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NON-HODGKIN'S LYMPHOMA AND FARMING: AN EXPANDED CASE-CONTROL STUDY

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A previously published case-control study of agricultural risk factors involved male cases of non-Hodgkin's lymphoma registered under code 202 of the International Classification of Diseases (ICD). This study has been expanded with the inclusion of cases registered under ICD code 200, and additional controls. The expanded study comprises 100 ICD 200 cases and 83 ICD 202 cases registered during the period 1977-81, together with 338 controls selected from other cancer registrations during the same period. The largest relative risk for specific farming types was for orchard workers (odds ratio = 3.7, 90% confidence limits 1.1-12.1). No elevated risks were observed for exposure to farm animals, nor for potential exposure to phenoxy herbicides (odds ratio = 1.0, 90% confidence limits 0.7-1.5), or chlorophenols (odds ratio = 1.4, 90% confidence limits 0.8-2.3). The previous finding of an excess risk associated with fencing work was weakly supported by the expanded study (odds ratio = 1.4, 90% confidence limits 1.0-2.0). However, the previous finding of an excess risk associated with meat works employment was more strongly supported (odds ratio = 1.8, 90% confidence limits 1.2-2.6). One relevant risk factor is 2,4,6-TCP which is used in the treatment of pelts, but the excess risks do not appear to be confined to pelt department workers. An alternative hypothesis is that meat workers may be exposed to oncogenic viruses.

A previous analysis of the occupations of male malignant lymphoma patients recorded by the New Zealand Cancer Registry during the period 1977-81, compared with other cancer controls, found that agricultural workers were at increased risk of developing malignant lymphoma (Pearce *et al.*, 1985). Similar excesses have been found in studies in other countries (Blair *et al.*, 1985; Buesching and Wollstadt, 1984; Burmeister, 1981; Burmeister *et al.*, 1983; Cantor, 1982; Goldsmith and Guidotti, 1977), including a Swedish study which found an association between malignant lymphoma and exposure to phenoxy herbicides or chlorophenols (Hardell *et al.*, 1981), both of which have been widely used in New Zealand since the late 1940's (Smith *et al.*, 1983).

The New Zealand non-Hodgkin's lymphoma excess occurred almost entirely among relatively young patients registered under code 202 (non-Hodgkin's lymphoma other than lymphosarcoma and reticulosarcoma) of the International Classification of Diseases (ICD) (WHO, 1967, 1977). Accordingly, interviews were conducted with patients from this subgroup and their matched controls with other cancers. The interview findings (Pearce *et al.*, 1986*a*) for exposure to phenoxy herbicides or chlorophenols were largely negative. However, the interview data suggested that the overall excess risk for farmers was attributable to excesses among farmers who had carried out fencing work or been employed in a meat works, with particularly high risks for those who had carried out both activities. As more resources became available it was decided also to interview the non-Hodgkin's lymphoma cases registered under ICD code 200 in order to provide a more complete comparison with findings from other studies. This report thus extends the previously published study in several ways. First, interview findings for the risk factors previously examined are presented for the additional group of cases registered under ICD 200. Second, the data for the previously interviewed ICD 202 cases are re-analysed with additional controls. Finally, for both case groups, data on additional risk factors are also presented, including: type of farming; contact with farm animals; and history of various medical conditions and allergies.

METHODS

The expanded target case population (Pearce *et al.*, 1985) comprised male public hospital patients who were registered under ICD codes 200 and 202 during the period 1977-81 and who were under 70 years of age at time of registration. ICD code 200 comprises lymphosarcoma and reticulosarcoma. The cases registered under ICD code 202 had been interviewed previously, and this group comprised all other non-Hodgkin's lymphomas, primarily nodular lymphoma and unspecified non-Hodgkin's lymphoma.

Table I shows the number of exclusions, the target population, and the response rates. Relevant laboratory reports of cases coded as non-Hodgkin's lymphoma were examined by one pathologist and 10 cases without a documented tissue diagnosis of non-Hodgkin's lymphoma were excluded. Reasons for other exclusions of cases or controls included: private hospital patients who had been wrongly coded at the Cancer Registry; duplication at the Cancer Registry; wrongly coded age; and persons who had come to New Zealand solely for medical treatment.

For each of the cases, 4 male cancer patients who had the same year of registration and were born within 2 years of patients' date of birth had previously been chosen as controls for the study on the basis of Cancer Registry information on occupation (Pearce *et al.*, 1985). For the cases registered under ICD code 202, 2 of the 4 control patients were selected at random for interview, and the same exclusion criteria were applied as had been used for the cases. The interviews were conducted concurrently with those of the other cancer controls for a case-control study of multiple myeloma and farming (Pearce *et al.*, 1986*b*), yielding a series of 315 interviews from a group of 389 eligible controls. The additional cases registered under ICD code 200 were interviewed towards the end of the time period during which the series of 315 controls was interviewed. An additional group of 30 controls was included in order to keep the interviewer "blind", and interviews were conducted with 23 of these. The expanded non-Hodgkin's lymphoma case-control study thus comprised interviews with 100 cases registered under ICD code 200, 83 cases registered

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TABLE I - TARGET SAMPLE, ACHIEVED SAMPLE, AND REASONS NOT INTERVIEWED

	ICD 200 cases	ICD 202 cases	Cancer controls
Initially identified in cancer registry 1977–81	136	106	446
Ineligible:			
Histology	4	6	—
Other reason	11	6	27
Target sample	121	94	419
Hospital could not identify or had no information	5	1	9
Medical advice not to contact	3	2	15
Refusal	2	0	14
Unable to contact	11	8	43
Achieved sample	100	83	338
Achieved sample as percentage of target sample (%)	83	88	81

TABLE II - DISTRIBUTION OF HISTOLOGICAL TYPES OF NON-HODGKIN'S LYMPHOMA CASES

Cell type	Number of cases
Nodular (42)	
Lymphocytic (28)	
Well differentiated	6
Poorly differentiated	22
Mixed	9
Histiocytic	4
Unclassified	1
Diffuse (115)	
Lymphocytic (44)	
Well differentiated	12
Poorly differentiated	32
Mixed	12
Histiocytic	54
Unclassified	5
Leukaemic reticuloendotheliosis	3
Mycosis fungoides	2
Unclassified	21
Total	183

under ICD code 202, and 338 controls. The entire control group was used in all analyses to provide greater precision for the estimates of control exposure.

Interviews were conducted by telephone with those patients considered to be well enough, or with the patients' next-of-kin. All interviews were conducted by one interviewer who was not aware of whether the patient had a non-Hodgkin's lymphoma or was a cancer control. The questionnaire was similar to that used in previously published case-control studies (Pearce et *al.*, 1986*a*,*b*; Smith et *al.*, 1984). As before, stem questions were used to identify whether or not study subjects had carried out activities, or worked in particular occupations, which entailed a potential exposure to phenoxy herbicides or chlorophenols. If the response to a stem question was affirmative, then a series of subsidiary questions were asked to clarify the work done and the actual potential for exposure, firstly in general terms, and then in specific terms, seeking the identity of the chemicals used. Additional questions were also asked concerning involvement in various types of farming, contact with various farm animals, and history of various medical conditions and allergies. The medical conditions selected for questioning were those which had been associated with tumors of the lymphatic and haemopoietic system in previous epidemiologic studies or case-series reports, and which were expected to have sufficiently high incidence in the control population.

The Statistical Analysis System logist procedure (Harrell, 1983) was used to perform an unconditional maximum likelihood logistic regression analysis, adjusting for decade of birth and whether the subject or the next-of-kin was interviewed.

RESULTS

Most cases of non-Hodgkin's lymphoma had been reported using Rappaport's classification (1966), and the others were reclassified according to this classification by one pathologist when sufficient detail was obtained from the histology reports. The remainder were included in unclassified categories (Table II). Unfortunately, appropriate information was not available to permit the use of other classifications. The case group included 3 cases of leukaemic reticuloendotheliosis, and 2 cases of Mycosis fungoides, which are not non-Hodgkin's lymphomas despite being registered under ICD code 202. However, excluding this small number of cases made no difference to the findings, and they were included in all analyses presented here in order to provide greater comparability with other studies based on the ICD classification.

Table III gives the findings for various occupations and activities potentially associated with exposure to phenoxy herbicides, and Table IV gives the specific findings relating to exposure. The proportions of cases and controls who had worked in the various occupations were very similar. Elevated odds ratios were observed in the ICD 200 case group for persons carrying out spraying for the Ministry of Works, or as forestry or railway workers, but each of these estimates was based on a single exposed case. None of the odds ratios relating to specific phenoxy herbicide exposure were elevated.

Table V gives the findings for various occupations and activities potentially associated with exposure to chlorophenols. The elevated odds ratios for meat works employment and fencing work in the ICD 202 case group were supported by the findings for the ICD 200 case-group, although the fencing work association was relatively weak. The findings for meat workers and fencers did not show any clear association with specific subtypes of non-Hodgkin's lymphoma, although this may be due to the small numbers involved in the comparisons (Table II), or because only the Rappaport classification was used.

Table VI reports the specific findings relating to chlorophenol exposure. The odds ratios for potential chlorophenol exposure were elevated, but this was largely due to the findings for meat workers which included workers potentially exposed to chlorophenols in pelt departments. The odds ratios for all non-Hodgkin's lymphoma for the 3 categories of chlorophenol exposure were 1.2, 1.1, and **1.0,** respectively, when meat workers were excluded from the analysis.

Our initial analysis (Pearce et *al.*, 1986*a*) suggested that there was a statistical interaction between the effects of fencing work and meat works employment, and this is further investigated in Table VII. In both studies, the odds ratio for exposure to both factors was greater than the product of the odds ratios for exposure to each factor alone.

The findings for various types of farming work are presented in Table VIII, and those for exposure to various farm animals in Table IX. There are few New Zealand farms solely involving cattle, but there are a number of "mixed/dry stock" farms with both sheep and cattle. Cropping farms primarily involve market gardens which grow vegetables and fruit for

TABLE III - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR OCCUPATIONS AND ACTIVITIES INVOLVING POTENTIAL EXPOSURE TO PHENOXY HERBICIDES[1]

Exposure	ICD 200			ICD 202			All NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Farming	41	0.9	0.6–1.3	40	1.2	0.8–1.8	81	143	1.0	0.8–1.4
Used any agricultural chemical spray	14	0.7	0.4–1.3	19	1.4	0.8–2.3	33	55	1.0	0.7–1.5
Sprayed gorse, blackberry, pasture, cereal or peas	11	0.7	0.4–1.4	14	1.2	0.7–2.2	25	43	0.9	0.6–1.5
Forestry worker	8	0.8	0.4–1.5	7	0.9	0.4–1.9	15	30	0.8	0.5–1.4
Sprayed chemicals	1	2.0	0.2–21.5	0	—	—	1	1	1.1	0.1–11.7
Railway worker	8	0.6	0.3–1.2	12	1.2	0.7–2.2	20	40	0.9	0.5–1.4
Sprayed chemicals	1	3.2	0.3–37.8	0	—	—	1	1	1.4	0.1–15.0
Ministry of works	9	1.2	0.6–2.3	6	0.9	0.4–1.9	15	27	1.0	0.6–1.8
Sprayed chemicals	1	6.1	0.6–65.8	0	—	—	1	1	2.1	0.2–21.6
Town council worker	9	0.7	0.4–1.3	9	0.8	0.4–1.6	18	44	0.7	0.5–1.2
Sprayed chemicals	2	0.5	0.1–2.0	1	0.4	0.1–2.4	3	10	0.5	0.2–1.5
Chemical sprayer	1	1.5	0.2–11.8	1	1.6	0.2–12.2	2	1	1.7	0.3–7.7
Aerial spray work	0	—	—	1	1.4	0.2–11.3	1	2	0.6	0.1–4.8
Ever sprayed an agricultural chemical	55	1.1	0.8–1.7	51	1.4	0.9–2.1	106	170	1.2	0.9–1.7

[1]Stratified for decade of birth and whether the subject or a relative was interviewed.

TABLE IV - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR VARIOUS CATEGORIES OF EXPOSURE TO PHENOXY HERBICIDES[1]

Exposure	ICD 200			ICD 202			All NHL			
	Exposed cases	Odds ratio	90% confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Ever potentially exposed before cancer registration	23	0.9	0.6–1.5	21	1.1	0.7–1.8	44	72	1.0	0.7–1.5
Potential exposure of more than 1 day at least 5 years before cancer registration	15	0.8	0.4–1.3	17	1.2	0.7–2.0	32	56	0.9	0.6–1.4
Probable or definite exposure of more than 1 day at least 5 years before cancer registration	13	0.7	0.4–1.3	16	1.2	0.7–2.1	29	50	1.0	0.6–1.5
Probable or definite exposure of at least 5 days more than 10 years before cancer registration	9	0.6	0.3–1.2	14	1.3	0.7–2.2	23	41	0.9	0.6–1.5

[1]Stratified for decade of birth and whether the subject or a relative was interviewed.

TABLE V - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR OCCUPATIONS AND ACTIVITIES INVOLVING POTENTIAL EXPOSURE TO CHLOROPHENOLS[1]

Exposure	ICD 200			ICD 202			All NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Fencing work	34	1.3	0.8–1.9	34	1.6	1.1–2.5	68	93	1.4	1.0–2.0
Treated own posts	1	0.3	0.1–1.8	1	0.4	0.1–2.6	2	8	0.3	0.1–1.3
Saw mill or timber merchant	14	1.0	0.6–1.7	10	0.9	0.5–1.6	24	45	0.9	0.6–1.5
Potential exposure at saw mill or timber merchant	7	1.1	0.5–2.5	4	0.8	0.3–2.1	11	18	1.0	0.5–2.0
Meat works	24	1.8	1.1–2.9	19	1.7	1.0–2.8	43	52	1.8	1.2–2.6
Pelt department in meat works	6	2.2	0.9–5.3	4	1.7	0.6–4.7	10	10	1.9	0.9–4.0
Tannery	0	—	—	2	1.0	0.3–4.1	2	7	0.5	0.1–1.8

[1]Stratified for decade of birth and whether the subject or a relative was interviewed.

TABLE VI - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR VARIOUS CATEGORIES OF EXPOSURE TO CHLOROPHENOLS[1]

Exposure	ICD 200			ICD 202			All NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Ever potentially exposed	12	1.4	0.8–2.7	9	1.3	0.7–2.7	21	27	1.4	0.8–2.3
Potential exposure of more than 1 day at least 5 years before cancer registration	11	1.3	0.7–2.4	9	1.3	0.7–2.7	20	27	1.3	0.8–2.3
Potential exposure of at least 5 days more than 10 years before cancer registration	7	1.1	0.5–2.4	7	1.4	0.6–2.9	14	21	1.3	0.7–2.3

[1]Stratified for decade of birth and whether the subject or a relative was interviewed.

TABLE VII - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR SEPARATE AND JOINT EFFECTS OF FENCING WORK AND MEAT WORKS EMPLOYMENT[1]

Fencing	Meat works	ICD 200			ICD 202			All NHL			
		Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
No	No	55	1.0		42	1.0		97	212	1.0	
Yes	No	21	1.6	0.8–3.1	22	1.9	0.9–4.1	43	74	1.7	1.0–3.0
No	Yes	11	1.5	0.8–2.9	7	1.2	0.6–2.6	18	33	1.4	0.8–2.3
Yes	Yes	13	3.4	0.8–14.3	12	4.0	0.8–19.5	25	19	3.8	1.2–12.1

[1]Stratified for farming, decade of birth, and whether the subject or a relative was interviewed.

TABLE VIII - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR VARIOUS TYPES OF FARMING[1]

Exposure	ICD 200			ICD 202			ALL NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% confidence limits	Exposed cases	Exposed control	Odds ratio	90% Confidence limits
Sheep farm	13	0.9	0.5–1.5	15	1.3	0.7–2.2	28	47	1.1	0.7–1.6
Dairy farm	19	0.8	0.5–1.4	18	0.9	0.6–1.5	37	75	0.9	0.6–1.3
Mixed/dry stock farm	12	0.9	0.5–1.7	9	0.8	0.4–1.5	21	38	0.9	0.5–1.4
Cropping farm	5	1.1	0.4–2.7	3	0.8	0.3–2.3	8	14	0.9	0.4–2.0
Poultry farm	1	0.7	0.1–4.9	0			1	4	0.4	0.1–2.5
Orchard	3	3.5	0.9–14.0	3	4.3	1.1–17.3	6	3	3.7	1.1–12.1

[1]Stratified for decade of birth and whether the subject or a relative was interviewed.

the consumer market, but some involve the production of wheat and other grains. The only elevated odds ratio was for orchard workers.

Finally, elevated risks were observed for persons with reported histories of rheumatoid arthritis, eczema and food allergies (Table X). No patterns were discernible concerning the association with food allergies, which included allergies to flour, dairy products, mushrooms, and seafood.

DISCUSSION

A major reason for conducting these case-control studies was to ascertain whether the association between exposure to phenoxy herbicides or chlorophenols and malignant lymphoma, which had been observed in the Swedish study (Hardell *et* al., 1981), existed in New Zealand. The initial analysis (Pearce et al., 1986*a*) of cases registered under ICD code 202 did not find an association of non-Hodgkin's lymphoma and phenoxy herbicide exposure, but was not strictly comparable to the Swedish study (Hardell et *al.*, 1981) which primarily involved cases of non-Hodgkin's lymphoma coded under ICD 200. The Swedish study also involved cases of Hodgkin's disease (ICD 201), but the findings were similar for the Hodgkin's disease and non-Hodgkin's lymphoma cases. The expanded New Zealand study thus has the advantage of greater comparability with the Swedish study. A 2-tailed test of heterogeneity of the findings in the 2 studies indicates that the differences go well beyond what might be expected by chance ($p < 0.01$), and the New Zealand findings suggest that, even if there was a real causal link, it is most unlikely that the true relative risk would be greater than 1.5 for persons exposed to phenoxy herbicides, or 2.3 for persons exposed to chlorophenols. The discrepancies in the findings of the two studies are puzzling, particularly in the light of the recent case-control study of non-Hodgkin's lymphoma in Kansas (Hoar et al., 1986) which found an overall relative risk of 2.2 for phenoxy herbicide exposure. The effect corresponded with the use of 2,4-dichlorophenoxyacetic acid (2,4-D), since usage of other phenoxy herbicides was small.

The New Zealand study differed from those in Sweden and Kansas in that the control group consisted of other cancers selected from the National Cancer Registry. The main advantages of using other registrants as controls lie in the minimi-

TABLE IX - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR CONTACT WITH VARIOUS FARM ANIMALS'

Exposure	ICD 200			ICD 202			ALL NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Sheep	36	0.9	0.6-1.4	37	1.3	0.9-2.0	73	122	1.1	0.8-1.5
cows	38	0.9	0.6-1.3	33	0.9	0.6-1.4	71	134	0.9	0.7-1.2
Cattle	27	0.8	0.5-1.3	30	1.3	0.8-2.0	57	96	1.0	0.7-1.4
Poultry	41	1.5	1.0-2.2	28	1.0	0.7-1.6	69	106	1.2	0.9-1.7
Pigs	29	1.0	0.6-1.5	27	1.0	0.7-1.6	56	97	1.0	0.7-1.4

'Stratified for decade of birth and whether the subject or a relative was interviewed

TABLE X - ODDS RATIO ESTIMATES FOR NON-HODGKIN'S LYMPHOMA FOR VARIOUS MEDICAL CONDITIONS AND ALLERGIES'

Exposure	ICD 200			ICD 202			ALL NHL			
	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Odds ratio	90% Confidence limits	Exposed cases	Exposed controls	Odds ratio	90% Confidence limits
Rheumatoid arthritis	3	1.5	0.4-4.7	4	2.2	0.7-6.3	7	7	1.7	0.7-4.2
Eczema	14	2.5	1.3-4.6	9	1.6	0.8-3.2	23	21	2.0	1.2-3.4
Asthma	6	0.6	0.3-1.3	9	1.2	0.6-2.3	15	29	0.9	0.5-1.5
Asthma medication	5	0.8	0.3-1.9	5	1.0	0.4-2.3	10	19	0.9	0.4-1.7
Hay fever	14	0.8	0.4-1.3	11	0.7	0.4-1.2	25	52	0.8	0.5-1.2
Food allergies	8	4.8	1.9-11.9	5	3.3	1.2-9.2	13	7	3.8	1.7-8.5
Drug allergies	2	0.4	0.1-1.3	10	2.1	1.1-4.3	12	20	1.2	0.6-2.2

'Stratified for decade of birth and whether the subject or a relative was interviewed.

zation of information bias since cases and controls are drawn from the same registry. This study design also minimizes selection bias due to geographical differences in registration, while any bias due to other cancers being associated with farming is likely to be small, since the overall cancer mortality in New Zealand farmers is identical to national mortality rates (Pearce and Howard, 1985). Furthermore, the previously published analysis (Pearce et *al.*, 1986*a*) also included a second control group from the general population as an additional check, and this gave very similar findings to those obtained with the main control group of other cancer patients. Lack of validation of the exposure data based on personal recall is also a potential problem in the present study. This might be expected to apply equally to cases and controls (since both groups involve cancer patients), and hence to reduce the observed relative risk (Copeland *et al.*, 1977). However, in Hoar's study (1986) there was little change in the findings when exposure was based on the records of pesticide suppliers, rather than on personal recall.

Hence, the phenoxy herbicide findings in the expanded study appear unlikely to be due to bias, although the possibility of unidentified confounding factors always exists. A further possibility (Pearce et al., 1986*a*), is that phenoxy herbicide and chlorophenol exposure could be carcinogenic only when occurring jointly with other exposures present in Sweden and Kansas, but not in New Zealand. However, this study provides no evidence that can be used to assess this speculation.

The major positive findings from the expanded study relate to fencing work and meat works employment.

We have previously suggested (Pearce *et al.*, 1986*a*) that the excess risk associated with fencing work could be due to exposure to pentachlorophenol (PCP) which is occasionally used for timber preservation, or to sodium pentachlorophenate (NaPCP) which is widely used for anti-sapstain treatment. On the other hand, it has been estimated that 99% of fencing timber produced in New Zealand since 1955 has been treated by vacuum-pressure impregnation with a copper chrome arsenate (CCA) solution (Department of Statistics, 1983), of which arsenic comprises 30-50% of the active ingredients (Timber Preservation Authority, 1980). Hence, another risk factor of interest is arsenic which has been associated with an increased risk of lymphatic and haemopoietic malignancies in several studies (Axelson et al., 1978; Baetjer et al., 1975; Fergusson, 1976; Ott et al., 1974). It has been suggested that arsenic may not generally act as a direct carcinogen, but may primarily act as a co-carcinogen (Pershagen, 1983), and the finding of a strong excess risk associated with joint exposure to fencing work and meat works employment is of interest in this regard. The findings for orchard workers may also be relevant due to the past use of lead arsenate spray in orchards (Nelson et *al.*, 1973), although many other chemicals may also have been used.

The previous finding of an association of non-Hodgkin's lymphoma with meat works employment has been supported by the expanded study. We have previously suggested (Smith et al., 1984) that one potential risk factor was exposure to 2,4,6-trichlorophenol (2,4,6-TCP) or other chemicals used in the treatment of pelts. 2,4,6-TCP is highly skin-permeating (Roberts et al., 1977) and the treatment of pelts has involved the workers' manually removing pelts from the treatment solutions and handling wet skins without protection. Some companies now use other systems involving less direct contact. Studies in rats and mice have shown that 2,4,6-TCP can cause lymphomas, leukaemias and hepatocellular carcinomas (National Cancer Institute, 1979).

However, we also noted that there was an overall excess of soft-tissue sarcomas among meat workers, and that focusing on the pelt departments could be misleading. This observation is supported by the findings presented here, since the relative risks for pelt-department workers are not markedly different from those for other meat workers. Furthermore, the proportion of meat workers reporting pelt-department work was small, and there is no association with other types of chlorophenol exposure in the expanded study.

In our previous report (Pearce et al., 1986*a*) we noted these problems with the 2,4,6-TCP hypothesis, and suggested an alternative hypothesis that meat workers may be exposed to zoonotic oncogenic viruses. In a recent report, Johnson et *al.*

(1986) also proposed this hypothesis and presented a comprehensive review of relevant evidence. In particular, they observed that the greatest risk for Hodgkin's disease in their cohort study of meat workers was associated with slaughtering, particularly of cattle, pigs and sheep, supporting the hypothesis of an infective origin for these cases.

The increased interest in recent years in a potential role of zoonotic oncogenic viruses stems from the generally increased interest in RNA tumor viruses, or retroviruses, since the discovery that sequences closely related to viral oncogenes were present in human cells (Hall, 1984). These cellular oncogenes, or proto-oncogenes, have been discovered in the genomes of all vertebrate cells examined so far and for each of the viral oncogenes discovered to date.

The major interest in the agricultural field centres on the possible role of the bovine leukaemia virus which causes lymphosarcoma in cattle (Heath *et al.*, 1975), and can induce antibody production in other species (Olson *et al.*, 1972). This is a c-type RNA virus, one of a group of viruses which represent the aetiologic agents of tumours of the lymphatic and haemopoietic system in all the higher non-human mammalian species studied to date (Armenian and Hamaden, 1983).

Bovine leukaemia virus has been found in New Zealand herds, although the prevalence of infection was low (Parrish *et al.*, 1981). The virus has been found in meat and unpasteurized milk in other countries (Ferrer *et al.*, 1981; Miller and Van der Maaten, 1979). Preliminary human studies have shown no evidence of infection (Donham *et al.*, 1977), but this may be because current laboratory techniques or knowledge of the mechanism of infection are not sufficiently developed (Johnson *et al.*, 1986).

Epidemiologic evidence for the role of zoonotic oncogenic viruses is currently weak (Blair *et al.*, 1985), although some studies have found associations between various haematologic malignancies and *dairy* (Bartsch *et al.*, 1975; Heath, 1970; Henricson *et al.*, 1968), cattle (Blair and Thomas, 1979) or poultry (Priester and Mason, 1974) farming. Most studies have been ecologic in nature and have not included serological tests for evidence of viral infection. However, it is not clear whether such tests would be informative without more adequate knowledge of the possible mechanism of infection. Furthermore, it appears that viruses can cause tumours in animals without serological evidence of viral replication (Francis *et al.*, 1981; Witter *et al.*, 1970). The picture is further complicated by the evidence suggesting that chemical leukaemogens activate leukaemogenic viruses, rather than inducing a somatic mutation (Armenian and Hamaden, 1983), and that some viruses may be oncogenic only when combined with other factors (Fraumeni, 1979). Hence, although the evidence is currently weak, the zoonotic oncogenic virus hypothesis clearly warrants further investigation.

Finally, although the main findings of this expanded study relate to agricultural risk factors, the finding for rheumatoid arthritis is of interest, since several other clinical reports and epidemiological studies have suggested that patients with rheumatoid arthritis are at increased risk of non-Hodgkin's lymphoma (Pearce and Porta, 1986).

In summary, this expanded study has supported the previous finding of an absence of association between non-Hodgkin's lymphoma and exposure to phenoxy herbicides in New Zealand. It also supports a similar absence of association with exposure to chlorophenols, although this finding is more open to question, due to the marginally elevated risks for overall chlorophenol exposure, and the major positive findings relating to fencing work and meat works employment. One relevant risk factor in meat works is 2,4,6-TCP which is used in the treatment of pelts, but the excess risks do not appear to be confined to pelt-department workers. An alternative hypothesis is that meat workers may be exposed to oncogenic viruses.

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REFERENCES

ARMENIAN, H.K., and HAMADEN, R.R., Epidemiology of non-Hodgkin's lymphoma. In: A.M. Lilienfeld (ed.), *Reviews in* cancer *epidemiology,* Vol. 2, Elsevier, New York **(1983).**

AXELSON, O., DAHLGREN, E., JANSSON, C.D., and REHNLUND, S.O., Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Brit. *J. industr. Med., 35,* **8–15 (1978).**

BAETJER, A.M., LILIENFELD, A.M., and LEVIN, M.L., Cancer and occupational exposure to inorganic arsenic. *Abstracts of the XVIII International Congress on Occupational Health,* Permanent Commission and International Association on Occupational Health, London **(1975).**

BARTSCH, D.C., SPRINGHER, F., and FALK, H., Acute nonlymphocytic leukemia. An adult cluster. **J.** *Amer. med. Ass., 232,* **1333–1336 (1975).**

BLAIR, A., MALKER, H., CANTOR, K.P., BURMEISTER, L., and WIKLUND, K., Cancer mortality among farmers: a review. *Scand.* **J.** Work *environ. Hlth, 11,* **397-407 (1985).**

BLAIR, A., and THOMAS, T.L., Leukemia among Nebraska farmers: a death certificate study. *Amer. J. Epidemiol., 110,* **264–273 (1979).**

BUESCHING, D.P., and WOLLSTADT, L., Cancer mortality among farmers. **J.** *nat. Cancer Inst.,* **72, 503 (1984).**

BURMEISTER, L.F., Cancer mortality in Iowa farmers, 1971-8. *J. nar. Cancer Inst..* **66,** 461–464 (1981).

BURMEISTER, L.F., EVERETT, G.D., VANLIER, S.F., and ISACSON, P., Selected cancer mortality and farm practices in Iowa. *Amer.* **J.** *Epidemiol.,* **118, 72–77 (1983).**

CANTOR, K.P., Farming and mortality from non-Hodgkin's lymphoma: a case-control study. *Int. J. Cancer,* **29, 239–247 (1982).**

COPELAND, K.T., CHECKOWAY, H., MCMICHAEL, A.J., and HOLBROOK, R.H., Bias due to misclassification in the estimation of relative risk. *Amer. J. Epidemiol.,* **105,488-495 (1977).**

DEPARTMENT OF STATISTICS. *Monthly Abstract of Statistics,* October, 1983, Department of Statistics, Wellington **(1983).**

DONHAM, K.J., VANDERMAATEN, M.J., MILLER, J.M., KRUSE, B.C., and RUBINO, M.J., Seroepidemiologic studies on the possible relationships of human and bovine leukemia: brief communication. *J. nat. Cancer Inst.,* **59, 851–853 (1977).**

FERGUSSON, W., Epidemiology of arsenic. In: B.W. Carnow (ed.), *Health effects of occupational lead and arsenic exposure: a symposium,* Department of Health, Education and Welfare, Washington, DC **(1976).**

FERRER, J.F., KENYON, S.J., and GUPTA, P., Milk of dairy cows frequently contains a leukemogenic virus. *Science,* 213, **1014–1016 (1981).**

FRANCIS, D.P., ESSEX, M., COTTER, S.M., GUTENSOHN, N., JOKOWSKI, R., and HARDY, W.D., Epidemiological association between virus-negative feline leukaemia and the horizontally transmitted feline leukaemia virus. Cancer Lett., **12, 37-42 (1981).**

FRAUMENI, J.F., Epidemiological studies of cancer. *In:* A.C. Griffin and C.R. Shaw (eds.), *Carcinogens: identification and mechanisms of action,* Raven Press, New York **(1979).**

GOLDSMITH, J.R., GUIDOTTI, T.L., Environmental factors in the epidemiology of lymphosarcoma. Path. Ann., **12,** 411-425 **(1977).**

HALL, A., Oncogenes—implications for human cancer: a review. **J.** *roy. Soc. Med.*, **77,410–416 (1984).**

HARDELL, L., ERIKSSON, M., LENNER, P., and LUNDGREN E., Malignant

lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Brit. J. Cancer,* **43, 169–176 (1981).**

HARRELL, **F.,** The logist procedure. *In: SAS supplemental library user's guide,* SAS Institute, Cary, NC **(1983).**

HEATH, C.W., Human leukemia: genetic and environmental clusters. ***Bibl. Haemat.*, *36,* 649–653 (1970).**

HEATH, C.W., CLADWELL, G.G., and FEORINO, P.C., Viruses and other microbes. *In:* J.F. Fraumeni (ed.), ***Persons at high risk of cancer,*** Academic Press, New York **(1975).**

HENRICSON, B., and RINGERTZ, N., Comparative statistical studies on the geographical distribution of human and bovine leukemia in Sweden. ***Bibl. Haemat.*, 31, 330–332 (1968).**

HOAR, **S.K.,** BLAIR, A., HOLMES, F.F., BOYSEN, C., ROBEL, R.J., HOOVER, R., and FRAUMENI, J.F., Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma. ***J. Amer. med. Ass.*, 256, 1141–1147 (1986).**

JOHNSON, E.S., FISCHMAN, H.R., MATANOWSKI, G.M., and DIAMOND, E,., Cancer mortality among white males in the meat industry. ***J. occup. Med.*, 28, 23–32 (1986).**

MILLER, J.M., and VANDERMAATEN, M.J., Infectivity tests of secretions and excretions from cattle infected with bovine leukemia virus. ***J. nat. Cancer Inst.*, 62, 425–428 (1979).**

NATIONAL CANCER INSTITUTE. ***Bioassay of 2,4,6-trichlorophenol for possible carcinogenicity,*** Technical Report Series **155,** Department of Health, Education and Welfare, Washington, DC **(1979).**

NELSON, W.C., LYKINS, M.H., MACKEY, J., NEWILL, V.A., FINKLEA, J.F., and HAMMER, **D.I.,** Mortality among orchard workers exposed *to* lead arsenate sprays: a cohort study. ***J. chron. Dis.*, *26,* 105–118 (1973).**

OLSON, C., MILLER, L.D., MILLER, J.M., and HOSS, H.E., Transmission of lymphosarcoma from cattle to sheep. ***J. nut. Cancer Inst.*, 49, 1463–1467 (1972).**

OTT, M.G., HOLDER, B.B., and GORDON, H.L., Respiratory cancer and occupational exposure to arsenicals. ***Arch. environ. Hlth*, 29, 250–255 (1974).**

PARRISH, C.R., OLIVER, R.E., WEDDELL, W., and ROSS, A.D., Bovine leukemia virus infection in New Zealand cattle. ***N. Z. vet. J.*, 30, 56–58 (1981).**

PEARCE, N.E., and HOWARD, **J.K.,** Occupational mortality in New Zealand males **1974–78.** ***Commun.*** Hlth ***Stud.*, 9,212–219 (1985).**

PEARCE, N.E., SMITH, A.H., and FISHER, D.O., Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand Cancer Registry based study. ***Amer. J. Epidemiol,* 121, 225–237 (1985).**

PEARCE, N.E., and PORTA, M., Association of non-Hodgkin's lymphoma with rheumatoid arthritis (letter). ***Amer. J. Med.,*** in press **(1986).**

PEARCE, N.E., SMITH, A.H., HOWARD, J.K., SHEPPARD, R.A., GILES, H.J., and TEAGUE, C.A., Non-Hodgkin's lymphoma and exposure to phenoxy herbicides, chlorophenols, fencing work and meat works employment: a case-control study. ***Brit. J. industr. Med.*, 43, 75–83 (1986*a*).**

PEARCE, N.E., SMITH, A.H., HOWARD, J.K., SHEPPARD, R.A., GILES, H.J., and TEAGUE, C.A., Case-control study of multiple myeloma and fanning. ***Brit. J. Cancer,*** in press (1986*b*).

PERSHAGEN, G., The epidemiology of human arsenic exposure. ***In:*** B.A. Fowler (ed.), ***Biological and environmental effects of arsenic,*** Elsevier, Amsterdam **(1983).**

PRIESTER, W.A., and MASON, T.J., Human cancer mortality in relation to poultry population, by county, in **10** southeastern states. ***J. nut. Cancer Inst.,* 53, 4549 (1974).**

RAPPAPORT, H., Tumors of the haemopoietic system. ***In: Atlas of Tumor Pathology,*** Fascicle ***8,*** **Armed** Forces Institute of Pathology, Washington, DC **(1966).**

ROBERTS, M.S., ANDERSON, R.A., and SWARBRICK, J., Permeability of human epidermis to phenolic compounds. ***J. Pharm. Pharmacol.*, 29, 677–683 (1977).**

SMITH, A.H., FISHER, D.O., GILES, H.J., and PEARCE, N.E., The New Zealand soft tissue sarcoma case-control study: interview findings concerning phenoxylacetic acid exposure. ***Chemosphere,* 12, 565–571 (1983).**

SMITH, A.H., PEARCE, N.E., FISHER, D.O., GILES, H.J., TEAGUE, C.A., and HOWARD, J.K., **Soft** tissue sarcoma and exposure to phenoxyherbicides and chlorophenols in New Zealand. ***J. nat. Cancer Inst.*, *73,* 1111–1117 (1984).**

TIMBER PRESERVATION AUTHORITY. ***Timber preservation in New Zealand: specifications,*** Amendment No. **4,** New Zealand Forest Service, Rotorua **(1980).**

WITTER, R.L., NAZERIAN, K., PURCHASE, H.G., and BURGOYNE, G.H., Isolation from turkeys of a cell-associated herpesvirus antigenically related to Marek's disease virus. Amer. ***J. vet. Res., 31,* 525–538 (1970).**

WORLD HEALTH ORGANISATION. ***Manual of the international statistical classification of diseases, injuries and causes of death,*** 8th revision, WHO, Geneva **(1967).**

WORLD HEALTH ORGANISATION. Manual of the international **statistical** classification of diseases, injuries and causes of death, 9th revision, **WHO,** Geneva **(1977).**