Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on a priori exposure matrices

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Abstract

Objectives—A population based case-control study was conducted in a highly agricultural area in Italy to investigate the association between chronic lymphocytic leukaemias (CLLs) and non-Hodgkin's lymphomas (NHLs), and subtypes, and exposure to pesticides in farming-animal breeding workers.

Methods—187 cases of CLLs and NHLs and 977 population controls were interviewed on medical, residential, family, and occupational history. Detailed information was collected about cultivated crops and animals bred from subjects who worked in farming and animal breeding. Information on crop diseases and pesticides used (and their quantity and duration) was also obtained. A priori job-exposure matrices were applied when a crop disease was reported, estimating the most probable pesticide and, when possible, an estimate of the cumulative dose. Odds ratios (ORs) were calculated by unconditional logistic analysis with adjustment for relevant confounders in farmers who bred animals and in farmers alone, for the main crops, types of animals, and pesticides categories. First recall and then the matrices were used for defining exposure, as it affected CLLs and NHLs and then separately on CLLs and low grade NHLs. Finally, the dose-response was investigated for those pesticides which had shown some association.

Results—No variable under study was associated with work in farming alone. In farming and animal breeding, no crop or animal showed an association with CLLs and NHLs when adjusted by exposure during childhood to farming and animal breeding (an indicator of life in a farming and animal breeding environment before the age of 13, which behaved as an independent risk variable). A non-significant association was found with stannates, arsenates, phosphates, and dichlorodiphenyl-trichloroethane (DDT) based on recall, and for stannates, arsenates, and DDT after the application of the matrices. When CLLs together with low grade NHLs were considered, the association with insecticides in general, carbamates, and phosphates became significant according to personal recall (ORs and

95% confidence intervals (95% CIs) 2.46, 1.07-5.63; 3.08, 1.05-9.00; 2.97, 1.28-6.91, respectively). The application of the matrices also showed a risk of borderline significance for stannates and dithiocarbamates. A significant dose-response effect was found for phosphates (for logarithmic unit increase, OR 1.17, 95% CI 1.00-1.57); a strong trend for stannates and carbamates did not reach significance.

Conclusion—The association of CLLs and NHLs with work in farming-animal breeding is partially explained by exposure to pesticides—namely insecticides (carbamates, phosphates, and DDT) and stannates—possibly related to their use in animal breeding. The association is limited to cases of CLL and low grade NHL. The independent effect of the variable exposure during childhood suggests that early exposures, including possible contact with animals, may play a part in the pathogenic process of these neoplasms.

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A population based case-control study of non-Hodgkin's lymphomas (NHLs) and chronic lymphocytic leukaemias (CLLs) in association with farming and animal breeding has been conducted in a high risk area (Forlì province, north eastern Italy). In this area, there is a high prevalence of farming and animal breeding associated with a wide use of pesticides. A priori job-exposure matrices have already been developed with the aim of estimating exposure to different chemicals; these were then integrated with the questionnaires, which used as guidelines the information on cultivated crops and on crop infestations.¹ In a previous paper, it was shown that subjects working in farming associated with animal breeding are at high risk of NHLs and CLLs (OR 1.8, 95% CI 1.2-2.6), particularly for CLLs and low grade NHLs (OR 2.3, 95% CI 0.9-5.8; OR 1.7, 95% CI 1.0-3.1, respectively, *v* no association with medium and high grade NHLs). Having worked only in farming was not a risk factor, nor was work in any other occupational cate-

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gory.² The category of farmers-animal breeders differed from the one of farmers not only because of a more likely and continuous contact with animals, but also because on average these subjects cultivated a wider variety of crops, farmed larger areas of land, had a longer median duration of employment, and personally used pesticides more often.² The two possible explanations mentioned for the increased risk were contact with oncogenic viruses related to animal breeding and use of pesticides.

In this paper, results are presented for specific categories of pesticides, analysed first according to personal recall, and then by estimating exposure according to a priori job-exposure matrices.

Materials and methods

The study has been previously described in detail.² Briefly, all incident cases of NHLs and CLLs in Forlì province (north east Italy) between January 1987 and December 1990, excluding people positive for HIV, have been interviewed ($n = 187$), together with 977 controls selected from the general population and matched by sex and five-year age group. Compliance was 97.5% in cases and 88.0% in controls. Cases were further classified by one pathologist (AS) with a modified Kiel classification³ in low grade ($n = 56$, 30%), medium grade ($n = 34$, 18%), high grade ($n = 72$, 38%) NHLs, CLLs ($n = 23$, 12%), and two cases of mycosis fungoides.

The questionnaire asked for residential history, community life, dietary habits, smoking, alcohol consumption, family history of cancer, medical history, use of drugs, exposure to radiation, and work history. Exposure in childhood was recorded asking if the subject used to help the family in farming and in animal breeding before the age of 13. Results on all these sections have been reported in a previous paper.²

The work history section was organised in two parts. The first part collected information on the entire work experience and relative periods. Only occupations lasting for one year or more were recorded.

Jobs were classified under one of 21 wide working categories and then further classified according to 254 job titles (modified International Labour Office (ILO) questionnaire). Subjects who reported having been employed in farming or animal breeding for at least one year were asked to complete the second section of the questionnaire in which they were asked to provide detailed information on each of the 10 most widely cultivated crops with reference both to each farm of employment and to types of animals bred. Crops were cereals, sugar beet, grapes, apples and pears, strawberries, other fruit trees, vegetables, seeds, flowers, and garden nursery. Animals were cattle, sheeps, pigs, poultry, horses, and rabbits. Animal breeders who did not work in farming were not included in this population.

Ten forms were developed, through which questions were presented on the possible diseases or infestations for each crop, and a spe-

cific list of chemicals was applied each time the subject answered positively about one of the crop diseases. For each identified pesticide, the subjects were asked about the usual dose for each treatment, the number of treatments a year, the surface area cultivated, and the period in years of cultivation. The use of pesticides and other chemicals was also asked with reference to animal breeding. The list of pesticides, including commercial names and active principles, was chosen on the basis of the frequency of use in the area and of the data available about chronic toxicity in humans. An a priori matrix had been developed for each crop and for each disease or infestation by an expert (CL). In this matrix one pesticide corresponded to one line and each of the following variables expressed as a mean value corresponded to each of the columns: weight (kg)/volume water; g/unit of surface area; number of treatments/year; and legal period of use. Finally, the last variable was the probability of use, scored by the expert for each pesticide with respect to the others mentioned in the matrix, taking into account the reported infestation and the legal period of use. The likely frequency (probability) with which each pesticide may have been used is based on data from the catalogues of pesticides producers, on the directory of widely used pesticides in farming, and on the wide experience of the phytopathologist (CL) involved in this study.

The method used to develop and apply the matrices, and results in terms of estimated information, have been presented elsewhere.¹ Briefly, although almost all subjects remembered in detail the cultivated crops and the diseases or infestations, they were less often able to report the specific pesticides, or specify the amounts and the periods. The matrices were applied to the crop each time a cultivated crop and one or more disease or infestation was reported. Assuming that crop diseases were always treated and that treatment protocols were well established, only the most probable pesticide was estimated for each reported infestation. This was substituted by the next most probable pesticide if the subject explicitly excluded the use of the first one. This choice may lead to an underestimation of the number of subjects exposed to less widely used pesticides.

The category of farmers-animal breeders was represented by 278 subjects (61 cases and 217 controls). Agricultural workers not involved in animal breeding (250 subjects: 31 cases, 219 controls) were also considered in relation to crops cultivated and pesticides used. Furthermore, they were kept in all models as a separate category. Of the remaining 636 subjects, 148 (21 cases and 127 controls), although never employed as farmers-animal breeders or agricultural workers, still stated that they had been cultivating crops and used pesticides as a second job or after retirement. These subjects were excluded from the analysis. In all models, the controls were subjects never involved in farming or animal breeding (488 subjects, 74 of the 187 cases and 414 of the 977 controls interviewed).

Table 1 Odds ratios for NHLs and CLLs in farming-animal breeding by cultivated crop and type of animal

Crop or animal	Farmers-animal breeders					
	Cases (n = 61)	Controls (n = 217)	Adjusted OR*	95% CI	Adjusted OR†	95% CI
Cereals	46	177	1.67	1.10-2.54	0.99	0.58-1.69
Grapes	28	102	1.68	1.02-2.76	1.01	0.55-1.83
Strawberries	15	43	2.02	1.05-3.88	1.21	0.59-2.49
Vegetables	36	120	1.75	1.09-2.78	1.04	0.59-1.84
Fruit trees	26	109	1.31	0.79-2.18	0.72	0.39-1.33
Seeds	11	23	2.56	1.16-5.63	1.52	0.65-3.75
Cattle	58	209	1.74	1.16-2.62	1.08	0.62-1.88
Sheep	29	83	2.38	1.42-3.99	1.45	0.78-2.70
Pigs	58	205	1.77	1.18-2.66	1.11	0.64-1.92
Horses	25	99	1.58	0.93-2.67	0.88	0.47-1.66

Controls were 488 subjects who had never worked in farming or animal breeding.

*Variables in the models were: sex, age (continuous), altitude of municipality (dichotomous), familiar history of a haematopoietic cancer (dichotomous), *Herpes zoster* infection (dichotomous), having worked in agriculture (dichotomous).

†Variables in the models were the same as * and exposure during childhood.

The associations were measured by the maximum likelihood estimate of the odds ratio (OR) as an estimate of the risk ratio (RR). Occupational variables were analysed after adjustment for sex and age, and because they were identified as significant variables in the previous analysis, altitude of municipality, first degree familial haemolymphopoietic cancer, and previous *Herpes zoster* infection. Case-control status was studied first by each type of crop and animal, then by exposure to specific pesticide categories as recalled by the subjects, finally by exposure estimated through the application of the matrices. All these variables were considered as dichotomous (yes or no). Each pesticide category was cross classified for its use in crops and in animal breeding. As in the previous analysis a significant independent risk was found for having helped in farming or animal breeding during childhood, independent of type of work in adult life (OR 2.1, 95% CI 1.45-3.0); this variable was also introduced in the models as an indicator of a possible undetermined exposure during childhood related to work in farming or animal breeding. Finally, the dose-response relation was studied for those pesticides which had shown some associations, estimating for each exposed subject a cumulative dose of exposure in kg, as estimated through the matrices according to the following formula: chemical (g/unit of surface area) $\times$ units of surface area cultivated (n) $\times$ treatments (n/y) $\times$ duration of cultivation (y). In the models, the logarithmic trans-

formation of the cumulative dose was used because of the skewed distribution of the exposure variables. The estimated cumulative dose was limited to a subset of subjects, as the necessary information was not available for pesticides used in animal breeding and in some questionnaires for some of the cultivated crops. Unconditional logistic regression analysis was used with case-control status or main histological type of cases as the response variable.⁴ The analysis was carried out with SAS.⁵

Results

In table 1 the association between CLLs and NHLs and cultivation of each of six crops is shown, first adjusted by the usual variables and then adding to the model the variable of having helped in farming-animal breeding during childhood (exposure during childhood). In the table, the group vegetables includes sugar beet, fruit trees includes apples and pears, whereas flower cultivation and nurseries were excluded because of small numbers.

In the same table, results are presented for four types of animals (cattle, sheep, pigs, horses). All but one worker reported having bred poultry, and all but four having bred rabbits; therefore the risk for those who bred these animals was coincident with the overall risk for that work category.

Although all crops with the exception of fruit trees, and all types of animals with the exception of horses seem to be associated with a significantly increased risk of NHLs and CLLs in the first type of model, on the contrary all the effects lost significance when the variable exposure during childhood was included, although for strawberries, seeds, and sheep breeding a slightly increased non-significant OR persisted. The RR for exposure during childhood was significant in all models on crops and on animals, ranging from OR 1.80 (95% CI 1.14-2.86) to OR 2.20 (95% CI 1.43-3.39). Exposure during childhood was then systematically introduced in all the following models.

To evaluate the association between NHLs and CLLs and type of chemical used, the chemicals were grouped into six categories: arsenates, stannates, herbicides, fungicides,

Table 2 Odds ratios for NHLs and CLLs in farming-animal breeding by category of pesticide used as defined by recall and by the matrices

Pesticide	Recall				Matrices			
	Cases (n = 61)	Control (n = 217)	OR*	95% CI	Cases (n = 61)	Control (n = 217)	OR*	95% CI
Arsenates	8	16	1.83	0.69-4.25	9	16	2.07	0.80-5.32
Stannates	5	6	2.44	0.68-8.76	11	22	1.63	0.70-3.83
Herbicides	7	24	0.93	0.36-2.44	13	46	0.90	0.42-1.92
Fumigants	33	116	1.15	0.71-1.85	33	116	1.15	0.71-1.85
Fungicides	21	70	1.13	0.64-2.00	30	97	1.19	0.72-1.95
Dithiocarbamates	21	67	1.07	0.54-2.08	30	94	1.13	0.62-2.08
Insecticides	40	111	1.43	0.80-2.55	43	142	1.12	0.64-1.96
Carbamates	10	28	1.26	0.53-2.94	11	29	1.34	0.58-3.06
Chlorinated compounds	30	84	1.35	0.74-2.49	35	111	1.15	0.65-2.06
DDT	27	61	1.74	0.93-3.27	28	65	1.70	0.91-3.17
Phosphates	35	82	1.70	0.94-3.09	42	121	1.32	0.75-2.73

Controls were 488 subjects who had never worked in farming or animal breeding.

* Variables in the models were: sex, age (continuous), altitude of municipality (dichotomous), familiar history of a haematopoietic cancer (dichotomous), *Herpes zoster* infection (dichotomous), having worked in agriculture (dichotomous), exposure during childhood (dichotomous).

Table 3 Odds ratios for CLLs and low grade NHLs in farming-animal breeding by category of pesticide used from recall and by the matrices

Pesticide	Recall				Matrices			
	Cases* (n = 31)	Control (n = 217)	OR†	95% CI	Cases* (n = 31)	Control (n = 217)	OR†	95% CI
Stannates	2	6	3.18	0.54-18.58	6	22	3.06	0.99-9.39
Herbicides	3	24	1.43	0.36-5.69	8	46	2.10	0.77-5.71
Fumigants	16	116	1.17	0.61-2.26	16	116	1.17	0.61-2.25
Fungicides	12	70	1.42	0.67-3.00	17	97	1.52	0.79-2.95
Dithiocarbamates	12	67	2.13	0.85-5.38	17	94	2.23	0.96-5.17
Insecticides	20	111	2.46	1.07-5.63	22	142	1.97	0.88-4.39
Carbamates	7	28	3.08	1.05-9.00	7	29	2.95	1.01-8.60
Chlorinated compounds	13	84	1.93	0.79-4.67	16	111	1.73	0.75-3.98
DDT	11	61	2.33	0.93-5.85	11	65	2.16	0.86-5.43
Phosphates	18	82	2.97	1.28-6.91	22	121	2.42	1.08-5.41

*Cases with CLLs or low grade NHLs.

Controls were 488 subjects who had never worked in agriculture or animal breeding.

†Variables in the models were: sex, age (continuous), altitude of municipality (dichotomous), familiar history of a haematopoietic cancer (dichotomous), *Herpes zoster* infection (dichotomous), having worked in farming (dichotomous), exposure during childhood (dichotomous).

insecticides, and fumigants. Further, dithiocarbamates among fungicides were examined separately. Insecticides were also split into carbamates, phosphates and chlorinated compounds among which, dichloro-diphenyl-trichloro-ethane (DDT) was examined separately because of its wide use. Table 2 shows results for each category classified by recall of the subjects and then by the application of the matrices.

The use of the matrices for estimating exposure increased the number of cases and controls classified as exposed for all categories of pesticides, with the exception of fumigants, as the fumigation process, well recalled by the subjects, was synonymous with the use of fumigants. No significant association was found with any of the pesticide categories, either from recall or the matrices.

However, a high (but non-significant) OR estimate was found before the application of the matrices for stannates (OR 2.44, 95% CI 0.68-8.76), arsenates (OR 1.83, 95% CI 0.69-4.85), phosphates (OR 1.70, 95% CI 0.94-3.09), and DDT (OR 1.74, 95% CI 0.93-3.27). After the application of the matrices, a non-significant high risk was maintained for arsenates (OR 2.07, 95% CI 0.80-5.32), stannates (OR 1.63, 95% CI 0.70-3.83), and DDT (OR 1.70, 95% CI 0.91-3.17).

In table 3, the same analysis is presented for only cases of CLLs and low grade NHLs. According to the previous analysis, CLLs and low grade NHLs were identified as the histological types in which all the risks of being a farmer-animal breeder were concentrated. Models for arsenates are not presented because of small numbers.

From recall, exposure to insecticides in general, to carbamates, and to phosphates was significantly associated with CLLs and low grade NHLs (OR 2.46, 95% CI 1.07-5.63; OR 3.08, 95% CI 1.05-9.00; OR 2.97, 95% CI 1.28-6.91, respectively). A positive but not significant association was also suggested for dithiocarbamates (OR 2.13, 95% CI 0.85-5.38) and for DDT (OR 2.33, 95% CI 0.93-5.85). When the matrices were used for defining exposure, in general the point estimates of the ORs were confirmed in direction and magnitude. Stannates and dithiocarbamates carried high risks with borderline significance in these models, and carbamates and phosphates were confirmed as positively associated with the diseases. An increased non-significant OR was also found for chlorinated compounds, DDT, and herbicides.

In farmers-animal breeders, the use of each category of pesticides was strongly correlated with the use of the others. Taking into account eight main categories (arsenates, stannates, herbicides, chlorinated compounds, fumigants, dithiocarbamates, carbamates, phosphates), out of 278 subjects, 21% did not use any category, only 18% used one, 24% used two to three, 25% were exposed to four to five, and 12% used more than five categories of pesticides. For this reason and because of small numbers, it was impossible to introduce in the same model more than one pesticide category to evaluate their separate effects.

The same variables analysed for those who worked in farming without having been involved in animal breeding did not show any positive association.

The cumulative dose of use (in kg) was esti-

Table 4 Cumulative dose of the pesticides positively associated with CLLs and low grade NHLs by case-control status

Pesticide	Cases*				Controls				OR†	95% CI
	n	Mean	Median	Range	n	Mean	Median	Range		
Stannates	6	29	18	< 1-86	22	23	12	< 1-108	1.41	0.98-2.02
Dithiocarbamates	14	1114	558	27-3508	88	1680	467	5-21600	1.11	0.97-1.26
Carbamates	6	34	29	6-70	28	41	22	1-263	1.34	0.98-1.84
Chlorinated compounds	12	264	64.5	< 1-2135	90	78.9	16.5	< 1-903	1.14	0.93-1.39
DDT	5	237	115	15-772	23	138	46	2-825	1.22	0.95-1.57
Phosphates	21	195	68	4-793	102	270	83	< 1-3074	1.17	1.00-1.36
Herbicides	8	296	78.5	2-971	43	190	96	1-1129	1.11	0.90-1.36

Mean, median, range in kg, and OR for unitary increase (log scale).

Controls were 488 subjects who had never worked in farming or animal breeding.

*Cases with CLLs and low grade NHLs.

†Variables in the models were: sex, age (continuous), altitude of municipality (dichotomous), familiar history of a haematopoietic cancer (dichotomous), *Herpes zoster* infection (dichotomous), having worked in farming (dichotomous), exposure during childhood (dichotomous).

mated through the matrices for stannates, carbamates, dithiocarbamates, phosphates, herbicides, chlorinated compounds, and DDT. It was possible to estimate the cumulative dose for 49 out of 53 cases and to 265 out of 307 controls. All subjects with a cumulative dose of < 1 kg were reported as non-exposed. Subjects with cumulative doses ≥ 1 kg were counted as exposed. The ORs and 95% CIs were calculated for the log of the increase of the cumulative dose.

Table 4 shows for each pesticide category the mean, median, and range of cumulative dose by case-control status and ORs for the logarithm of the differences between the cumulative dose of cases and that of controls.

Although only borderline significance was reached for unitary increase in the dose of phosphates (OR 1.17, 95% CI 1.00–1.36), an association with increasing dose, based on small numbers, was also strongly suggested for stannates (OR 1.41, 95% CI 0.97–1.26), carbamates (OR 1.34, 95% CI 0.98–1.84), and DDT (OR 1.22, 95% CI 0.95–1.57).

Discussion

This paper evaluates exposure to pesticides in farmers-animal breeders as a risk factor for NHLs and CLLs, compared with subjects who were never involved in farming or farming-animal breeding. In agricultural workers who were not animal breeders, no association was found with the diseases under study in analyses for the cultivation of crops and the exposure to specific pesticide categories. This confirms the results of a simplified previous analysis.²

The analysis by cultivated crop and by type of animal bred by farmers-animal breeders did not show any significant association with NHLs and CLLs when the ORs were adjusted for exposure during childhood. In fact, this variable behaved as a strong confounder, as ORs were uniformly increased for almost all crops and animals before adjustment, although the excess disappeared systematically after adjustment. The variable originates from one question: whether the subject had been involved in some farming-animal breeding activity before the 13th year of age. Exposure to unknown factor(s) during childhood is confirmed as a relevant and unexpected risk variable in the results presented here, but the nature of the exposure cannot be specified given the structure of the questionnaire.

Some studies reported an association between the use of pesticides in farmers and risk of NHLs, but some others were negative.^{6–10} Some studies included CLLs; in general, the high misclassification between CLLs and low grade NHLs justifies their grouping.^{10–11} Pesticides which were found to be associated with NHLs were phenoxy herbicides, insecticides in general, chlorinated insecticides, and DDT.⁹ Fungicides and fumigants have also been associated with increased risks of NHLs.⁸ It has been noted that farmers may also be exposed to other chemicals, such as solvents, emulsifiers, fuels, and oils.^{6–12} No

information on the content of solvents in pesticides was available in this study, but other working categories exposed to solvents were not at high risk.² Among Iowa and Minnesota farmers, the increased risk of CLLs was attributed to the use of insecticides in relation with animal breeding, which could be linked with high exposure because of use in confined quarters.¹³ In another study, a threefold risk of NHLs in women was associated with dairy cattle, and a high risk was confirmed for women who personally handled chlorinated hydrocarbon insecticides.¹⁴ Contact with animals used for breeding has also been suspected of exposing the handler to oncogenic viruses, some of which are recognised as causal factors of animal haemolymphopoietic cancers or related diseases (Marek's disease in poultry, avian leukosis, papillomas in cattle, bovine lymphosarcomas).⁶ This hypothesis is reinforced by the finding that abattoir workers and possibly veterinarians and meat inspectors are at high risk of NHLs.^{15–16}

In the present study, the results for all cases by category of pesticide or by specific pesticides did not show any significant association for any of the 11 exposures considered, by either recall and matrices. The ORs for arsenates, stannates, DDT, and phosphates were increased, but not significantly. When the analysis was limited to CLLs and low grade NHLs, despite the reduction in the number of cases, a positive significant association emerged for insecticides in general, carbamates, and phosphates when recall was used, and to carbamates, phosphates, stannates, and dithiocarbamates (the last two were of borderline significance) when the matrices were applied. The risk associated with DDT was also increased, but did not reach significance. The limitation of the analysis to CLLs and low grade NHLs seems to avoid the dilution of the effect by medium and high grade NHLs.

A separate analysis referred to the excluded cases and confirmed that no association was found with any of the pesticides under study. No other study on exposure to pesticides and CLLs and NHLs reported results by this classification of histological type. In one previous study¹⁷ a higher risk was reported among those exposed to 2,4 dichlorophenoxy acetic acid (2,4,D) for the follicular large cell variety of NHLs compared with other histological types. Although the two classifications are not immediately comparable, follicular NHLs are more often classified in the low grade category.¹⁸

The use of matrices is expected to increase the power of the study, allowing exposed classification of those farmers-animal breeders that despite their not recalling the specific use of pesticides, very likely used them.^{19–20} It is worthwhile noting that in the present study the matrices were based both on existing knowledge of the pesticides in use in the area and on the information gathered from the questionnaire on the crop diseases and infestations, which was systematically used as a guideline for estimating the exposure to pesticide. The estimation was also based on the probability of use of the pesticide thought to be most likely

to have been used in each infestation. Possibly, with the use of matrices most of the recall bias was avoided, as recall of cultivated crops and crop diseases is more likely to be independent of case-control status than is recall of pesticides. It is likely, however, that the problem of non-differential misclassification remained, which means that the measured risks, although quite high, are still underestimated.

This population of workers is characterised by the contemporary use of all kinds of pesticides. The high correlation among categories made it impossible to disentangle the effect of each pesticide category from the others and may explain the high number of associations found.

The hypothesis of a causal association is strengthened by the finding of a dose-response relation: this was significant only for phosphated insecticides (11% increase of risk for each log unit of increase of the cumulative dose), but was suggested also for stannates, carbamates, chlorinated compounds, and for DDT (point estimate of the increase in risk = 41%, 34%, and 22%, respectively).

The results on pesticides favour of the hypothesis that some of the excess risk of CLLs and low grade NHLs in farmers-animal breeders is due to the wide and personal use of pesticides by this group of workers compared with other farmers. About 80% of farmers-animal breeders were estimated to have used at least one pesticide compared with 38% of farmers. Among these, phosphated insecticides were used by 41% of farmers-animal breeders and by 23% of farmers, carbamates were used by 14% of farmers-animal breeders and by 7% of farmers, DDT was used by 29% of farmers-animal breeders and by 10% of farmers. Among those who used at least one pesticide, more than 50% of the farmers-animal breeders versus 23% of the farmers reported that they usually spread it personally. The results reported here are also consistent with animal breeding itself increasing the risk of disease. The persisting effect of exposure in childhood suggests that contact with animals in childhood could have a role in the pathogenetic process, possibly due to viruses acting as oncogenic initiators or as immunosuppressors.

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