Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study.

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Abstract

Objectives

Investigating the relationship between occupational exposure to pesticides and the risk of lymphoid neoplasms (LN) in men.

Methods

A hospital-based case-control study was conducted in six centres in France between 2000 and 2004. The cases were incident cases with a diagnosis of lymphoid neoplasm aged 18 to 75 years. During the same period, controls of the same age and gender as the cases were recruited in the same hospital, mainly in the orthopaedic and rheumatological departments. Exposures to pesticides were evaluated through specific interviews and case-by-case expert reviews. Four hundred and ninety-one cases (244 cases of non-Hodgkin's lymphoma (NHL), 87 of Hodgkin's lymphoma (HL), 104 of lymphoproliferative syndromes (LPS) and 56 of multiple myeloma (MM) cases) and 456 controls were included in the analyses. The odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regressions.

Results

Positive associations between HL and occupational exposure to triazole fungicides and urea herbicides were observed (OR=8.4 [2.2–32.4], 10.8 [2.4–48.1] respectively). Exposure to insecticides, fungicides and herbicides were linked to a three-fold increases in MM risk (OR=2.8 [1.2–6.5], 3.2 [1.4–7.2], 2.9 [1.3–6.5]). For LPS subtypes, associations restricted to hairy-cell leukaemia (HCL) were evidenced for exposure to organochlorine insecticides, phenoxy herbicides and triazine herbicides (OR=4.9 [1.1–21.2], 4.1 [1.1–15.5], 5.1 [1.4–19.3]), although based on small numbers. Lastly, despite the increased odds ratios for organochlorine and organophosphate insecticides, carbamate fungicides and triazine herbicides, no significant associations were evidenced for NHL.

Conclusions

The results, based on case-by-case expert review of occupation-specific questionnaires, support the hypothesis that occupational pesticide exposures may be involved in HL, MM and HCL and do not rule out a role in NHL. The analyses identified specific pesticides that deserve further investigation and the findings were consistent with those of previous studies.

MESH Keywords Adolescent ; Adult ; Aged ; Case-Control Studies ; Employment ; statistics & numerical data ; France ; epidemiology ; Fungicides, Industrial ; toxicity ; Herbicides ; toxicity ; Hodgkin Disease ; chemically induced ; epidemiology ; Humans ; Insecticides ; toxicity ; Leukemia, Hairy Cell ; chemically induced ; epidemiology ; Lymphoma ; chemically induced ; epidemiology ; Lymphoma, Non-Hodgkin ; chemically induced ; epidemiology ; Male ; Middle Aged ; Multiple Myeloma ; chemically induced ; epidemiology ; Occupational Diseases ; chemically induced ; epidemiology ; Occupational Exposure ; adverse effects ; statistics & numerical data ; Pesticides ; toxicity ; Young Adult

Author Keywords occupation ; pesticides ; farming ; lymphoma ; epidemiology.

INTRODUCTION

Lymphoid neoplasms (LN) are the most frequent cancers in France after smoking-related cancers, with around 17,000 new cases diagnosed each year.[1] The incidence of non-Hodgkin's lymphomas (NHL) increased in France over the 1980–2005 period, at an annual rate of 3% on average (2.7% in men), but the rate has leveled off over the last five years.[1]. The increase probably cannot be entirely explained by changes in registration. One hypothesis is that pesticide use may explain the increase. Although the prevalence of farming has decreased, the use and variety of pesticides increased until 2000, particularly among farmers[2]. Numerous studies have investigated the association between farming and the main types of LN. Meta-analyses have shown that farming was positively, but weakly, associated with NHL[3], Hodgkin's lymphoma (HL)[4] and multiple myeloma (MM)[5], and that the associations were more marked in the USA. Regarding occupational exposure to pesticides, case-control studies conducted in the USA[6–11], Canada[12, 13], Australia[14] and Europe [15–22] have shown associations between LN, especially NHL and MM, and various pesticide classes or chemical sub-families. Lymphoproliferative syndrome (LPS) has been less documented, but a French[23] and a Swedish case-control study[24] have shown positive relationships with hairy-cell leukaemia (HCL), a rare LPS subtype. The reports on the prospective Agricultural Health Study also evidenced increased NHL risks with the highest exposure to the herbicide, atrazine[25] and organochlorine insecticide, lindane[26], and increased MM risks with the highest exposure to the herbicides, alachlor[27] and glyphosate.[28] The roles of farming, crop growing and pesticide exposure in the main categories of LN (HL, NHL, LPS and MM), were investigated in a multicentre case-control study. In the present study, the role of occupational exposures to pesticides was evaluated through specific interviews and case-by-case expert reviews.

MATERIAL AND METHODS

Subjects

A hospital-based case-control study was carried out in the main hospitals of the French cities of Brest, Caen, Nantes, Lille, Toulouse and Bordeaux between September 2000 and December 2004. Pursuant to the French regulations at the time the study was conducted, the hospital-based design of the study was chosen to address the need for case and control blood samples. Eligible cases were subjects of either gender, aged 20–75 years, residing in the hospital's catchment area and recently diagnosed with any lymphoid neoplasm except acute lymphoid leukaemia. The diagnoses were classified using the WHO ICD-O-3 codes. All the diagnoses were cytologically or histologically confirmed and reviewed by a panel of pathologists and haematologists. Patients with a history of immunosuppression or taking immunosuppressant drugs were not eligible. The present analysis only includes men, whose occupational pesticide use was nearly three times more prevalent than that for women. Of the 513 male eligible cases during the recruitment period, 22 (4.3%) refused the interview. Thus, the study sample comprised 491 incident cases of LN, classified using the ICD-O-3 codes (Table 1), and further divided into four broad categories: HL (n=87), NHL (n=244), MM (n=56) and LPS (n=104).

Except for the LPS cases, most of the cases (88.1%) were recruited within 3 months of diagnosis (median: 34 days). Inclusion of LPS cases was allowed up to 18 months post-diagnosis due to their excellent survival and the usual uncertainty with respect to the actual date of disease onset

The controls were patients with no prior history of LN, recruited in the same hospitals as the cases, mainly in orthopaedic and rheumatological departments and residing in the hospital's catchment area (i.e. in the hospital département or in the immediately neighbouring départements). In order to avoid overestimation of factors of interest, patients admitted for cancer or a disease directly related to occupation, smoking or alcohol abuse were not eligible as controls, but a history of such diseases did not prevent control selection. The controls were individually matched with the cases by centre, age (± 3 years) and gender. The aim of the matching was to ensure that at least one control would be available for each case. Out of the 501 eligible male controls ascertained during the recruitment period, 44 (8.8%) refused to participate. A further control was excluded since his interview was incomplete. Thus, 456 men were included as controls in the analysis. The reasons for hospitalization were most often orthopaedic or rheumatological (fractures (21.3%), wounds (1.3 %), other non-occupational injuries (12.5%), osteoarthritis (23.0%), back diseases (15.6%), polyarticular diseases (2.9%), infectious diseases of the bones and joints (2.6%), minor musculoskeletal malformations (2.0%), other diseases of the bones and joints (6.8%), peripheral nervous disorders (1.3%)), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue diseases (1.8%) and infections (3.0%).

Data collection

Both the patients and interviewers were blind to the study hypotheses. Data collection was conducted in two stages. The case and control patients first completed a standardized self-administered questionnaire on their socioeconomic characteristics, familial medical history, and lifelong residential and occupational histories. For each job held for at least six months, the subjects were asked to report the job title, company name and business (if appropriate), the start and end dates of the job, and a description of the specific tasks and products personally handled (open-ended question).

The patients then underwent a face-to-face interview (average duration: 80 minutes) by trained staff using a structured standardized questionnaire eliciting personal and familial medical histories, lifestyle characteristics (smoking and alcohol, tea and coffee consumption) and outdoor leisure activities. Non-occupational exposure to pesticides was sought through questions about gardening (use of insecticides, fungicides and herbicides, pesticide targets and periods of use) and use of insecticides in the home (with questions on insect target and period of use). At the end of the interview, the self-administered questionnaire was reviewed with the interviewer. Finally, a specific agricultural occupational questionnaire was systematically administered to each patient who had worked as a farmer or gardener for at least 6 months during any period of his life. This questionnaire was designed to allow standardized case-by-case pesticide exposure assessment by experts. First, all the farms where the patient had worked for at least 6 months were listed with location, period of occupation and area, and with the farmer's status (owner, worker, helper) at that time. A farm was considered to become a different farm if its size changed. Secondly, for each farm, the crops and animal husbandry were listed with their mean sizes. Then, all the pesticides used on each crop during a given period were reported. The subjects were asked whether they had personally prepared the pesticide mixture and whether they had personally sprayed it. They were also asked to state the chemical used and, if possible, its brand name, main use, type of spraying equipment used, and the annual number and duration of applications. The questionnaire also elicited the use of pesticides in farm buildings for animals, grain, hay or straw, or to clear lanes and yards. The interviewers underwent a short specific training course on farming given by occupational hygienists, and were asked to systematically request consent to possible repeat interviews.

Blood samples were obtained from the cases and controls after consent form signature and the biological specimens (sera, constitutional DNA, tumour tissue) were placed on storage. The study protocol complied with the French regulations relating to databases and ethics and the pertinent approvals (CNIL No. 90003 and DGS No. 2000/0107, respectively) were obtained.

Case-by-case pesticide exposure assessment

Two persons, one occupational hygienist (LD) trained on retrospective evaluation of farming exposures for epidemiology and an agronomist specialized in the technical aspects of pesticide handling (PD), individually reviewed each self-administered questionnaire and specific questionnaire. Most of the 168 subjects who were administered the specific agricultural occupational questionnaire had to be re-interviewed by telephone because the information was insufficient. Repeat interviews of 95 subjects (56.8%) were conducted, but not of 35 others (20.8%), who refused (n=15), had died, were in poor health (n=10), or could not be contacted (n=15). The whole process was blind to case-control status and the proportion of patients re-interviewed was the same for the cases and controls. The experts reviewed the consistency of the subjects' statements with respect to product availability dates, type and size of the crops, geographic location of the farm and frequency of treatment, and coded the chemical using a 3-digit ad hoc code (1st digit: pesticide category: insecticides, fungicide, herbicide; 2nd digit: chemical family [e.g. organochlorine insecticide, carbamate fungicide, etc.]; 3rd digit: chemical sub-family [e.g. DDT, Lindane, etc.]. A database was constructed using the annual directories of phytochemicals published by the Association de Coordination Technique Agricole and used to facilitate the process. The directories include the recommendations for use of the products, which are identified by their chemical and brand names, by crop and pest.

When information on pesticides was missing or unreliable, the experts were asked to allocate a list of chemicals that may have been used, based on the crops treated, method of spraying, period and frequency of treatment and pests targeted. They also provided the likelihood of each suggested exposure.

Variables analysed

Jobs were coded using the 1968 edition of the International Labour Office (ILO) classification. Socioeconomic categories were generated from the last job held and encoded at the two-digit level. For all exposure variables, the subjects never exposed to the specific crop, animal or pesticide were taken as the reference category. Dichotomous variables were generated for exposure to crops, animal husbandry, each pesticide category (insecticide, fungicide, herbicide) and chemical family. Two exposure definitions were used. The wider definition, possible or definite exposure, included any declared exposures and those assessed by the experts for missing values. The narrower definition, definite exposure, was restricted to the exposures that were considered certain by the experts, and those that had been assigned to missing values with a probability of at least 70%. The duration of exposure to each crop, animal, pesticide category or chemical family was obtained by summing all the periods in which the specific crop, animal, pesticide or chemical family was present. The resulting variables were classified with respect to the median durations of exposure among the exposed controls as: never exposed; duration <median; duration ≥median. The intensities of exposure as a function of the type of spraying equipment and annual number of passages could not be quantified because there were too many missing values.

Statistical analysis

All the analyses were performed using SAS software V.9.1. The initial pair-matching used as a basis for the recruitment was broken to allow the use of the whole control group for the analysis of all LN types, with stratification by age (5-year age groups) and centre. The controls that belonged to strata without a case of the subgroup LPS, HL, NHL or MM under study were excluded from the corresponding

unconditional analyses. Odds ratios (OR) and their 95% confidence intervals (95% CI) were estimated using unconditional logistic regression models including the stratification variables, age and centre, as categorical variables. Tests for trend of duration were conducted by fitting models using a quantitative variable equal to the median value of the exposure classes (0, duration <overall median, duration ≥ overall median). Analyses were conducted separately for the LN subgroups (HL, NHL, LPS and MM) and for all LN taken together. Additional analyses by NHL subtype (diffuse large B-cell lymphoma [DLCL], follicular lymphoma [FL], other NHL) and LPS subtype (chronic lymphocytic leukaemia [CLL], hairy-cell leukaemia [HCL]) were conducted by polytomous logistic regression with a nominal non-ordered response variable in which the comparator group was the specific LN subgroup's control set.

In order to check the robustness of the results, conditional logistic regressions restricted to the pair-matched case-control samples were also conducted and sensitivity analyses were performed by excluding the subjects in each centre and the controls sharing the same broad reason-for-admission category, in turn, from the analyses.

In an attempt to disentangle multiple pesticide exposures, all the combinations of pesticide families associated with the LN subtype considered and with a p-value of at least 10%, were included, two by two, in the logistic models.

All p-values were two-sided and considered significant at the 0.05 level.

Study power

For NHL, with a power of 80% and a two-sided alpha error of 5%, the size of the study sample was sufficient to evidence OR ranging from 1.7 to 3.3 for exposures with prevalences ranging from 2 to 20%. For the other types of LN (HL, LPS, MM), OR between 2.0 and 6.0 could be evidenced for the same exposure prevalences.

RESULTS

Distribution of cases and controls by stratification and socioeconomic variable

The use of the whole control group assigned more than 2 controls per case in most strata, except for the youngest categories, in which HL predominated. This led to significant age difference between the cases and controls. Significant differences between the centres were also observed, mainly because Caen hospital recruited a higher proportion of LPS than the other centres. With regard to socioeconomic characteristics, the cases and controls were well balanced with respect to socioeconomic category, urban or rural residential status and educational level, except for the HL cases, who were less often factory workers than the controls (supplementary Table A).

Farming practices

Agricultural questionnaires were administered to the 168 subjects who reported having worked on a farm (97 cases, 71 controls) and 257 different farms were thus described. Mixed farming predominated since only 16 farms (6.2%) were specialised in a specific crop with no animal husbandry and only 3 (1.2%) in specific animal husbandry with no crop growing. Cereal growing and cattle farming were the main prevalent practices, despite the fact that their weight in farming practices decreased over time. Most of the farms were of medium size, and the overall size had increased with time over the 3 last decades in all regions. The largest farms were located in the south-west of France while large cattle farms were located in the west and north. As expected, vineyards were more prevalent in the south-west (supplementary Table B).

Farming, crop growing and animal husbandry

The associations between farming (crops and animal husbandry) and the main categories of LN are shown in Table 2. Employment for at least 6 months in an agriculture-related job was significantly associated with all LN except LPS. The associations were more marked for farm owners and for agricultural workers employed for more than 20 years.

Cereal growing and corn growing were significantly and positively associated with both NHL and HL and marginally with MM. Beet and colza growing were also associated with NHL. Positive associations between vines and MM (OR [95% CI]: 4.6 [1.4–14.9]) and between forage and HL (3.0 [1.1–8.5]) were observed. No crop was related to LPS considered overall, but subtype analyses revealed estimates near 1.0 for CLL. The associations for HCL were greater and significant for cereal, corn and vine growing (3.5 [1.1–11.3], 7.6 [2.1–28.1] and 8.5 [1.6–44.6], respectively). No difference between the DLCL and FL NHL subtypes was observed, irrespective of crop. With regard to animal husbandry, pig breeding was related to HL (3.8 [1.3–11.1]) and sheep breeding to the FL (5.6 [1.7–18.6]) subtype. No other significant association was observed.

Occupational exposure to pesticides

Table 3 shows the associations between pesticides and the main LN subgroups. Overall, the OR associated with exposure to pesticides were 1.5, 2.1 and 3.5 for NHL, HL and MM, respectively. The association was significant for MM. Only 2 cases and no controls were exposed to insecticides only; 9 cases and 2 controls were exposed to fungicides only; 3 cases and 3 controls were exposed to herbicides

only. Most of the subjects (40 cases and 26 controls) were exposed to all three pesticide categories. Overall, significant associations between MM and the use of insecticides, fungicides and herbicides and between HL and the use of fungicides and insecticides (borderline significance) were observed. Detailed analyses showed significant associations between MM and fungicides (benzene, amide, and morpholine derivatives) and herbicides (picoline and urea derivatives) but not with particular insecticides. For HL, positive associations with all organic insecticides were evidenced, although the association was only marginally significant for organophosphates. HL was also significantly associated with carbamate and triazole fungicides and with the herbicide groups: carbamates, phenoxy and picoline derivatives, amides and urea derivatives. In an attempt to disentangle multiple pesticide exposures, all the combinations of pesticide families associated with the LN subtype considered with a p-value of at least 10% were included, two by two, in the logistic models. Some exposures were highly correlated and could not be separated. HL was significantly associated with triazole fungicides and urea herbicides. However, the exposures could not be distinguished since 8 of the 9 subjects who had used urea herbicides had also used triazole fungicides, both pesticides being applied to cereals, corn and sunflowers. Similarly, all the subjects who had used carbamate insecticides had also used pyrethrin insecticides. No significant association was evidenced for NHL or LPS. The analyses by NHL and LPS subtypes showed similar estimates for the DLCL and FL subtypes (Table 4). In contrast, the associations with LPS subtypes differed, with lower OR for CLL and higher OR for HCL, for most exposures. Although the numbers were very small, HCL was significantly associated with organochlorine insecticides, phenoxyacetic herbicides and triazine herbicides (4.9 [1.1–21.2], 4.1 [1.1–15.5], 5.1 [1.4–19.3], respectively).

Non-occupational exposure to pesticides

The use of pesticides taken together and the uses of insecticides, fungicides or herbicides for gardening were not associated with LN or any LN subtype (Table 3). The domestic use of insecticides was more frequent among HL cases than among controls.

Stability of the results

Similar patterns were observed when different lag times were considered, i.e. when the 10, 20, 30 or 40 years prior to diagnosis or interview were considered unexposed. However, for HL, it was impossible to investigate long latency periods (Supplementary Table C). The patterns were also similar when the exposure was restricted to time windows of 0–10, 10–20, 20–30, 30–40 years before diagnosis or interview.

With a view to limiting exposure to definite exposure, the subjects possibly exposed were pooled with the unexposed subjects. The analyses based on that definition gave higher estimates for all the significant associations evidenced for HL, while for MM the OR became lower and non-significant. Lastly, the results were the same when the category ‘never used any pesticides' was taken as reference. It is noteworthy that the relationship with agricultural jobs was restricted to pesticides users (1.7 [1.1–2.7] and 1.3 [0.8–2.1] for users and non-users, respectively).

The results remained stable after adjustment for the rural/urban status of the place of residence, type of housing (flat/house), educational level and factors related to LN in previous analyses (history of mononucleosis, history of influenza immunization, familial history of cancer, skin characteristics, smoking status, alcohol drinking status). The results were also unchanged when conditional analyses were performed, or when the missing values were all considered “never used” or “ever used”. Lastly, the estimates did not change when each centre and each group of controls sharing a similar reason for admission were excluded, in turn, from the analysis.

DISCUSSION

In the present study, MM was significantly associated with insecticides, fungicides and herbicides and HL, with all organic insecticides, carbamate and triazole fungicides and urea derivatives. Significant associations between HCL and organochlorine insecticides, and phenoxyacetic and triazine herbicides were observed. Despite increased OR with organochlorine and organophosphate insecticides, carbamate fungicides and triazine herbicides, no significant associations were evidenced for NHL. A clear relationship between HL and domestic use of insecticides, in line with the relationship observed with pyrethrins, was also observed.

The hospital-based design, required for the blood samples, was carefully implemented in order to recruit the cases and controls from the same population. Recruitment was restricted to cases and controls residing in the hospital catchment areas and the cases were recruited from the main hospital and not from private clinics. Recruitment from clinics might have attracted a specific population that might have been better informed and/or receiving better care. All the cases diagnosed in the hospitals during the recruitment period were systematically contacted and the refusal rate was low (4.3%). Thus, there is no obvious reason for preferential selection of cases more exposed to specific occupational exposures, particularly pesticides. Moreover, the results were shown to be robust in the sensitivity analyses in which each center was excluded in turn. This suggests that the results are not explained by local selection. Selection by survival could have occurred if exposure to pesticides is related to the seriousness of the disease or the response to treatment, which is unlikely. In addition, only incident cases were recruited and inclusion took place within 6 months of diagnosis and within 3 months for most subjects (88.1%), which minimizes the possibility of a survival bias.

The controls were mainly recruited in rheumatological and orthopaedic departments and were residents of the hospital catchment areas. The controls had not been admitted for diseases related to smoking or drinking in order to avoid overrepresentation of those habits, which are known to be less frequent among farmers. Inclusion of those diseases could thus have led to under-representation of farmers among the controls. The controls were not admitted for occupational diseases or injuries. Overall, the control diseases are not known to be related to farming or exposure to pesticides. Control non-eligibility was based on the reason for hospital admission and not on the subject's medical history. Controls who had had smoking- or alcohol-related or occupational diseases/injuries in the past were eligible. Furthermore, the results are unlikely to be due to a particular control subgroup since the sensitivity analyses, in which each group of controls sharing similar reasons for admission was excluded in turn, did not generate different results. Similarly, conditional analyses, in which independent control groups were used for each LN case subgroup, yielded estimates similar to those of the unconditional regression analyses. Smoking and drinking were as prevalent in the control group as in the national survey, 'Enquête Décennale Santé', for the same geographical areas and age groups.[29] Lastly, the controls reported the specific regional farming practices expected on the basis of the surveys by the French Ministry of Agriculture.[30]

In order to limit differential misclassifications, the information was collected from the cases and controls, under very similar conditions, in hospital and by the same interviewer, using standardized structured questionnaires. The patients and interviewers were informed that the study was related to 'the environment and health', but were unaware of any specific hypotheses connected to a particular practice or product. Occupational pesticide exposure was elicited using a standardized structured ad hoc occupational questionnaire and case-by-case exposure was assessed blind to case/control status. The occupational hygienist reviewed each questionnaire blind to case/control status; the additional telephone interviews that were made to obtain more precise data or correct inconsistencies were administrated as frequently for cases as for controls. Lastly, the same proportions of missing values were observed for cases and controls. Because of those measures, differential misclassification is unlikely to explain the results.

Non-differential misclassification is probably more important since exposure was based on the patient's recall, but it is expected to be more marked for pesticide reports than for crop or husbandry reports.[31–34] Non-differential misclassification may have reduced power, particularly for specific pesticides and/or for products used long before inclusion or for a short period. The use of a sensitive definition of exposure ('possible exposure') may also have contributed to non-differential misclassification; use of a more specific definition (definite exposure) yielded similar or stronger results.

All the analyses were adjusted for age and centre for all LN, and for socioeconomic category also for HL. Additional analyses in which education, housing and socioeconomic category were included as potential confounders were performed even though the cases and controls did not differ with respect to those characteristics. The results were unchanged. In addition, factors previously evidenced in other reports on the study, such as influenza immunization, previous history of mononucleosis[35], skin type[36] and smoking and alcohol drinking status[37], were also accounted for. There was no substantial change in the results. Confounding by other pesticide exposures could not be controlled since all pesticide uses were closely related to each other.

The number of exposures and LN categories led to multiple comparisons. Therefore, some of the results, particularly those for HL and MM, may have been observed by chance. Conversely, true associations may have remained undetected due to lack of power. That could be the case for NHL, which was positively, but not significantly, related to several pesticides. For NHL, the size of the study allowed minimum detectable OR ranging from 1.9 to 4.6, for an alpha error of 5%, a power of 80%, and a risk factor prevalence ranging from 1 to 10%.

Nevertheless, the non-significant associations between NHL and organochlorine (1.8 [0.9–3.8]) and organophosphate (1.7 [0.9–3.3]) insecticides observed are consistent with those previously reported in the literature and have similar orders of magnitude. Among the LN, NHL has been most investigated with respect to occupational exposure to pesticides, although the definition of NHL varies across the studies. Case-control studies carried out in the USA[38, 39], Australia[14] and Canada[40] have shown positive associations with occupational exposure to organochlorine insecticides. Exposure to organophosphate insecticides was also related to NHL in the pooled analysis of the three case-control studies conducted by the NCI.[41] It is noteworthy that, in the present study, almost all the subjects who reported having used organophosphate also reported having used organochlorine insecticides. The two exposures cannot therefore really be distinguished. The association between NHL and exposure to triazine herbicides (OR=1.9 [0.9–3.8]) observed in the present study is consistent with the association with atrazine reported by the agricultural health study[25] and in the pooled analysis of the NCI case-control studies.[10] Phenoxy herbicides (including 2,4-D, 2,4,5-T, MCPA) were associated with NHL in some[40, 42, 43], but not all[10, 19] studies. In the present study, there was no indication of any association with phenoxy herbicides (OR=0.9 [0.4–1.9]).

Several studies have also reported associations between MM and pesticide exposure.[18] Phenoxy herbicides were positively related to MM in case-control studies carried out in Sweden[16] and Canada.[13] Recently, the Agricultural Health Study also evidenced increased risks of MM for the highest category of exposure to the herbicides Alachlor[27] and Atrazine.[25]

The relationships between LPS and pesticide exposure remain poorly documented. Nevertheless, the associations with HCL observed in the present study, although based on very small numbers, are consistent with the findings reported by Clavel et al [23] and Nordström et al..[24]

Even fewer studies have investigated the relationship between HL and occupational pesticide exposure. Franceschi et al.[44] reported increased OR for the longest occupational and non-occupational exposures to pesticides and herbicides, while a recent Canadian case-control study[13] failed to reveal any association with exposure to phenoxy herbicides.

CONCLUSION

The results of this study, based on case-by-case expert review of occupation-specific questionnaires, support the hypothesis that occupational pesticide exposures may be involved in HL, MM and HCL and do not rule out a role in NHL. Consistently with previous publications, the analyses identified specific pesticides that deserve further investigation.

MAIN MESSAGES

The case-control study incorporated careful expert case-by-case review of occupational exposure to pesticides.

Occupational exposures to several pesticides were significantly associated with multiple myeloma, Hodgkin's lymphoma and hairy-cell leukaemia. Non-significant positive associations with non-Hodgkin's lymphoma were also observed.

POLICY IMPLICATIONS

The results strengthen the hypothesis that occupational pesticide exposures may be involved in the aetiology of lymphoid neoplasms.

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Footnotes:

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Abbreviations

CLL: chronic lymphocytic leukaemia
DLCL: diffuse large cell lymphoma
FL: follicular lymphoma
HCL: hairy-cell leukaemia
HL: Hodgkin's lymphoma
ICD-O-3: international classification of disease for oncology, third edition
ILO: international labour office
LN: lymphoid neoplasm
LPS: lymphoproliferative syndrome
MM: multiple myeloma
NHL: non Hodgkin's lymphoma
SEC: socioeconomic category

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Table 1

Distribution of cases by ICD-O-3 classification

Diagnosis	ICD-O-3 Codes	n
Hodgkin's lymphoma (HL)	9650-9667/3	**87**
non-Hodgkin's lymphoma (NHL)		**244**
B-cell		204
Diffuse large B-cell (DLCL)	9679-9680/3	107
Follicular (FL)	9690/3	50
Waldenstrom macroglobulinaemia	9671/3	16
Marginal zone B-cell (MALT type)	9699/3	9
Splenic marginal zone B- cell	9689/3	1
Mantle-cell	9673/3	21
T-cell		21
Mature T-cell, NOS	9702/3	3
Angioimmunoblastic T-cell	9705/3	2
Cutaneous T-cell, NOS	9709/3	1
Anaplastic large cell, T cell and Null cell type	9714/3	8
Intestinal T-cell	9717/3	1
Precursor T-cell lymphoblastic	9729/3	6
other		19
Non-Hodgkin lymphoma, NOS	9591/3	12
Burkitt-like lymphoma	9687/3	7
Multiple Myeloma (MM)	9732/3	**56**
Lymphoproliferative syndrome (LPS)		**104**
Chronic lymphocytic leukaemia (CLL)	9823/3, 9670/3	77
Hairy-cell leukaemia (HCL)	9940/3	27

Table 2

Association between farming, exposure to crops and animal husbandry and LN.

	NHL (244 Ca/436 Co)			HL (87 Ca/265 Co)			LPS (104 Ca/305 Co)			MM (56 Ca/313 Co)			All LN (491 Ca/456 Co)		
	Ca/Co	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**
Job title															
Farmers, agricultural or forestry workers (ILO 6)	59/92	1.5	[1.0–2.3]	15/56	1.5	[0.7–3.2]	33/77	1.4	[0.8–2.4]	19/71	2.2	[1.1–4.6]	126/94	1.6	[1.1–2.2]
Farm owners (ILO 6.1)	19/25	1.9	[1.0–3.7]	7/13	5.3	[1.6–17.2]	9/23	1.3	[0.5–3.1]	10/23	4.1	[1.6–10.5]	45/25	2.3	[1.3–3.9]
Agricultural workers (ILO 6.2)	51/73	1.7	[1.1–2.7]	11/41	1.5	[0.6–3.3]	30/62	1.5	[0.8–2.7]	14/55	1.9	[0.8–4.2]	106/75	1.7	[1.1–2.4]
Crops															
Cereals	33/42	1.9	[1.1–3.2]	9/18	4.0	[1.5–10.7]	22/41	1.5	[0.8–2.9]	11/35	2.2	[1.0–5.2]	75/43	2.0	[1.3–3.1]
Corn	21/23	1.9	[1.0–3.7]	6/11	3.2	[1.0–10.3]	10/18	1.8	[0.8–4.4]	7/19	2.7	[1.0–7.2]	44/23	2.0	[1.2–3.5]
Beet	24/26	2.3	[1.2–4.3]	3/9	2.2	[0.5–10.0]	17/24	1.9	[0.9–4.0]	5/21	1.4	[0.4–4.3]	49/26	2.1	[1.2–3.5]
Grape vines	12/13	1.8	[0.8–4.2]	1/8	0.8	[0.1–7.3]	6/11	2.3	[0.7–7.2]	6/11	4.6	[1.4–14.9]	25/13	2.0	[1.0–4.2]
Potatoes	19/27	1.5	[0.8–3.0]	4/8	3.6	[0.9–14.3]	13/25	1.3	[0.6–2.9]	6/22	1.5	[0.5–4.4]	42/27	1.6	[0.9–2.7]
Vegetables	14/26	1.0	[0.5–2.1]	3/13	0.9	[0.2–3.8]	12/21	1.9	[0.8–4.2]	5/19	1.6	[0.5–4.9]	34/26	1.3	[0.8–2.3]
Forage	25/37	1.5	[0.8–2.7]	7/17	3.0	[1.1–8.5]	15/38	0.9	[0.4–1.8]	9/34	1.6	[0.7–3.9]	56/38	1.6	[1.0–2.5]
Animal husbandry															
Cattle	37/54	1.5	[0.9–2.5]	7/24	1.6	[0.6–4.4]	24/49	1.4	[0.7–2.6]	10/46	1.3	[0.6–3.1]	78/55	1.5	[1.0–2.3]
Sheep	10/17	1.3	[0.6–3.1]	2/6	1.6	[0.3–9.4]	4/16	0.5	[0.2–1.7]	1/15	0.3	[0.0–2.8]	17/17	1.0	[0.5–2.0]
Pigs	19/34	1.1	[0.6–2.1]	7/13	3.8	[1.3–11.1]	17/31	1.6	[0.8–3.2]	5/28	1.0	[0.3–2.9]	48/34	1.4	[0.9–2.4]
Horses	21/33	1.4	[0.7–2.6]	3/14	1.3	[0.3–5.3]	19/32	1.8	[0.9–3.6]	3/28	0.5	[0.1–1.8]	46/34	1.4	[0.9–2.3]
Rabbits	11/27	0.9	[0.4–1.9]	4/11	2.4	[0.6–8.6]	16/26	1.6	[0.8–3.4]	5/24	1.3	[0.4–3.8]	36/27	1.4	[0.8–2.4]
Poultry	23/39	1.3	[0.7–2.3]	6/15	2.2	[0.7–6.6]	20/35	1.6	[0.8–3.1]	6/32	1.0	[0.4–2.8]	55/39	1.5	[0.9–2.3]

OR [95%CI] were estimated by unconditional logistic regression including the stratification variables, age, centre and SEC (white collar/blue collar); NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma, LPS: Lymphoproliferative syndrome; MM: Multiple myeloma; LN: Lymphoid neoplasm.

Table 3

Association between pesticides exposure and lymphoid neoplasm (LN)

	NHL (244 Ca/436 Co)			HL (87 Ca/265 Co)			LPS (104 Ca/305 Co)			MM (56 Ca/313 Co)			All LN (491 Ca/456 Co)		
	Ca/Co	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**	**Ca/Co**	**OR**	**[95% CI]**
Occupational pesticide use	32/47	1.5	[0.9–2.5]	9/24	2.1	[0.8–5.2]	15/39	1.2	[0.6–2.4]	15/37	3.5	[1.6–7.7]	71/47	1.7	[1.1–2.5]
Insecticides	26/37	1.5	[0.8–2.6]	8/19	2.3	[0.9–6.0]	11/30	1.1	[0.5–2.5]	11/29	2.8	[1.2–6.5]	56/37	1.6	[1.0–2.5]
Organochlorine	15/17	1.8	[0.9–3.8]	4/6	4.7	[1.1–20.8]	8/15	1.7	[0.7–4.4]	4/16	1.4	[0.4–4.8]	31/17	1.9	[1.0–3.5]
Organophosphate	20/24	1.7	[0.9–3.3]	6/12	3.0	[1.0–9.4]	5/20	0.8	[0.3–2.2]	6/20	2.2	[0.8–6.2]	37/24	1.6	[0.9–2.8]
Pyrethrin	10/17	1.3	[0.5–2.9]	7/11	3.6	[1.2–11.2]	1/14	0.2	[0.0–1.8]	5/14	3.1	[1.0–10.0]	23/17	1.4	[0.7–2.7]
Fungicides	26/35	1.6	[0.9–2.8]	9/17	4.5	[1.6–12.2]	11/34	1.0	[0.5–2.2]	13/32	3.2	[1.4–7.2]	59/35	1.8	[1.2–2.9]
Carbamates	15/17	1.8	[0.9–3.7]	5/9	5.1	[1.4–18.4]	4/16	0.8	[0.3–2.7]	6/15	2.9	[1.0–8.6]	30/17	1.9	[1.0–3.5]
Imide	6/10	1.1	[0.4–3.2]	3/4	5.2	[1.0–27.8]	2/10	0.6	[0.1–2.9]	5/10	3.3	[1.0–11.0]	16/10	1.6	[0.7–3.6]
Triazole	8/9	1.9	[0.7–5.3]	6/6	8.4	[2.2–32.4]	1/9	0.4	[0.0–3.1]	3/8	3.4	[0.8–14.6]	18/9	2.2	[0.9–4.9]
Herbicides	25/42	1.3	[0.7–2.2]	7/22	1.5	[0.6–4.1]	9/34	0.7	[0.3–1.7]	12/32	2.9	[1.3–6.5]	53/42	1.3	[0.8–2.0]
Phenoline	13/17	1.7	[0.8–3.7]	4/8	4.3	[1.1–17.2]	5/15	0.8	[0.3–2.4]	5/16	2.0	[0.6–6.1]	27/17	1.7	[0.9–3.2]
Phenoxy	11/25	0.9	[0.4–1.9]	6/14	2.5	[0.8–7.7]	7/20	1.0	[0.4–2.5]	7/20	2.6	[0.9–7.0]	31/25	1.3	[0.7–2.2]
Picoline	5/10	1.0	[0.3–3.2]	5/4	9.4	[2.0–43.1]	0/8	.	.	4/8	3.9	[1.0–14.7]	14/10	1.5	[0.6–3.4]
Triazine	17/20	1.9	[0.9–3.8]	5/10	3.2	[0.9–10.9]	8/17	1.6	[0.6–4.0]	4/17	1.7	[0.5–5.9]	34/20	1.8	[1.0–3.3]
Amide	5/12	0.9	[0.3–2.8]	6/8	3.8	[1.1–12.7]	2/8	0.6	[0.1–3.2]	1/8	0.8	[0.1–7.0]	14/12	1.2	[0.5–2.7]
Urea	5/7	1.8	[0.5–6.0]	5/4	10.8	[2.4–48.1]	4/7	1.7	[0.4–6.4]	5/6	7.2	[1.8–28.4]	19/7	2.9	[1.2–7.0]
Quaternary ammonium	4/12	0.7	[0.2–2.3]	2/7	1.3	[0.2–7.3]	5/11	1.5	[0.5–4.9]	2/9	1.6	[0.3–8.2]	13/12	1.1	[0.5–2.5]
Glyphosate	12/24	1.0	[0.5–2.2]	6/15	1.7	[0.6–5.0]	4/18	0.6	[0.2–2.1]	5/18	2.4	[0.8–7.3]	27/24	1.2	[0.6–2.1]
Garden pesticide use	123/194	1.4	[1.0–2.0]	23/103	0.9	[0.5–1.6]	61/164	0.9	[0.6–1.6]	26/146	0.9	[0.5–1.7]	233/201	1.1	[0.9–1.5]
Insecticides	81/133	1.2	[0.8–1.7]	11/68	0.6	[0.3–1.3]	39/112	0.9	[0.5–1.5]	13/97	0.6	[0.3–1.2]	144/138	0.9	[0.7–1.2]
Fungicides	38/60	1.2	[0.7–1.9]	4/31	0.6	[0.2–1.7]	23/49	1.7	[0.9–3.0]	9/50	1.1	[0.5–2.4]	74/61	1.2	[0.8–1.7]
Herbicides	86/155	1.0	[0.7–1.5]	19/84	0.8	[0.4–1.6]	49/130	1.0	[0.6–1.6]	22/115	1.0	[0.6–2.0]	176/161	1.0	[0.7–1.3]
Domestic insecticide use	74/142	1.1	[0.7–1.5]	38/74	2.9	[1.6–5.4]	46/114	0.9	[0.5–1.6]	16/108	0.6	[0.3–1.3]	174/150	1.2	[0.9–1.6]

OR [95%CI] were estimated by unconditional logistic regression including the stratification variables, age, centre and SEC (white collar/blue collar); NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; LPS: Lymphoproliferative syndrome; MM: Multiple myeloma; LN: Lymphoid neoplasm.

Table 4

Occupational pesticide use by non-Hodgkin's lymphoma (NHL) and lymphoproliferative syndrome (LPS) subtype

	NHL						LPS					
	Diffuse Large Cell lymphoma (n=107)			Follicular Lymphoma (n=50)			Chronic Lymphocytic Leukaemia (n=77)			Hairy-cell Leukaemia (n=27)		
	Ca/Co	OR	[95% CI]	Ca/Co	OR	[95% CI]	Ca/Co	OR	[95% CI]	Ca/Co	OR	[95% CI]
Pesticides	16/47	1.7	[0.9–3.4]	6/47	1.3	[0.5–3.5]	10/39	0.9	[0.4–2.0]	5/39	3.0	[0.9–10.2]
Insecticides	13/37	1.8	[0.9–3.7]	6/37	1.7	[0.6–4.5]	7/30	0.8	[0.3–2.1]	4/30	2.8	[0.8–10.1]
Organochlorine	7/17	2.0	[0.8–5.2]	4/17	2.5	[0.7–8.3]	5/15	1.2	[0.4–3.7]	3/15	4.9	[1.1–21.2]
Organophosphate	8/24	1.5	[0.6–3.7]	6/24	2.7	[1.0–7.7]	4/20	0.7	[0.2–2.4]	1/20	0.9	[0.1–7.6]
Pyrethrin	3/17	0.8	[0.2–3.0]	4/17	3.0	[0.9–10.4]	0/14	-	-	1/14	1.1	[0.1–10.4]
Fungicides	12/35	1.7	[0.8–3.5]	6/35	1.9	[0.7–5.3]	7/34	0.7	[0.3–1.8]	4/34	2.7	[0.7–9.6]
Carbamate	5/17	1.3	[0.5–3.7]	5/17	3.5	[1.1–10.7]	1/16	0.2	[0.0–1.9]	3/16	3.7	[0.9–15.6]
Imide	2/10	1.0	[0.2–4.8]	1/10	0.8	[0.1–6.8]	0/10	-	-	2/10	3.5	[0.6–19.6]
Triazole	3/9	1.8	[0.5–7.1]	3/9	4.1	[1.0–17.7]	0/9	-	-	1/9	1.4	[0.2–12.9]
Herbicides	12/42	1.5	[0.7–3.0]	5/42	1.2	[0.4–3.4]	5/34	0.5	[0.2–1.3]	4/34	2.4	[0.7–8.6]
Phenoline	7/17	2.3	[0.9–6.1]	3/17	1.9	[0.5–7.3]	2/15	0.3	[0.1–1.6]	3/15	3.7	[0.9–16.1]
Phenoxy	5/25	1.0	[0.4–2.8]	2/25	0.8	[0.2–3.6]	3/20	0.4	[0.1–1.7]	4/20	4.1	[1.1–15.5]
Picoline	3/10	1.3	[0.3–5.0]	1/10	1.1	[0.1–9.7]	0/8	-	-	0/8	-	-
Triazine	8/20	2.1	[0.8–5.0]	4/20	2.3	[0.7–7.7]	4/17	0.9	[0.3–3.0]	4/17	5.1	[1.4–19.3]
Amide	1/12	0.4	[0.0–3.0]	2/12	1.8	[0.4–9.3]	0/8	-	-	2/8	3.8	[0.6–23.0]
Urea	3/7	2.7	[0.6–11.5]	2/7	4.7	[0.8–28.6]	2/7	0.9	[0.2–4.8]	2/7	5.7	[0.9–34.6]
Glyphosate	5/24	1.0	[0.3–2.7]	3/24	1.4	[0.4–5.2]	2/18	0.4	[0.1–1.8]	2/18	1.8	[0.3–9.3]

OR [95%CI] were estimated by polytomous logistic regression including the stratification variables, age, centre and SEC (white collar/blue collar); NHL: non-Hodgkin's lymphoma; LPS: Lymphoproliferative syndrome.