)	4396 (96.8 %)	4904 (96.1 %)	4871 (96.0 %)	1344 (81.7 %)	568 (31.3 %)	1085 (45.1 %)	-
Missing	300	1188	626	656	4085	3915	3325	-
Usually wear personal protective equipment								
No	4764 (88.4 %)	496 (11.0 %)	545 (10.7 %)	414 (8.2 %)	393 (23.7 %)	322 (17.1 %)	761 (31.0 %)	1974 (44.1 %)
Yes	626 (11.6 %)	4020 (89.0 %)	4540 (89.3 %)	4662 (91.8 %)	1264 (76.3 %)	1559 (82.9 %)	1690 (69.0 %)	2503 (55.9 %)
Missing	341	1215	646	655	4074	3850	3280	1254

a, No or Not applicable

Self-reported health

Cohort members were asked to report any doctor diagnosed health outcomes. The categories of disease included were respiratory, neurological, circulatory, ophthalmic, dermatological, musculoskeletal, metabolic and other conditions including glandular fever, lead poisoning, pesticide poisoning, ulcerative colitis or Crohn's disease, injury (excluding head injury) from farm machinery, and head injury requiring medical attention. The lifetime prevalence was greater than 10 % for work related musculoskeletal injuries (23.5 %), high blood pressure (14.8 %) and asthma (10.4 %). Injury from farm machinery (9.9 %) and head injury (7.1 %) were also common in this occupational group. Health outcomes with a lifetime prevalence of less than 1 % included Alzheimer's disease, chronic obstructive pulmonary disease, chronic kidney infections, epilepsy, multiple sclerosis and Parkinson's disease.

Strengths and limitations

A key strength of the PIPAH Study is the breadth of the data, including comprehensive demographic, lifestyle and socioeconomic data and detailed information about use of pesticides, that have been and will be collected from a large group (>5000) of clearly defined professional pesticide users. These data, in combination with the data collected about past and current health conditions and the prospective design of the study, will allow the research team to conduct novel analyses exploring the relationships between pesticide exposure and health outcomes.

Another important strength of the study design is the planned repeated assessment of pesticide use, basic demographic and lifestyle factors, and self-reported health outcomes. Keeping this information current will improve assessment of exposure in future analyses, and repeat assessments will provide opportunities to add new question sets into the questionnaires. Flagging cohort members for notification of hospital episodes, and cancer or death registrations provides a very effective objective means of following up long-term health outcomes with minimal loss to follow up and no burden on participants.

Potential limitations of the study include the possibility of participation bias due to self-selective decisions to take part in the study. However, there is no evidence to suggest that the decision to take part in the study was influenced by participants' exposure or health. The proportions of males and females in the study sampling frame and the cohort were identical, but the age structure differed in that the cohort members were a little older.

The study relies on self-reported pesticide use rather than objective exposure measurements, which is a potential weakness. Exposure misclassification may occur, which may affect the ability of the study to investigate the real associations between pesticide exposure and health. Biological monitoring would provide a more accurate measure of the pesticide exposure actually experienced, but costs and logistics prevent this from being carried out on the full cohort. Future research investigating the health risks associated with particular pesticides and using biological monitoring to assess exposure could be undertaken on a subset of the cohort.

Collaboration

The PIPAH study was established as a national resource to enable the Health and Safety Executive and other researchers to conduct research into pesticide related health outcomes. The information collected has been designed to be comparable with other similar cohort studies and to enable data pooling. The PIPAH study is a member of AGRICOH, the international consortium of agricultural cohort studies, and we would welcome opportunities for research collaboration. For further information on accessing the anonymised research data already collected as part of this study or to contact researchers with research proposals, please contact the PIPAH study team (PIPAH@hsl.gsi.gov.uk). A copy of the baseline general questionnaire and the follow-up pesticide use questionnaire is available on the PIPAH webpage (http://www.hsl.gov.uk/resources/major-projects/pipah).

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Acknowledgements

The authors would like to thank the participants for their contribution and continuing support for the study. The authors would like to acknowledge the contributions of Neil Pierce, Professor of Epidemiology and Biostatistics London School of Hygiene and Tropical Medicine, during the establishment the study. The authors would also like to thank City & Guilds for their assistance in recruiting the pesticide users into the study, and for enabling active engagement with study participants at the agricultural shows. Finally, the authors would like to thank the PIPAH study team for their many and varied contributions.

Contributors

DFo, GF, YC, DFi and AHH are all members of the study team, and were involved in the original concept and design of the study. DFo, GF, YC and AHH were responsible for developing the survey tools, and for data collection, analysis, interpretation and drafting the manuscript. All the authors revised the manuscript, agreed with the findings and approved the final version.

Funding

This publication and the work it describes were funded by the GB Health and Safety Executive (HSE) and the GB Department for Environment, Food and Rural Affairs (Defra). Its contents, including any opinions and/or conclusions expressed, are those of the authors alone and do not necessarily reflect HSE or Defra policy.

Competing interests

None declared

Ethics approval

This study was reviewed and given a favourable opinion by the National Research Ethics Service Committee North West-Greater Manchester North (reference 12/NW/0654).

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding The characteristics of the cohort are described using summary statistics (counts and percentages). There is no control for confounding.	12-19
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable

		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-19
		(b) Indicate number of participants with missing data for each variable of interest	11-19
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-19
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-15; 17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-19
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Prospective Investigation of Pesticide Applicators' Health (PIPAH) Study, a cohort study of professional pesticide users in Great Britain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018212.R1
Article Type:	Cohort profile
Date Submitted by the Author:	28-Aug-2017
Complete List of Authors:	Harding, Anne-Helen; Health and Safety Executive Fox, David; Health and Safety Executive Chen, Yiqun; Health and Safety Executive Pearce, Neil; London School of Hygiene and Tropical Medicine Fishwick, David; Health and Safety Executive Frost , Gillian; Health and Safety Executive, UK
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine
Keywords:	PESTICIDE, OCCUPATIONAL HEALTH, PROSPECTIVE COHORT STUDY

The Prospective Investigation of Pesticide Applicators' Health (PIPAH) Study, a cohort study of professional pesticide users in Great Britain

Anne-Helen Harding,[1*] David Fox, [1] Yiqun Chen, [1] Neil Pearce, [2] David Fishwick, [1] and Gillian Frost [1]

Purpose

The purpose of the study is to monitor the exposure and health of workers in Great Britain (GB) who use pesticides as a part of their job, and to gain a better understanding of the relationship between long-term exposure to pesticides and health.

Participants

Study participants are professional pesticide users who are certified in the safe use of pesticides or who were born before 1965 and apply pesticides under 'grandfather rights'. Overall response rate was 20 %; participants are mostly male (98 %) and the average age is 54 years, ranging from 17 to over 80 years.

Findings to date

Participants have completed a baseline general questionnaire and three follow-up questionnaires on the use of pesticides. These data will enable investigations into the relationship between occupational pesticide exposure and health outcomes taking into account non-occupational confounding factors.

Future plans

There is no set end date for data collection. Recruitment into the cohort will continue, and for the foreseeable future there will be annual pesticide use questionnaires and five-yearly follow-up general questionnaires.

The intention is to validate the pesticide use questionnaire, and to develop a crop/ job exposure matrix (C/JEM) which can be updated regularly. This C/JEM will be able to look at general categories

of pesticide, such as insecticides, structurally related pesticides, such as organochlorines, or individual active ingredients. Data collected on use of personal protective equipment and method of application will provide information on how potential exposure to pesticide during application may have been modified. The study will be able to estimate changes in individual pesticide use over time, and to examine the associations between pesticide use and both baseline and long-term health outcomes.

The cohort members will be linked to national databases for notification of hospital episode statistics, cancer incidence, and mortality for follow-up of health outcomes.

Strengths and limitations of this study

Key strengths include:

- Breadth of data collected comprising comprehensive demographic, lifestyle and socioeconomic data, general history of pesticide use and detailed prospective information on pesticide use
- Objective assessment of health by flagging the cohort for notification of hospital admissions, and cancer and death registrations
- Repeat assessments of pesticide use, potential confounding factors, and self-reported health outcomes planned

Main limitations include:

- The lack of objective exposure measurement which may result in exposure misclassification
- There may be some participation bias but this is unlikely to be large

Introduction

Pesticides and biocides are designed and developed to be toxic to specific plant or animal pests. There is a long history of their use; compared to the simple treatments used in earlier times, such as arsenic, the pesticides developed for use today have active ingredients which are usually highly effective against particular pests[1]. Pesticides are almost as diverse as the pests they target, but they should have all been tested for their efficacy and for their effect on the environment and on non-target organisms, including humans. In Great Britain (GB), all pesticide products must be authorised by the Chemicals Regulation Division (CRD), of the Health and Safety Executive, before they can be sold, distributed, stored or used (https://www.gov.uk/pesticide-approval). Despite their potential for harm, pesticides are widely used because of the important role they play in improving public health and protecting food supplies[2].

Many epidemiological studies have investigated the association between the use of pesticides and adverse long-term health effects. However, ascertaining the causes of disease within pesticide-exposed populations is complex because of the multifactorial nature of many diseases and the presence of other potential risk factors[3]. Genetic susceptibility, lifestyle factors and environmental exposures may all affect risk of disease, either independently or through interactions with one another. In addition, the term pesticide covers a wide range and diverse group of chemicals or products. When investigating the health risks associated with pesticide exposure, identifying the cause of disease is complicated by the fact that individuals are often exposed to several types of pesticide, which may have different modes of action, and they may also be exposed to other potential risk factors, such as fuel and exhaust fumes, solvents, ultraviolet radiation, organic and inorganic dusts, and animal pathogens.

Many epidemiological studies have researched occupational groups who use or are exposed to pesticides as part of their daily activities[3]. Workers for these studies were recruited from the agricultural, horticultural, forestry, amenity or pesticide manufacturing sectors, because they are likely to regularly handle one or more types of pesticide during the course of their work. The body of evidence on the association between exposure to pesticides and disease provides a mixed picture, and the meta-analyses undertaken often report significant heterogeneity between studies[3-5]. This heterogeneity may be attributable to a variety of factors, including differences in exposure assessment, disease status ascertainment and study design, and to confounding.

A recent systematic review of epidemiological studies linking pesticide exposure to health effects was commissioned by the European Food Safety Authority (EFSA)[3] and published in 2013. They reviewed over 600 articles published between 2006 and 2012, which included nearly 6500 different analyses of the association between pesticide exposure and health outcomes. The majority of studies (55 %) investigated occupational exposures. The health outcomes identified in the review were assigned to 23 major disease categories; the commonest outcomes reported in the studies reviewed were cancer (29 %), child health (15 %), reproductive diseases (11 %) and neurological conditions (11 %). However despite the very large amount of data available, encompassing all adverse health outcomes identified in the literature review, the authors report that findings were inconclusive for the majority of health outcomes studied. Some of the strongest evidence linking pesticide exposure to disease was found for certain cancers, particularly childhood cancers, and neurological conditions. Other health effects, including asthma, allergies, obesity and endocrine disorders, also showed an increased risk[3].

Mostafalou and Abdollahi[2] also published a review of pesticides and chronic diseases in 2013. Their comprehensive review covered publications between 1975 and 2013, and it included a wide range of diseases. However, the review was not systematic and the authors did not focus on epidemiological studies, but instead they gave an insight into possible causal molecular mechanisms. The major disease categories included in this review were cancer, cardiovascular disease, diabetes, developmental and reproductive disorders, kidney disease, neurological conditions, respiratory disease, and autoimmune disease. Pesticide exposure has been linked with genetic damage and epigenetic changes, both of which are associated with cancer. Epigenetic changes have also been implicated in neurological conditions, diabetes, aging, chronic kidney disease and atherosclerosis. Whether the epigenetic changes in these diseases are related to pesticide exposure or are markers of exposure[6], has not been established. Some pesticides have been shown to impair mitochondrial function, increase oxidative and endoplasmic reticular stress, affect the unfolded protein response and protein degradation, or to be endocrine disruptors[2]. These mechanisms have all been implicated in the development of chronic disease but further research is needed to confirm whether exposure to particular pesticides is on the causal pathway.

The body of evidence reporting on the association between pesticides and ill health is largely inconclusive, and despite the large number of studies in this area, more information is needed on the potential adverse effects of pesticide exposure on chronic disease risk. In 1998 the GB Health and Safety Executive (HSE) established the Pesticide Users' Health Study (PUHS), a prospective study of nearly 67,000 professional pesticide users[7]. Their aim was to monitor the long-term health of pesticide users who are potentially exposed to low levels of pesticide. Individuals obtaining certificates of competence in the safe use of pesticides were invited to take part in the study, and the cohort was followed-up for long-term health outcomes through national registers for notification of cancer and death registrations. Cancer incidence overall was lower, and standardised mortality ratios for all causes and all cancers were significantly lower in these pesticide users than in the general population. Incidence of multiple myeloma, cancer of the testes, and non-melanoma skin cancer were higher than expected in men, and in women non-melanoma skin cancer was higher. None of the standardised mortality ratios for specific causes of death, including respiratory and neurological diseases, was higher than expected. However, being certified for the safe use of pesticides may not necessarily indicate using pesticides regularly and there is no active follow up of the study participants to monitor the changes in their pesticide use. Furthermore, only basic demographic information was available for this cohort so interpretation of the findings in terms of causal relationships is not possible.

In 2013, HSE established the Prospective Investigation of Pesticide Applicators' Health (PIPAH) study. Professional pesticide users were enrolled into the PIPAH study, and baseline data were collected on self-reported health and potential risk factors. The PIPAH study is smaller than the PUHS, but it is collecting the detailed information which is lacking in the PUHS, such as information on pesticide exposure at product level and potential confounding factors. The PIPAH study's aims are similar to those of the PUHS: the overall aims are to monitor the long-term health of workers in GB who use pesticides as a part of their job, and to gain a better understanding of the relationship between long-term exposure to pesticides and health. A profile of the cohort, including a detailed description of the cohort design, methods and baseline population characteristics, is presented in this paper.

Cohort description

Study design

The study is a prospective cohort study, which includes a baseline cross-sectional survey at recruitment and ongoing follow-up of study participants' pesticide use and health outcomes. Data will be collected by conducting periodical surveys and through linkage to administrative health records.

Target population and sampling frame

The target population for the PIPAH study is men and women in GB who apply pesticides as a part of their job. Individuals belonging to this population were identified through a number of registers. Until November 2015, individuals applying pesticides on a professional basis in GB were required to be certified in the safe use of pesticides, unless they were born before 1965 in which case they could apply pesticides under 'grandfather rights'. From November 2015, 'grandfather rights' were revoked and everyone wishing to apply a professional pesticide must now be certified. City & Guilds (http://www.cityandguilds.com/) offer the necessary training and keep a register of all individuals who hold certificates of competence. Members of the PUHS were recruited from this training register. In addition to this register, City & Guilds maintain the National Register of Sprayer Operators (NRoSO, https://www.nroso.org.uk/) and previously also the National Amenity Sprayer Operators' Register (NAsOR). These are central registers of sprayer operators in GB who use continuing professional development as a means of ensuring ongoing training. The relationship between the registers, the PUHS and the target population is shown in Figure 1. The members of NRoSO and NAsOR, and the sub-group of the PUHS who responded to a study questionnaire in 2004-2006, were invited to take part in the PIPAH study.

Recruitment and response rates

Enrolment in the baseline phase of the PIPAH study was carried out in two stages: NRoSO and NAsOR members were recruited during the first half of 2013, and the subset of PUHS members were recruited in early 2014. Approximately 21 000 members of NRoSO and NAsOR, and around 7500 PUHS members were sent a survey pack inviting them to participate in the PIPAH study. The packs contained an information leaflet, consent form, questionnaire and a postage paid envelope for the return of completed questionnaires. During the first stage, when recruiting members of NRoSO and

NAsOR, a reminder postcard was sent to everyone a week after the first invitation pack. During the second stage, when recruiting members of the PUHS, a full survey pack was sent to everyone who had not responded four weeks after the first invitation. In addition to the baseline phase, all new members of NRoSO are invited to take part in the PIPAH study in an on-going rolling recruitment programme. Recruitment activities have resulted in the collection of baseline data from 5731 GB based pesticide users by March 2014. Recruitment data and response rates are described in Table 1. Response rates for men and women were similar at around 20 %.

Table 1 Recruitment data and overall response rates

	Responders		Non-responders		All		Response rate
	Number	Percent	Number	Percent	Number	Percent	Percent
Recruitment phase							
NRoSO/NAsOR	3948	68.9	17103	74.3	21051	73.5	18.8
PUHS	1676	29.2	5921	25.7	7597	26.5	22.1
Sub-total	**5624**		**23024**	**100.0**	**28648**	**100.0**	**19.6[a]**
Rolling recruitment	107	1.9					
Total	**5731**	**100.0**					

a, Overall response rate

Data collection and follow-up

A baseline general questionnaire was developed. Where possible, questions were based on validated questions used in other cohort studies. The questionnaire was tested in face-to-face interviews with professional pesticide users before being included in the study invitation pack. On joining the study participants completed the baseline general questionnaire which included sections on demographic, diet, lifestyle, and socioeconomic factors, job history and history of pesticide use, family medical history, and self-reported ill health. It was unrealistic to gather accurate detailed lifetime pesticide use information retrospectively using a self-completion questionnaire. So the history of pesticide use questions concentrated on pesticide groups and crops which could be refined using a Crop/Job Exposure Matrix. Follow-up general questionnaires will be sent to study participants every five years (Figure 2). This will provide updated information on self-reported ill health and potential risk factors. The follow-up general questionnaires will incorporate additional disease-specific question sets, for example on respiratory health, which are relevant to this occupational cohort.

Information on pesticide exposure is collected on an annual basis. Pilot pesticide use questionnaires were sent to age-stratified random samples of 400 participants in early 2014, 2015 and 2016. The remaining participants were sent a short postcard questionnaire which requested information on the main areas of their pesticide work. The postcard questions are included in the full pilot questionnaires. After validating the pilot questionnaire, the detailed pesticide use questionnaire was sent to all study members in 2017.

The data collected in the general questionnaire and the pesticide use questionnaires are summarised in Table 2.

Study participants will be linked with GB central registers for notification of hospital episode statistics, and cancer and death registrations. This is an efficient and effective method of following-up on participants' health outcomes in the long-term.

Table 2 Data collected by the General Questionnaire and the Pesticide Use Questionnaire

Baseline General Questionnaire
Age
Time lived on a farm and farm type
Work History
Crops where pesticides have been used (current and past)
Number of years applying specific types of pesticides (e.g. herbicides)
Number of days spent applying specific types of pesticides in a typical year
Decade when a specific type of pesticide was first used
Use of personal protective equipment
Use of pesticide concentrate
Application methods
Repair and maintenance of application/mixing equipment
General health
Ever been doctor diagnosed with a range of specified health conditions
Self-report of a range of ill health symptoms
Family medical history
Lifestyle
Physical activity
Time spent outdoors and use of sun protection measures
Diet
Tobacco and alcohol consumption
Circumstances
Marital status
Home ownership
Qualifications
Employment status
Follow-up Pesticide Use Questionnaire
Work history during the last year
Pesticide products used in last year
The number of days each pesticide product was used in last year
The typical number of hours per day each pesticide product was used in last year
Whether each pesticide product was liquid, dry or a gas (added in 2016)
Application method
Use of personal protective equipment

Baseline characteristics of the study participants

The mean age for the cohort overall was 54 years. The mean age of the NRoSO (52 years) and NAsOR (53 years) participants was similar, while the PUHS members were older (mean age 60 years). Study participants are predominantly male (98 %) which reflects the male-female proportion in the sampling frame.

The highest level of education achieved is shown in Table 3. The proportion of cohort members who reported that their highest level of education was GCSE or equivalent was similar to the general population of England and Wales (28 %)[8]. A smaller proportion of study participants had A-levels (or equivalent), or a degree/higher degree than the general population (12 % and 27 % respectively[8]), but 25 % of the cohort had vocational qualifications and a substantial proportion had other (most likely vocationally based) qualifications. Almost three quarters of the cohort reported being married, which is substantially higher than the 47 % who reported being married in the general population[8]. The proportion of study participants who were divorced or separated was approximately half that in the general population (12 %)[8]. The majority of the cohort (52 %) described themselves as self-employed compared with nearly 15 % in the population of the UK[9]. Approximately 36 % of the cohort reported that they were employed compared with almost 75 % for England and Wales[8]. These differences are likely to be attributable to the high proportion of farmers in the cohort, many of whom are self-employed. The educational, marital and employment profiles of the cohort differ from those of the general population in a number of respects but these comparisons are not adjusted for the differences in age and gender between the study participants and the general population.

Table 3 Education, marital, and employment status

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Education status						
GCSE, O-level or equivalent	1339	24.8	15	12.4	1361	24.5
A-level or equivalent	415	7.7	13	10.7	428	7.7
Vocational	1379	25.6	13	10.7	1406	25.3
Degree or higher degree	897	16.6	66	54.5	972	17.5
No formal or Other[b]	1363	25.3	14	11.6	1383	24.9
Sub-total	**5393**	**100.0**	**121**	**100.0**	**5550**	**100.0**
Missing	154		5		181	
Total	**5547**		**126**		**5731**	
Marital status						
Never married	509	9.5	18	15.0	529	9.6
Married	4069	75.7	64	53.3	4161	75.3

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Living together	404	7.5	17	14.2	424	7.7
Widowed	104	1.9	8	6.7	112	2.0
Divorced/separated	288	5.4	13	10.8	303	5.5
Sub-total	**5374**	**100.0**	**120**	**100.0**	**5529**	**100.0**
Missing or Other [c]	173		6		202	
Total	**5547**		**126**		**5731**	
Employment status						
Employed	1968	36.2	59	48.8	2031	36.3
Self employed	2867	52.7	42	34.7	2932	52.4
Other	607	11.2	20	16.5	637	11.4
Sub-total	**5442**	**100.0**	**121**	**100.0**	**5600**	**100.0**
Missing	105		5		131	
Total	**5547**		**126**		**5731**	

a, includes 58 people missing response for sex; b, No formal category includes small numbers; c, Other category includes small numbers

Lifestyle characteristics at baseline

Table 4 summarises the status of the cohort with regard to alcohol consumption and smoking status. The majority of the cohort (94 %) reported that they currently drink alcohol, which is just over nine percentage points higher than GB based comparator statistics[10]. The reported proportion of current smokers in the cohort at 9 % is around half of the estimated 19 % smoking rate in England[11], although about 28 % report that they have smoked in the past. These comparisons between the cohort and population wide statistics are not adjusted for age or sex, but the statistics suggest that the study participants differ from the general population, particularly with respect to their smoking status.

Some of the important components of diet are summarised in Figure 3. Altogether 9.5 % (n = 290) reported eating five or more portions of fruit and vegetables per day, compared with 30 % of adults aged 19 to 64 years in GB who meet the government minimum target of five portions of fruit and vegetables per day[12]. Overall 94 % (n = 4962) of the cohort reported eating one portion of red or processed meat less than once a day and 62 % (n = 3508) reported eating oily fish at least once a week. The GB nutritional guidelines recommend that adults do not eat more than one portion of red or processed meat per day, and that they should eat two portions of fish per week. The latter should include one portion of oily fish.

Table 4 Alcohol consumption and smoking status

	Male		Female		All [a]	
	Number	Percent	Number	Percent	Number	Percent
Alcohol consumption status						
Never drinker	118	2.2	4	3.3	122	2.2
Former drinker	189	3.6	7	5.9	196	3.6
Current drinker	4988	94.2	108	90.8	5132	94.2
Sub-total	**5295**	**100.0**	**119**	**100.0**	**5450**	**100.0**
Missing	252		7		281	
Total	**5547**		**126**		**5731**	
Smoking status						
Never smoked	3216	63.4	77	67.5	3311	63.4
Former smoker	1403	27.7	25	21.9	1439	27.6
Current smoker	454	8.9	12	10.5	471	9.0
Sub-total	**5073**	**100.0**	**114**	**100.0**	**5221**	**100.0**
Missing	474		12		510	
Total	**5547**		**126**		**5731**	

a, includes 58 people missing response for sex

Main areas of pesticide work

The men and women who enrolled in the PIPAH study applied pesticides in a wide range of work areas. Cereals, oilseeds and grassland/fodder crops currently involve the highest proportions of cohort members (65 %, 48 % and 40 % respectively) all of which belong to the agricultural sector (Figure 4). Smaller proportions of participants were involved in other areas of pesticide work such as the amenity sector (9.6 %), forestry (3.4 %), and orchard crops (2.8 %). There were substantial increases in the proportions working in cereals, oilseeds and grassland/fodder crops compared to their past areas of work and there was a notable reduction in the proportion of the cohort reporting involvement in potato related pesticide work.

History of working with pesticides

Table 5 summarises the participants' history of working with pesticides before joining the study. The large majority of participants (over 80%) have worked with herbicides, plant growth regulators, fungicides, insecticides and treated seed, while smaller percentages have worked with poultry, livestock and animal house area insecticides, fumigants and wood preservatives. The largest proportion of participants began working with pesticides during the 1970s, 1980s and 1990s, and across all of the pesticide groups most participants had worked with pesticides for more than 10 years. This distribution reflects the age structure of the cohort. The majority of participants have handled pesticide concentrate, which has previously been observed to increase the risk of reporting 'ill health'[13]. Except when working with herbicides, most participants used personal protective equipment when mixing, handling or applying pesticides; only 12% reported using personal protective equipment when working with herbicides.

Table 5 History of working with each type of pesticide: summary statistics

	Herbicides	Plant growth regulators	Fungicides	Insecticides	Poultry, livestock, or animal house area insecticides	Fumigants	Wood preservatives	Treated seed
Ever mixed or applied pesticide								
No	120 (2.2 %)	1078 (19.2%)	500 (8.9 %)	495 (8.8 %)	3868 (70.1 %)	3660 (66.1 %)	2462 (44.7 %)	1042 (18.5 %)
Yes	5410 (97.8 %)	4537 (80.8 %)	5105 (91.1 %)	5114 (91.2 %)	1653 (29.9 %)	1874 (33.9 %)	3047 (55.3 %)	4595 (81.5 %)
Missing	201	116	126	122	210	197	222	94
First used pesticide								
In the 2010s	130 (2.4 %)	151 (3.3 %)	152 (3.0 %)	147 (2.9 %)	34 (2.0 %)	30 (1.6 %)	35 (1.4 %)	94 (2.0 %)
In the 2000s	436 (8.0 %)	500 (11.0 %)	449 (8.8 %)	467 (9.1 %)	149 (8.9 %)	245 (12.9 %)	135 (5.5 %)	368 (8.0 %)
In the 1990s	853 (15.7 %)	953 (21.0 %)	873 (17.1 %)	915 (17.9 %)	252 (15.1 %)	447 (23.5 %)	364 (14.8 %)	738 (16.1 %)
In the 1980s	1596 (29.4 %)	1679 (37.0 %)	1704 (33.4 %)	1715 (33.5 %)	493 (29.5 %)	633 (33.3 %)	719 (29.2 %)	1379 (30.0 %)
In the 1970s	1413 (26.1 %)	1021 (22.5 %)	1393 (27.3 %)	1271 (24.8 %)	481 (28.8 %)	368 (19.4 %)	680 (27.6 %)	1234 (26.9 %)
In the 1960s	790 (14.6 %)	211 (4.6 %)	456 (8.9 %)	499 (9.7 %)	211 (12.6 %)	149 (7.8 %)	397 (16.1 %)	614 (13.4 %)
Before 1960	206 (3.8 %)	26 (0.6 %)	80 (1.6 %)	104 (2.0 %)	50 (3.0 %)	28 (1.5 %)	135 (5.5 %)	165 (3.6 %)
Missing	307	1190	624	613	4061	3831	3266	1139
Years used pesticide								
More than 20	3739 (69.2 %)	2632 (57.9 %)	3304 (64.8 %)	3185 (62.4 %)	716 (42.9 %)	631 (33.3 %)	1098 (44.6 %)	3081 (67.2 %)
11-20	906 (16.8 %)	927 (20.4 %)	912 (17.9 %)	982 (19.3 %)	400 (24.0 %)	441 (23.3 %)	431 (17.5 %)	786 (17.1 %)
6-10	338 (6.3 %)	395 (8.7 %)	389 (7.6 %)	396 (7.8 %)	247 (14.8 %)	317 (16.7 %)	314 (12.8 %)	325 (7.1 %)
2-5	333 (6.2 %)	447 (9.8 %)	392 (7.7 %)	427 (8.4 %)	247 (14.8 %)	369 (19.5 %)	424 (17.2 %)	297 (6.5 %)
1 year or less	85 (1.6 %)	141 (3.1 %)	102 (2.0 %)	112 (2.2 %)	58 (3.5 %)	135 (7.1 %)	193 (7.8 %)	97 (2.1 %)
Missing	330	1189	632	629	4063	3838	3271	1145

	Herbicides	Plant growth regulators	Fungicides	Insecticides	Poultry, livestock, or animal house area insecticides	Fumigants	Wood preservatives	Treated seed
Ever handled pesticide concentrate								
No	241 (4.5 %)	230 (5.1 %)	236 (4.6 %)	255 (5.0 %)	139 (8.4 %)	397 (21.1 %)[a]	454 (18.5 %)	-
Yes, sometimes	1139 (21.1 %)	1304 (28.7 %)	1178 (23.1 %)	1360 (26.6 %)	715 (43.2 %)	884 (47.1 %)	1160 (47.2 %)	-
Yes, often	4019 (74.4 %)	3002 (66.2 %)	3693 (72.3 %)	3491 (68.4 %)	800 (48.4 %)	597 (31.8 %)	846 (34.4 %)	-
Missing	332	1195	624	625	4077	3853	3271	-
Repair or maintain application or mixing equipment								
No	225 (4.1 %)	147 (3.2 %)	201 (3.9 %)	204 (4.0 %)	302 (18.3 %)	1248 (68.7 %)	1321 (54.9 %)	-
Yes	5206 (95.9 %)	4396 (96.8 %)	4904 (96.1 %)	4871 (96.0 %)	1344 (81.7 %)	568 (31.3 %)	1085 (45.1 %)	-
Missing	300	1188	626	656	4085	3915	3325	-
Usually wear personal protective equipment								
No	4764 (88.4 %)	496 (11.0 %)	545 (10.7 %)	414 (8.2 %)	393 (23.7 %)	322 (17.1 %)	761 (31.0 %)	1974 (44.1 %)
Yes	626 (11.6 %)	4020 (89.0 %)	4540 (89.3 %)	4662 (91.8 %)	1264 (76.3 %)	1559 (82.9 %)	1690 (69.0 %)	2503 (55.9 %)
Missing	341	1215	646	655	4074	3850	3280	1254

a, No or Not applicable

Self-reported health

Cohort members were asked to report any doctor diagnosed health outcomes. The categories of disease included were respiratory, neurological, circulatory, ophthalmic, dermatological, musculoskeletal, metabolic and other conditions including glandular fever, lead poisoning, pesticide poisoning, ulcerative colitis or Crohn's disease, injury (excluding head injury) from farm machinery, and head injury requiring medical attention. The lifetime prevalence was greater than 10 % for work related musculoskeletal injuries (23.5 %), high blood pressure (14.8 %) and asthma (10.4 %). Injury from farm machinery (9.9 %) and head injury (7.1 %) were also common in this occupational group. Health outcomes with a lifetime prevalence of less than 1 % included Alzheimer's disease, chronic obstructive pulmonary disease, chronic kidney infections, epilepsy, multiple sclerosis and Parkinson's disease.

Strengths and limitations

A key strength of the PIPAH Study is the breadth of the data, including comprehensive demographic, lifestyle and socioeconomic data and detailed information about use of pesticides, that have been and will be collected from a large group (>5000) of clearly defined professional pesticide users. These data, in combination with the data collected about past and current health conditions and the prospective design of the study, will allow the research team to conduct novel analyses exploring the relationships between pesticide exposure and health outcomes.

Another important strength of the study design is the planned repeated assessment of pesticide use, basic demographic and lifestyle factors, and self-reported health outcomes. Keeping this information current will improve assessment of exposure in future analyses, and repeat assessments will provide opportunities to add new question sets into the questionnaires. Flagging cohort members for notification of hospital episodes, and cancer or death registrations provides a very effective objective means of following up long-term health outcomes with minimal loss to follow up and no burden on participants.

Potential limitations of the study include the possibility of participation bias due to self-selective decisions to take part in the study. However, there is no evidence to suggest that the decision to take part in the study was influenced by participants' exposure or health. The proportions of males and females in the study sampling frame and the cohort were identical, but the age structure differed in that the cohort members were a little older.

The study relies on self-reported pesticide use rather than objective exposure measurements, which is a potential weakness. Exposure misclassification may occur, which may affect the ability of the study to investigate the real associations between pesticide exposure and health. Biological monitoring would provide a more accurate measure of the pesticide exposure actually experienced, but costs and logistics prevent this from being carried out on the full cohort. Future research investigating the health risks associated with particular pesticides and using biological monitoring to assess exposure could be undertaken on a subset of the cohort.

Collaboration

The PIPAH study was established as a national resource to enable the Health and Safety Executive and other researchers to conduct research into pesticide related health outcomes. The information collected has been designed to be comparable with other similar cohort studies and to enable data pooling. The PIPAH study is a member of AGRICOH, the international consortium of agricultural cohort studies, and we would welcome opportunities for research collaboration. For further information on accessing the anonymised research data already collected as part of this study or to contact researchers with research proposals, please contact the PIPAH study team (PIPAH@hsl.gsi.gov.uk). A copy of the baseline general questionnaire and the follow-up pesticide use questionnaire is available on the PIPAH webpage (http://www.hsl.gov.uk/resources/major-projects/pipah).

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Acknowledgements

The authors would like to thank the participants for their contribution and continuing support for the study. The authors would also like to thank City & Guilds for their assistance in recruiting the pesticide users into the study, and for enabling active engagement with study participants at the agricultural shows. Finally, the authors would like to thank the PIPAH study team for their many and varied contributions.

Contributors

DFo, GF, YC, DFi and AHH are all members of the study team, and were involved in the original concept and design of the study. NP contributed to the design of the study and the survey instruments. DFo, GF, YC and AHH were responsible for developing the survey tools, and for data collection, analysis, interpretation and drafting the manuscript. All the authors revised the manuscript, agreed with the findings and approved the final version.

Funding

This publication and the work it describes were funded by the GB Health and Safety Executive (HSE) and the GB Department for Environment, Food and Rural Affairs (Defra). Its contents, including any opinions and/or conclusions expressed, are those of the authors alone and do not necessarily reflect HSE or Defra policy.

Competing interests

None declared

Ethics approval

This study was reviewed and given a favourable opinion by the National Research Ethics Service Committee North West-Greater Manchester North (reference 12/NW/0654).

Data sharing statement

The PIPAH study was established as a national resource to enable the Health and Safety Executive and other researchers to conduct research into pesticide related health outcomes. The information collected has been designed to be comparable with other similar cohort studies and to enable data pooling. The PIPAH study is a member of AGRICOH, the international consortium of agricultural cohort studies, and we would welcome opportunities for research collaboration. For further information on accessing the anonymised research data already collected as part of this study or to contact researchers with research proposals, please contact the PIPAH study team (PIPAH@hsl.gsi.gov.uk). A copy of the baseline general questionnaire and the follow-up pesticide use questionnaire is available on the PIPAH webpage (http://www.hsl.gov.uk/resources/major-projects/pipah).

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Figure Legends (Titles)

Figure 1 The relationship between the registers of pesticide users, the PUHS and the target population

Figure 2 The PIPAH study flow chart

Figure 3 Frequency of fruit and vegetable, red and processed meat, and oily fish consumption

Figure 4 Past and current areas of pesticide work

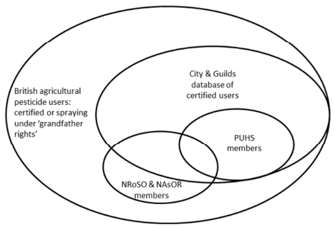

Figure 1 The relationship between the registers of pesticide users, the PUHS and the target population

555x396mm (96 x 96 DPI)

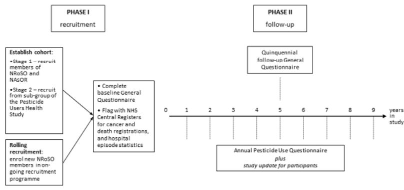

Figure 2 The PIPAH study flow chart

555x396mm (96 x 96 DPI)

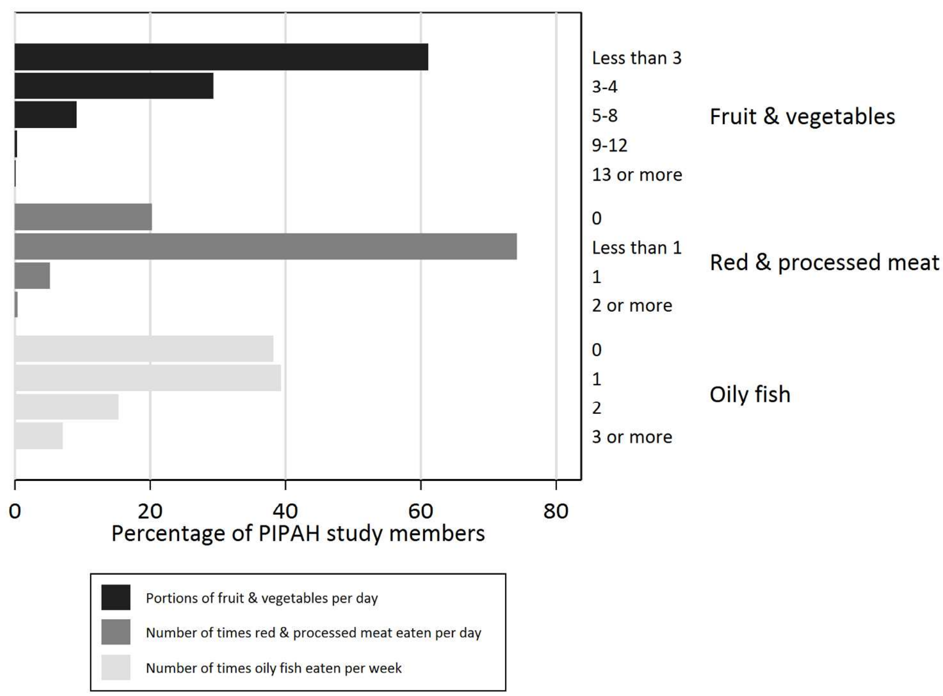

Figure 3 Frequency of fruit and vegetable, red and processed meat, and oily fish consumption

740x538mm (72 x 72 DPI)

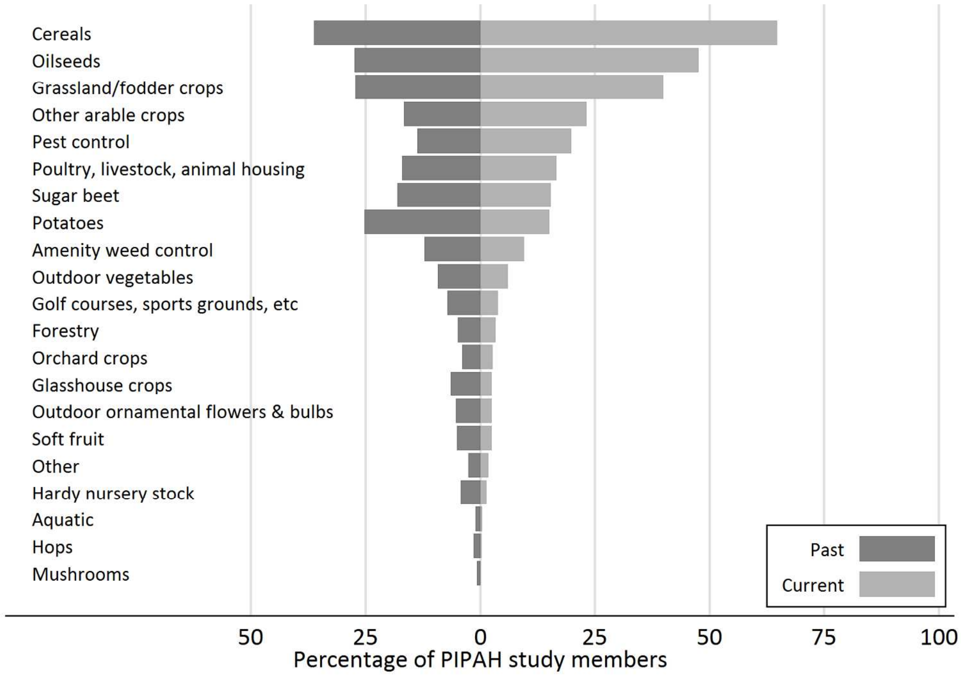

Figure 4 Past and current areas of pesticide work

740x538mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding The characteristics of the cohort are described using summary statistics (counts and percentages). There is no control for confounding.	12-19
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable

		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-19
		(b) Indicate number of participants with missing data for each variable of interest	11-19
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-19
		(*b*) Report category boundaries when continuous variables were categorized	17-18
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-15; 17-18
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-19
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.