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Farming, pesticide use and hairy-cell leukemia

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Objectives This paper analyzes the role of farming and pesticide exposures in the occurrence of hairy-cell leukemia (HCL).

Methods The study included 226 men with HCL and 425 matched hospital referents. Pesticide exposure was assessed by expert review of detailed interview data on occupational histories and agricultural activities and exposures.

Results Altogether, 77 cases and 116 referents had farmed for at least six months, giving an odds ratio (OR) of 1.5 [95% confidence interval (95% CI) 1.0—2.2]. Forage growing was reported by 20.8% of the cases and 11.1% of the referents and was associated with HCL (OR 2.8, 95% CI 1.6—4.9), even among farmers who had never handled pesticides (OR 3.4, 95% CI 1.0—11.0). A significant association was found between HCL and pesticide use, the overall odds ratios for insecticide, fungicide, and herbicide use ranging from 1.5 to 2.4. Organophosphorus insecticides were the only agrochemicals with a positive association with HCL after other pesticide exposures, smoking, and forage growing were accounted for. A clear-cut negative interaction was found between smoking and exposure to organophosphorus insecticides. A multivariate analysis yielded odds ratio estimates of 2.8 (95% CI 1.4—5.6) for exposure to forage and 7.5 (95% CI 0.9—61.5) for nonsmokers exposed to organophosphorus insecticides.

Conclusions The present study argues for a role of organophosphorus insecticides in HCL among nonsmoking farmers and shows an unexpected association with forage growing. No evidence of an association with phenoxyacetic acids, triazines, or organochlorine insecticides was found.

Key terms agriculture, case-referent study, pesticides, smoking.

Hairy-cell leukemia is a rare B-lymphoid chronic leukemia which has only been investigated in a few epidemiologic studies to date. However, the narrow definition of this disease makes it an interesting model for etiologic research on leukemias since its etiology may be less heterogeneous than that of other more common groups of leukemias.

A slight overall excess of mortality related to hematopoietic malignancies has been reported among farmers in many countries (1, 2). Since the early 1980s, numerous studies have been conducted to investigate the role of pesticides in this excess, particularly with respect to lymphoid malignancies (chronic lymphoid leukemias, non-Hodgkin's lymphomas, multiple myelomas), chlorinated aromatic pesticides such as phenoxyacetic acids, chlorophenols, and organochlorine insecticides being the main suspects (1—7). Disentangling specific exposure to pesticides from the complex web of farm practices is a difficult methodological challenge. The International Agency for Research on Cancer finally considered nonarsenical insecticide use as a whole for evaluation as to its carcinogenicity and classified such use into group 2A (ie, exposures probably carcinogenic to humans) although no single insecticide was individually classified into this group (7). Some fungicides and herbicides have been classified as probably (captafol) or possibly (pentachlorophenol, atrazine, amitrole, phenoxyacetic acids) carcinogenic in humans. In addition to pesticide exposure, farming usually involves exposure to farm animals. Combined exposures are frequent, especially so in the

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past when mixed farming was standard practice. Many authors have raised the possibility that a virus could be transmitted to humans by animals. Bovine leukemia virus is the disease most commonly proposed for investigation but, to date, there is no firm evidence for such transmission (2, 8).

With respect to hairy-cell leukemia, Oleske et al (9) reported an almost significant threefold increase in risk for farmers and forestry workers; the same result was not found in studies by Bernstein et al (10), McKinney et al (11) and Staines & Cartwright (12), who reported an odds ratio of 1.7 in association with contact with farm animals. However, the latter two findings were based on very small numbers of farmers.

The present study analyzes data from 226 men with hairy-cell leukemia and 425 matched referents, with an attempt to detail farm practices and pesticide uses through specific interviews. Exposure was assessed by expert case-by-case review of interview data.

Subjects and methods

Selection of men with hairy-cell leukemia and referents

Men with hairy-cell leukemia, who served as cases, and their referents were retrospectively recruited from 18 French hospitals spread over most of the regions of France (Angers, Bayonne, Bordeaux, Caen, Chambéry, Lille, Limoges, Lyon, Nancy, Nantes, Nice, Nimes, Paris, Poitiers, Rennes, Rouen, Strasbourg, Toulouse). All cases diagnosed from January 1980 to January 1990, even under circumstances of death, were identified and registered, but data were only obtained from the living cases. The diagnoses were histologically confirmed (presence of hairy cells and reticulin fibrosis in the bone marrow biopsy material).

The referents were chosen from persons hospitalized at about the same time in the same hospital, mostly in orthopedic and rheumatology departments, from their lists of admissions throughout the 10-year period. The choice of reference departments was guided both by the necessity of targeting the same age bracket as cases, without selection of particular diseases, habits, or socioeconomic status, and by the need to concentrate the retrospective sampling on a few admission records in each city. Persons admitted for cancer or for work-related diseases or accidents were not eligible. Two referents were individually matched with each case according to gender, date of birth (±3 years), date of admission (±3 years), and residence [inside or outside the "département" (one of the 95 administrative subdivisions of France) where the hospital was located].

The cases and referents were sent a self-administered questionnaire by mail. The nonrespondents were sent the questionnaire a maximum of two additional times. If a referent still had not answered after three attempts, he was replaced by another person from the list according to the same selection criteria.

All told, 378 men with hairy-cell leukemia were identified from the 18 hematology departments. Among them, 226 living cases (60%) were included. Among the 152 cases excluded, 100 men were dead, 68 of them having died before 1984, and 52 men did not return the questionnaire. A total of 809 men were eligible as referents and were sent the questionnaire; 465 (57%) returned it. Forty respondents were excluded because their matched case was dead or a nonrespondent, and they could not be matched with another case. Thus 425 male referents were finally included. The distribution of the reasons for hospital admission is given in table 1.

Finally, 30% of the cases were matched with a single referent, 56% with two referents, and 14% with three to five referents.

Table 1. Causes of hospitalization of the referents.

Cause	Men	
	N	%
Rheumatological diseases	166	39.1
Injuries	124	29.2
Urological diseases	25	5.9
Osteopathies	21	4.9
Benign tumors (eg, lipomas)	15	3.5
Neurological diseases	13	3.1
Cardiovascular diseases	12	2.8
Infectious diseases	8	1.9
Respiratory diseases	7	1.6
Other	22	5.2
Unknown	12	2.8
Total	425	100

Data collection

The self-administered questionnaires included questions on sociodemographic characteristics, tobacco smoking, and lifelong occupations and leisure-time activities. Subjects who had been employed as farmers were interviewed at home by occupational physicians specializing in agricultural work. Data could not be obtained by the same interviewer for the whole study, but the interviewers were the same for each "département". Both the patients and the interviewers were blinded as to the study hypotheses.

The supplementary questionnaires were designed to allow expert case-by-case review for pesticide exposure assessment. They included forms to identify and quantify the crops in the different periods of the occupational histories, forms on insecticides, fungicides and herbicides applied to each crop for each period, and forms to detail the handling of pesticides. The interviewers were asked to request data on agrochemical purchases as often as they could. Only a few farmers were able to provide such information.

Exposure definition

A case-by-case review of the interview data was performed by two of the authors (BD and FS) blind to the case or referent status, one of the reviewers having extensive experience with the occupational hygiene of farmers and the other with the technical and protective aspects of pesticide handling. These authors reviewed the consistency of the patients' statements with respect to product availability dates, types and size of the crops, region of France, and type of farm. The experts classified the subjects as possibly or definitely exposed to chemical categories of pesticides. Two lifelong dichotomic variables of exposure were used, one with a narrow definition (definite exposure) and one with a wide definition (possible or definite exposure), depending on whether missing values were assigned to the base line or to the exposed.

An attempt was made to quantify the exposure to pesticides. In addition to the treated amount of land and number of days of treatment per year, a quantitative index of exposure level was calculated, as a function of the spray height, spraying equipment, and exposure route. The experts assigned a score of 1 for mechanical ground spraying, a score of 3 for use of a portable sprayer and for mechanical spraying on vines or fruit trees, and a score of 8 for the treatment of seeds, application on livestock and treatments in greenhouses. The scale used for low, medium, and high exposure was, in the experts' opinion, consistent with their experience. The cumulative index of exposure was then computed by multiplying the score by the number of treatments per year and by the number of years of exposure.

No correction of this index was needed for protection or product mixing because none of the exposed subjects declared any use of protective measures and none of them applied pesticides without having personally prepared the mixtures. Only two of them prepared the mixtures without applying the pesticides themselves.

Statistical analysis

The odds ratios (OR) were estimated by conditional logistic regression for matched sets with a variable number of referents by pair, using the SAS PHREG procedure (13). The OR estimates are given with their corresponding 95% confidence intervals (95% CI). The means of the quantitative variables are given with their standard error. Cut-off points were defined as the median of the number of exposed referents.

Confounding, effect modification and bias

In a previous analysis (14), we observed a clearcut negative association between smoking and hairy-cell leukemia, the odds ratios decreasing as daily cigarette consumption increased, and lower odds ratios for current smokers than for former smokers. This finding was consistent with observations from other case-referent studies on hairy-cell leukemia (9, 12). Smoking was therefore considered a potential confounder or effect modifier in the present analysis. As mortality was markedly lower after 1984 than earlier, the analysis was sometimes restricted to pairs in which the cases were diagnosed later than 1984.

Results

Comparability of the cases and referents

Matching gave good comparability of the cases and referents for age and residential area. The mean age was 55.7 (SE 0.7) years for the cases and 56.0 (SE 0.6) years for the referents, and 77% of the cases and 78% of the referents lived inside the administrative area of the hospital. The socioeconomic status and educational levels were also similar for the cases and referents, as shown in table 2. The negative association between smoking and hairy-cell leukemia described in a previous analysis (14) is also shown in this table.

Table 2. Sociodemographic and smoking characteristics of the cases and referents. (OR = odds ratio, 95% CI = 95% confidence interval)

	Cases (N = 226) (%)	Referents (N = 425) (%)	OR[a]	95% CI
Socioeconomic status				
Professional, technical workers, administrators and managers[b]	29.7	27.3	..	..
Clerical, sales and service workers	24.8	26.3	..	..
Production and agricultural workers	44.7	45.9	..	..
Never employed	0.4	0.0	..	..
Unknown	0.4	0.5	..	..
School level (highest diploma)				
No diploma	21	18	..	..
Primary school	32	33	..	..
Junior high school	31	32	..	..
High school or university graduate	16	16	..	..
Smoking				
Smoking status				
Nonsmokers	36.7	23.5	1.0	—
Former smokers	34.5	34.1	0.6	0.4—0.9
Current smokers	24.3	38.3	0.4	0.2—0.6
Unknown	4.4	4.0		
Cumulative cigarette consumption				
Nonsmokers	36.7	23.5	1.0	—
< 10 pack-years	19.9	16.7	0.6	0.4—1.0
10—23 pack-years	16.4	19.1	0.5	0.3—0.8
≥ 24 pack-years	12.4	22.6	0.3	0.2—0.5
Unknown	14.6	18.1	..	..

[a] Estimated using conditional logistic regression in which the base-line category was constituted by nonsmokers.
[b] Including farm owners.

Table 3. Association between hairy-cell leukemia and farming. (OR = odds ratio, 95% CI = 95% confidence interval)

	Farm owners				Agricultural laborers				All farmers			
	Cases N = 37 (%)	Referents N = 43 (%)	OR[a]	95% CI	Cases N = 38 (%)	Referents N = 73 (%)	OR[a]	95% CI	Cases N = 77 (%)	Referents N = 116 (%)	OR[a]	95% CI
Having farmed	·	·	1.9	1.1—3.2	·	·	1.2	0.7—1.9	·	·	1.5	1.0—2.2
Start of farming[b]												
< 1950	43	42	1.5	0.7—3.2	76	82	1.1	0.6—1.9	75	83	1.4	0.9—2.2
≥ 1950	57	58	1.9	0.9—3.9	25	18	1.6	0.6—4.0	25	17	2.1	1.0—4.2
End of farming[b]												
< 1960	3	7	0.6	0.1—7.0	34	60	1.3	0.7—2.3	34	38	1.4	0.8—2.3
≥ 1960	97	93	1.8	1.0—3.2	66	40	1.1	0.5—2.3	66	62	1.7	1.1—2.6
Farming duration[b]												
< 20 years	16	23	1.4	0.5—4.0	76	75	1.0	0.6—1.7	41	50	1.2	0.7—2.0
≥ 20 years	84	70	2.3	1.3—4.5	24	25	1.1	0.5—2.5	59	50	1.8	1.1—3.0

[a] Estimated using conditional logistic regression, in which the baseline category is constituted, for each kind of farmer, by subjects who had never farmed.
[b] Percentages of case or reference farm owners, agricultural laborers, or all farmers.

Farming

Altogether, 77 cases and 116 referents had farmed for at least six months, giving an odds ratio of 1.5 (95% CI 1.0—2.2) (table 3). The odds ratio was higher for farm owners (OR 1.9, 95% CI 1.1—3.2), who represented 48% of the farmer cases and 37% of the farmer referents. The agricultural workers and farm owners had different work histories in that the farm owners began work earlier and finished later than did the agricultural workers. The mean farming duration was 16.4 (SE 2.4) years for the reference agricultural workers and 28.8 (SE 2.0) years for the reference farm owners.

Crops and animal husbandry

The odds ratios associated with different crops are shown in table 4. Hairy-cell leukemia was significantly associated with cereal, corn, vine, and forage growing and with

Table 4. Relationship between exposures to crop or animal husbandry and HCL. (OR = odds ratio, 95% CI = 95% confidence interval)

	Cases (N = 226)	Referents (N = 425)	OR[a]	95% CI
Crops				
Cereals	56	77	1.6	1.1—2.5
Corn	27	25	3.2	1.6—6.2
Grape vines	29	29	2.5	1.3—4.8
Forage	47	47	2.8	1.6—4.9
Potatoes	34	51	1.5	0.9—2.6
Vegetables	23	40	1.2	0.7—2.2
Fruit trees	11	14	2.0	0.8—4.8
Beets	11	10	2.4	0.9—6.6
Animal husbandry				
Cattle	54	72	1.9	1.2—3.0
Sheep	21	34	1.5	0.8—2.8
Pigs	31	49	1.5	0.8—2.5
Poultry	34	51	1.5	0.9—2.6
Rabbits	34	43	1.9	1.1—3.2

[a] Estimated using conditional logistic regression; for each exposure considered, the base-line category is constituted by the unexposed subjects.

cattle and rabbit breeding. Interestingly, the odds ratio associated with forage was higher in the southwest of France (OR 13.3, 95% CI 3.0—59.2), where corn is frequently used as forage. Forage was not detailed in the questionnaire and could refer as well to hay, beet or corn for animal feed.

An increase in the odds ratios with the size of the crops was also found for corn (OR 2.8, 95% CI 1.2—6.6, and OR 4.0, 95% CI 1.5—10.9, for ≤ 10 ha and >10 ha, respectively) and vines (OR 2.0, 95% CI 0.7—5.4, and OR 2.9, 95% CI 1.2—7.0, for ≤ 1 ha and >1 ha, respectively).

Forage growing seemed to be a confounder for the associations between hairy-cell leukemia and cereal growing, cattle breeding, beet growing, and rabbit breeding. Only one case and eight referents had grown corn and not forage, and therefore separating the role of corn from that of forage was prevented. Increased odds ratios were observed for the subjects who had grown forage with or without corn or vines. However, the odds ratios were higher when forage was associated with the growing of corn or vines. No increase in risk seemed to be associated with vines without forage or corn.

Pesticides

In addition to the farmers, only six carpenters (3 cases and 3 referents) had undergone exposure to pesticides. Pesticides were handled by about half of the subjects who had farmed. Definite exposures to insecticides, fungicides, and herbicides were reported by 41%, 42%, and 26% of the reference farmers, respectively (table 5).

The overall odds ratio associated with possible or definite pesticide exposure was 1.5 (95% CI 1.0—2.3). The use of insecticides, fungicides, and herbicides was also significantly related to the occurrence of hairy-cell leukemia, the odds ratios ranging from 1.5 to 2.4.

Table 5. Relationships between exposure to the main pesticides and hairy-cell leukemia according to a broad (possible or definite) or narrow (definite) definition of the exposure. (OR = odds ratio, 95% CI = 95% confidence interval)

	Possible or definite exposure				Definite exposure			
	Cases (N)	Referents (N)	OR[a]	95% CI	Cases (N)	Referents (N)	OR[a]	95% CI
Pesticides	51	77	1.5	1.0—2.3	47	65	1.7	1.0—2.6
Insecticides	41	65	1.4	0.9—2.2	37	47	1.8	1.1—3.0
Arsenic	15	29	1.1	0.5—2.2	11	17	1.3	1.6—3.3
Organic insecticides	39	50	1.8	1.1—3.0	36	29	2.2	1.3—3.7
Organochlorines	36	44	1.8	1.1—3.0	28	29	2.1	1.2—3.7
Organophosphorus	23	24	2.2	1.1—4.1	14	11	2.6	1.1—5.7
Pyrethrins	16	21	1.7	0.8—3.5	10	13	1.6	0.7—3.9
Carbamates	14	20	1.5	0.7—3.1	3	8	0.7	0.2—2.8
Fungicides	44	63	1.7	1.0—2.7	40	49	2.0	1.2—3.2
Copper	38	57	1.6	1.0—2.6	32	41	1.9	1.1—3.3
Sulfur	17	25	1.5	0.8—2.8	11	15	1.6	0.7—3.8
Organic fungicides	27	25	2.4	1.3—4.2	25	19	2.9	1.5—5.3
Carbamates	24	24	2.1	1.2—3.9	18	17	2.2	1.1—4.5
Triazoles	17	17	2.0	1.0—4.0	11	6	3.3	1.2—9.0
Phthalimides	11	15	1.5	0.7—3.3	5	4	2.3	0.6—8.9
Herbicides	28	34	1.8	1.0—3.1	27	30	2.0	1.1—3.5
Carbamates	9	12	1.4	0.6—3.4	4	3	2.4	0.5—10.7
Phenols	10	12	1.5	0.7—3.6	5	5	1.8	0.5—6.1
Phenoxyacetic acids	18	22	1.6	0.8—3.1	14	15	1.9	0.9—3.9
Triazine	23	25	1.9	1.0—3.5	20	18	2.4	1.2—4.8
Ureas	17	16	2.1	1.1—4.3	12	8	3.0	1.2—7.5
Amitrole	11	9	2.3	0.9—5.5	5	1	8.2	1.0—71.3
Paraquat	13	13	2.1	0.9—4.8	8	4	4.8	1.3—18.5

[a] Estimated using conditional logistic regression; for each exposure considered, the base-line category was constituted by the unexposed subjects.

Within the insecticide category, the elevated odds ratios seemed to be only related to organochlorine and organophosphorus exposure. As regards organic fungicides, both carbamates and triazoles were associated with a risk of hairy-cell leukemia. The association with exposure to copper compounds disappeared after adjustment for organic fungicides. With regard to herbicides, all the chemical subgroups were associated with elevated odds ratios without statistical significance being reached for phenoxyacetic acid, carbamate, or phenol exposure.

Interestingly, the narrow definition of exposure (ie, definite exposure) gave higher estimates for all the significant associations, the odds ratios ranging from 1.7 to 4.8.

A relationship was found between duration of definite exposure to organic fungicides and hairy-cell leukemia (OR 2.6, 95% CI 0.9—7.5, and OR 3.5, 95% CI 1.4—8.3, for ≤ 10 years and > 10 years of exposure, respectively). A slight relationship was also found with the amount of land treated with organic fungicides (OR 2.1, 95% CI 0.9—4.6, and OR 3.5, 95% CI 0.9—14.5, for ≤ 1 ha and for >1 ha, respectively), the number of days of treatment per year (OR 2.9, 95% CI 1.0—8.5, and OR 3.6, 95% CI 1.3—10.1, for ≤ 50 d a year and >50 d a year, respectively), and with the cumulative dose index, integrating the duration of treatment and spraying method (OR 2.3, 95% CI 0.8—6.5, and OR 6.3, 95% CI 1.7—23.2, for a cumulative index of ≤ 500 and > 500, respectively). However, the quantitative data were missing for about 50% of the exposed subjects. No dose-response relationship with cumulative index was observed for organic insecticides, herbicides, or phenoxy herbicides. A study of dose-response relationships could not be carried out for individual chemical insecticides, organic fungicides, or herbicides other than phenoxy herbicides because of the small numbers and missing data.

Only one case and two referents were exposed to fungicides only, and no case and five referents were exposed to herbicides only. Most of the subjects (17 cases and 11 referents) were exposed to all three categories of pesticides.

Confounding and effect modification related to smoking

The broad definition of exposure to pesticides (possible or definite exposure) was used to increase the numbers for the multivariate analysis. A negative interaction term with smoking was significant at the 10% level for the pesticides significantly associated with hairy-cell leukemia.

Joint effect of crops, pesticides and smoking

The association between forage growing and hairy-cell leukemia remained significant even when the analysis was restricted to subjects who had never handled pesticides (OR 3.4, 95% CI 1.0—11.0).

Many associations existed between crops, between pesticides, and between crops and pesticides. Because of the strength of these associations, all the exposure variables could not be included together in a multivariate model. The variables to be included in a multivariate model were thus selected by estimating the odds ratios for combined exposures and adjusting the bivariate models.

Pesticide use was highly correlated with corn growing and, to a less extent, with forage growing. There was no correlation between these crops and smoking. Very few subjects were exposed to pesticides and did not cultivate forage. The proportion of subjects exposed to forage was higher in the groups with the highest level of cumulative exposure to organic fungicides (91% and 100% of the cases and referents, respectively) than in the lowest level (73% and 56% of the cases and referents, respectively). This correlation was sufficient to explain totally the dose-response relationship observed between the cumulative index of organic fungicide exposure and hairy-cell leukemia.

Exposure to organophosphorus insecticides was highly correlated with the use of other pesticides. Among the farmer referents, 54% of those exposed to organochlorine were also exposed to organophosphorus insecticides, as were 64% of those exposed to organic fungicides, 64% of those exposed to triazine herbicides, and 50% of those exposed to phenoxy herbicides. Restricting the analysis to subjects who were unexposed to organophosphorus insecticides or using a multivariate analysis removed the dose-effect relationships observed with corn and vines. Neither triazine herbicides nor organochlorine insecticides were found to be associated with hairy-cell leukemia in the absence of exposure to organophosphorus insecticides (table 6).

After the preceding steps of the analysis, a multivariate model was fitted to the data. It included forage growing, smoking, exposure to organophosphorus insecticides, and its interaction term with smoking (table 7). The positive association with forage growing and the negative association with smoking remained statistically significant, and the estimated odds ratios were not affected by the introduction of the other variables. A multivariate analysis yielded OR estimates of 2.8 (95% CI 1.4—5.6) for exposure to forage and 7.5 (95% CI 0.9—61.5) for nonsmokers exposed to organophosphorus insecticides.

The estimates were very similar when the analysis was restricted to pairs in which the cases were diagnosed after 1984, when mortality was three times lower.

Table 6. Odds ratios associated with the main pesticide exposures with smoking, exposure to organophosphorus insecticides and forage growing accounted for. (OR = odds ratio, 95% CI = 95% confidence internal)

	OR[a]	95% CI[a]	OR[b]	95% CI[b]
Organic insecticides	1.6	0.7—3.4	1.2	0.5—2.9
Organochlorines	1.8	0.8—4.1	1.5	0.6—3.8
Organic fungicides	2.0	0.7—5.5	1.5	0.5—4.5
Carbamates	1.8	0.6—5.6	1.3	0.4—4.5
Triazoles	1.9	0.5—7.3	2.0	0.4—9.2
Herbicides	1.1	0.4—2.9	0.7	0.2—2.0
Phenoxy	0.7	0.2—2.7	0.4	0.09—1.8
Triazines	2.0	0.7—5.6	1.5	0.5—4.9
Ureas	1.0	0.08—11.9	0.5	0.03—6.1
Paraquat	0.6	0.05—6.7	0.4	0.03—5.1

[a] Adjusted for smoking status, estimated by conditional regression after restriction to unexposed to organophosphorus insecticides.
[b] Item with additional adjustment for forage growing.

Table 7. Multivariate model of conditional logistic regression including exposure to organophosphorus insecticides, forage growing, tobacco smoking, and interaction between organophosphorus insecticides exposure and smoking. (OR = odds ratio, 95% CI = 95% confidence internal)

	OR	95% CI
Organophosphorus insecticides	7.5	0.9—61.6
Forage	2.8	1.4—5.6
Smoking	0.6	0.4—0.9
Organophosphorus insecticides times smoking	0.07	0.01—0.7

Discussion

The present study investigated farming exposures for a sample of 226 men with hairy-cell leukemia from most of the regions of France and 425 matched referents. Overall, an odds ratio of 1.5 (95% CI 1.0—2.2) was observed for the farmers when compared with the nonfarmers. Forage growing was related to hairy-cell leukemia, even among farmers who had never used pesticides. The association of hairy-cell leukemia with organophosphorus insecticides remained statistically significant after all other pesticide exposure had been accounted for, and a clear-cut negative interaction was found with smoking. Odds ratios of 2.8 (95% CI 1.4—5.6) for forage growing and 7.5 (95% CI 0.9—61.5) for exposure to organophosphorus insecticides, with a strong negative interaction between smoking and pesticide exposure, were estimated in a multivariate analysis.

Bias may possibly have been introduced by the fact that the recruitment was retrospective from among the prevalent cases. Mortality from hairy-cell leukemia was high before the introduction of alpha-interferon, in 1983. In our sample, the proportion of dead cases was 59% and 15% for cases diagnosed prior to and after 1984, respectively. However, the results were very similar after the analysis was restricted to pairs in which the cases were diagnosed later than 1984. The nonrespondent rate was high for both the cases (40%) and the referents (43%). For the cases, the information that about two-thirds of the nonrespondents were dead was available. This information was not available for the referents. This difference could have induced selection bias if farming was related to the response rate of the referents. However, the distribution of socioeconomic status and tobacco smoking in the reference group was very similar to that published for the French population during the same period (14).

Matching resulted in good case-referent comparability, especially with respect to socioeconomic status. The elevated odds ratio for farming is therefore unlikely to be explained by selection bias. The increase in the odds ratio with employment as a farmer is consistent with the findings of Oleske et al (9), who found a threefold increase in hairy-cell leukemia risk, bordering on significance, for farmers and forestry workers, and with the preliminary report from Hagberg et al (16). In contrast, neither McKinney et al (11) nor Staines & Cartwright (12) reported this association, but both studies included very small numbers of farmers. The association reported in this study is also consistent with that frequently observed between blood malignancies and farming in various countries (1, 2, 15).

Organophosphorus insecticides were the only pesticides significantly related to hairy-cell leukemia when other pesticide exposure, smoking, and forage growing were accounted for. Unfortunately, quantitative data on exposure were lacking for about 50% of the farmers exposed to organophosphorus insecticides, and therefore testing for a dose-response relationship was prevented. The associations between organophosphorus insecticides and non-Hodgkin's lymphoma (17, 18) and chronic lymphoid leukemia (19) have been previously described in studies conducted in the United States. The interaction between smoking and organophosphorus insecticides is interesting because both factors are known to influence, in opposite directions, the balance of P450 monooxygenase activity, organophosphorus compounds inhibiting enzymatic activity and smoking activating it (20). If the present finding reflected a causal relationship between exposure to organophosphorus insecticides and hairy-cell leukemia, this effect might well be indirect, involving interference with the metabolic transformation of some risk factor.

The findings of this study do not support an association between hairy-cell leukemia and phenoxyacetic acids, probably the most investigated herbicides, although the number of exposed subjects was not that small. The odds ratios did not increase with either exposure duration or dose (acreage and cumulative index). To date, epidemiologic studies have not enabled definitive conclusions on the carcinogenic effect of phenoxyacid herbicides (6, 21—32). Neither triazine herbicides nor organochlorine insecticides were found to be associated with hairy-cell leukemia in the absence of exposure to organophosphorus insecticides. The power of the present study suffered from the small numbers of subjects available for numerous pesticide exposures. The analysis was complicated by strong correlations between pesticide use, and therefore the study of many specific associations was prevented. For instance, it is noteworthy that most subjects exposed to organophosphorus insecticides were also exposed to organochlorines, and therefore the investigation of the role of organophosphorus insecticides alone was prevented. Nondifferential misclassifications of pesticide exposures were also likely to occur because of probable recall difficulties and because pesticides with differing chemical structures were grouped into the same class (eg, parathion, dichlorvos and malathion as organophosphorus insecticides). As observed by Blair & Hoar Zahm (33), recall difficulties are unlikely to differ between cases and referents. Hairy-cell leukemia was not known to be related to farm practices at the time of the interview, and both the cases and referents were interviewed in a systematic manner using a semi-structured questionnaire.

An unexpected association was observed with forage growing. Confounding by pesticide exposure is unlikely since the relationship between forage and hairy-cell leukemia was also found when pesticide users were excluded from the analysis. While forage was almost always associated with cattle, a sufficient number of beef cattle farmers did not grow forage, and no increase in the odds ratio was observed in this group. However, no accurate information on animal diseases was available, and all those exposed to forage were also exposed to cattle. In consequence, confounding of the observed association by a cattle disease, bovine leukemia in particular, cannot be excluded. The results of this study may also suggest the hypothesis of a role of forage or corn contaminants such as mycotoxins produced by fungi during storage under traditional conditions (no drier). *Fusarium* is one of the forage fungi which particularly affects corn and produces mycotoxins known to be immunosuppressive and myelotoxic, high exposures inhibiting hematopoiesis and, conversely, low-level exposures stimulating lymphoid hematopoiesis (34, 35). Exposure may result from the consumption of contaminated farm products but also, perhaps, from contact with moldy forage. The likelihood and extent of such exposure among farmers requires evaluation.

In conclusion, the present study argues in favor of a role of organophosphorus insecticides in the occurrence of hairy-cell leukemia among nonsmoking farmers and shows an unexpected association with forage growing. No evidence of an association with phenoxyacetic acids, triazines, or organochlorine insecticides was found.

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