

# **Occupational Exposures and Non-Hodgkin's Lymphoma: Canadian Case-Control Study**

Chandima P. Karunanayake, PhD<sup>1</sup>, Helen H McDuffie, PhD<sup>1</sup>, James A Dosman, MD<sup>1</sup>, John J Spinelli, PhD<sup>2</sup>, Punam Pahwa, PhD<sup>1,3</sup> and the Cross Canada Study of Pesticides and Health Researchers.

<sup>1</sup>Canadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Saskatoon, SK, Canada.

<sup>2</sup>Cancer Control Research, British Columbia Cancer Agency, British Columbia, Canada.

<sup>3</sup>Department of Community Health & Epidemiology, University of Saskatchewan, Saskatoon, SK, Canada.

## **Corresponding Author: Punam Pahwa, PhD,**

Canadian Centre for Health and Safety in Agriculture,  
University of Saskatchewan, Royal University Hospital,  
103 Hospital Drive,  
Saskatoon, SK, S7N 0W8, Canada

Phone :( 306) 966-8300

Fax: (306) 966-8799

Email addresses:

CPK: [cpk646@mail.usask.ca](mailto:cpk646@mail.usask.ca)

HHM: [mcduffie@sask.usask.ca](mailto:mcduffie@sask.usask.ca)

JAM: [james.dosman@usask.ca](mailto:james.dosman@usask.ca)

JJS: [jspinelli@bccrc.ca](mailto:jspinelli@bccrc.ca)

PP: [pup165@mail.usask.ca](mailto:pup165@mail.usask.ca)

## **Abstract**

### **Background**

The objective was to study the association between Non-Hodgkin's Lymphoma (NHL) and occupational exposures among males in six provinces of Canada.

### **Methods**

A population based case-control study was conducted from 1991 to 1994. Males with newly diagnosed NHL (ICD-9 code 200 or 202) were stratified by province of residence and age group. A total of 513 incident cases, and 1506 population based controls were included in the analysis. Conditional logistic regression was conducted to fit multivariate statistical models.

### **Results**

Based on conditional logistic multivariate regression modeling, the following factors independently increased the risk of NHL: farmer, driver and machinist as a longest held job; seed cleaner as a short-term job; ever exposed to radium at work; and personal history of another cancer. Exposure to oils at work was negatively associated with NHL. The risks for these associations increased with duration of employment. Men who had worked for 30 years or more years as longest held job were the most likely to develop NHL.

### **Conclusion**

An increased risk of developing NHL is associated with longest held job as farmer, driver, machinist; and short term job as seed cleaner; and exposure to radium at work. The risk of NHL increased with the duration of employment.

## **Background**

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic system [1-2]. Even though NHL is a relatively rare disease, its incidence rates have been increasing worldwide for both men and women. The incidence rates in Canada have increased and the number of deaths each year from NHL has almost tripled over the last 30 years. Age-standardized rates have increased faster among males than among females [1-4]. A number of factors, including inherited and acquired immunodeficiency states [5], and infectious, physical, and chemical agents have been associated with an increased risk for NHL [5-6].

Epidemiological studies have reported positive associations between NHL and certain occupations including those of farmers [7-15], pesticide applicators [11, 16-19], drivers [20-21], and managers [22-23]. Several studies have reported no association between development of NHL and farmers, agricultural and forestry workers and pesticide applicators [24-26]. Occupational exposures of a priori interest include pesticides [27-32], dusts (cement [33], grain [17], soil/field [17], etc), paints [7, 34], diesel exhaust fumes [20, 34], cleaning fluids [7], cutting oils [35], and solvents [36-37]. In this paper, we examined the association between NHL and selected long term occupations, short-term occupations, and occupational exposures based on an individual's occupational history and duration of employment.

## **Methods**

Details of the study design and methodology have been previously published [38-40]. Briefly, we conducted a six province Canadian population based case-control study of men with incident first diagnosis of NHL (ICD-9 200, 202) between 1991 to 1994 and control

subjects were frequency matched by age  $\pm$  2 years to be comparable with the age distribution of the entire case group (Soft Tissue Sarcoma (STS), Hodgkin's Disease (HD), NHL, and Multiple Myeloma (MM)) within each province of residence. The study had approximately three matched controls for each NHL case. Deceased subjects were ineligible as either cases or controls. All participating control subjects were used in the statistical analysis of each cancer site. Cases were identified from provincial cancer registries except in Quebec where hospital records were used. A reference pathologist reviewed the tumour tissue slides. Control subjects were identified through provincial health insurance programs except in Ontario (telephone listing) and British Columbia (voter's lists), as generally described [38-40].

The study design consisted of two stages: Stage 1 - a self-administered postal questionnaire; and Stage 2 - detailed pesticide exposure information collected via telephone interview. With permission, we modified a pesticide exposure questionnaire developed by Hoar et al. [41] to create the study questionnaire. The results in this manuscript are based on the Stage 1 - postal questionnaire only.

The postal questionnaire captured demographic details, personal medical history, lifetime occupational history and specific occupational exposures of interest. Occupational information included a list of all full time jobs held for at least one year. For each job held, we collected information on job title, business, industry or service, total number of years worked for each job and the last year worked at each job. Additional questions probed for information on specific occupations of interest which were held for less than one year at a

time on a summer, casual or temporary basis. These were grouped into forest industry, farming, roadside brush and weed control, ground maintenance, manufacturing and pesticide application. A list of occupational exposures that have been epidemiologically linked to NHL or to one of the other three types of cancers which we studied simultaneously was grouped into dusts, coal products, printing products, paints, metals, pesticides, and radiation and miscellaneous. Additional details of exposure to agricultural chemicals in broad classes i.e. herbicides, fertilizers etc, were obtained. Job titles and industries coding were provided by Statistics Canada [42].

### **Statistical Analysis**

Data were entered into a custom designed SPSS-data entry program. Results were presented as frequencies for categorical variables and mean, standard deviation (SD) or standard error (SE) for continuous variables for cases and controls separately. We had information about the duration of the employment (in years) for each individual. Based on that information, we derived a new variable called longest held job and used in the statistical analysis.

Occupations defined as longest held job if they had been worked at least one year or longer at a time. Duration of employment is the total of number of years in each longest held job.

Mean years worked in longest held job was compared using two sample t-tests for NHL cases and controls. A bivariate analysis was conducted to determine the association between each explanatory variable and NHL outcome. Based on this model building procedure explanatory variables with  $p < 0.20$  were selected for the multivariate model. Statistically significant ( $p \leq 0.05$ ) variables and important explanatory variables were considered for the final multivariate model. Conditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (95% CI) with strata for age and province of residence.

## **Ethics**

The letters of informed consent, questionnaires, and all other correspondence with study participants were approved by the relevant ethics agencies in each province. All of the information that could be used to identify study participants remained within each province of origin under the supervision of the provincial principle investigators.

## **Results**

This study includes responses from 513 cases with NHL and 1506 control subjects. The mean age  $\pm$  standard deviation (SD) of cases was  $57.7 \pm 14.0$  years and of controls  $54.1 \pm 16.0$  years. More cases ( $n=74$ , 14.4%) than controls ( $n=87$ , 5.8%) had a personal history of cancer other than NHL ( $OR_{adj}$  (95 % CI): 2.56 (1.81, 3.62)). More cases ( $n=225$ , 44.9%) than controls ( $n=498$ , 33.8%) had a positive family history of cancer in first-degree relatives ( $OR_{adj}$  (95% CI): 1.43 (1.15, 1.77)). There were no significant difference between NHL cases and controls with respect to their education level and ever lived/worked on a farm. Results are shown in Table 1.

Table 2 shows the distribution of longest held job titles during a lifetime stratified by case-control status. In each group, farmers, managers, salesman and drivers were the most frequently reported longest held job titles. The longest held job title information was missing for 23 cases and 57 controls. For longest held jobs as farming, professional driving, machinist and managerial, the mean number of years did not show any significant difference between cases and controls. The adjusted odds ratios ( $OR_{adj}$ ) and 95% confidence intervals (95% CI) for the longest held job during the lifetime as farmer, driver, machinist or manager

were 1.45 (1.01, 2.10); 1.52 (0.95, 2.42); 2.07 (1.05, 4.09) and 0.89 (0.59, 1.35) respectively. The risk of NHL increased with duration of exposure more than 10 years as longest held job. There is a significant risk increase for NHL when the exposure is > 30 years compared to none exposed (OR<sub>adj</sub> (95% CI): 1.90 (1.05, 3.45)) (see Table 3).

Of the 45 specific occupational exposures grouped into six classes (dusts, coal products, printing, paints, metals and miscellaneous), only exposure to diesel exhaust fumes showed an association with NHL (Table 4). Of the 42 less than one-year short term employments, only chicken farming and seed cleaning jobs showed an association with NHL. The adjusted odds ratios (95% CI) were 1.51 (1.06, 2.13) and 2.20 (1.11, 4.35) respectively (Table 4). Exposure to radium showed a significant association between NHL (OR adj (95% CI): 3.26 (1.38, 7.73)).

Table 5 shows the results of a multivariate conditional logistic regression model that include longest held jobs and other covariates. The variables that remained statistically significantly associated with increased risk of NHL were personal history of another cancer, exposed to radium, longest held jobs as farmer, driver and machinist and short term employment as seed cleaner. Odds ratio of those who were ever exposed to cutting oils was significantly lower than those who were not exposed. Duration of exposure as the longest held job was not significant ( $p=0.088$ ) but it shows increased risk of NHL with longer duration of exposure.

## **Discussion**

Our study investigated the association between NHL and several occupations and occupational exposures. The findings revealed that the three longest held jobs (> one year): farmer, driver and machinist were significantly associated with increased risk of developing NHL. One of the possible explanations is that farmers and drivers might be exposed to pesticides and engine exhaust and machinists might be exposed to solvents or engine exhaust at the work place. The increased risk of NHL for farmers, drivers, and machinist seen in our study is consistent with the findings from other studies [7-15, 20-21].

In the study by Tatham et al. [37], exposure to solvents and exposure to meat work appeared to increase the risk of NHL. Pesticides including herbicide and insecticides have been associated with non-Hodgkin's lymphoma in studies of farmers, agricultural related workers, other pesticide applicators, manufacturing workers and other exposed populations [38,43]. Grain handlers exposed to pesticides, grain dusts, and organic solvents shown a five-fold risk of NHL [44]. Our study confirms that the longest held job title as a farmer (farmer, farm labourer and farm managers) had 1.5 times risk of being diagnosed with NHL compared to the category of non-farmer.

Our results confirm previously reported associations of NHL and a personal history of cancer [45-46]. Exposure to cutting oils at work independently was associated with decreased risk of developing NHL, the rationale for which is unclear. In our study, short term jobs (< one year at a time) in orchard farming, mixed farming, cattle farming, hog farming, sheep farming and other small animal farming did not show associations with NHL. However chicken

farming and a seed cleaning were associated with increased risk of developing NHL. Orchard workers and the meat working employment had larger relative risks for NHL [47]. A population-based case-control study by Amadori et al. [10] suggest that subjects working in agriculture associated with animal breeding are at high risk of NHL. This could be related to the use of chemicals in agriculture or to exposure to animal transmitted diseases or specific chemicals used in animal breeding [10].

The mechanism of cancer induction by radiation shown in our study is not clear. The most widely accepted hypothesis is that some of the ionizing events, which occur when radiation is absorbed in tissue, produce a change in the genes or chromosomes of one or more cells [48]. There are many potential sources of radiation to workers. There is suggestive evidence that exposure to ultraviolet (uv) light, an established cause of immune suppression, may increase the risk of NHL [49-50]. The most recent epidemiologic literature suggests that there is no association between exposure to sunlight and NHL [51-52]. In a case-referent study conducted to investigate the possible association between occupation and occupational exposures and risk of hematological malignancies showed that exposure to asbestos, hydrocarbons, fertilizer, radiation, pesticides and mineral oils were highly associated with hematological malignancies [9]. Another matched case-control study done in the nuclear industry [53] found no significant excess of NHL at any radiation level. Archer [48] stated that uranium mill workers appear to have excess lymphomas. In our study any form of radiation exposure at work was considered. Exposure to radium is significantly associated with increase risk of NHL which suggests fairly equivocal evidence of an association with

NHL presented by Ron [54]. Our study did not find any association between exposure to ultra violet (uv) light and uranium with NHL.

Wood and wood products are among the most common occupational exposures and several studies have reported excesses of hematological cancers in wood workers [55]. It is currently unclear whether the excess risk is due to the wood dust itself, the various chemicals that are applied to the wood, or other carcinogenic agents involved in working with wood. The related occupations of forestry work [56] and pulp and paper work [57] also have shown an increased risk of lymphomas, although these findings have been inconsistent. Forest and the soil conservationists are often occupationally exposed from mixing and /or applying pesticides as a part of their regular duties [17] are at increased risk of NHL. In our study job categories related to wood and wood products: carpenter, logger, sawmill operator, wood preserver, pulp/paper worker, forester were not related to NHL.

Solvents have been associated with NHL in a number of studies [58-60], including studies of rubber workers [61], aircraft maintenance workers [62], and dry cleaners [63]. In particular, benzene exposure may increase the risk of NHL and this may be due to its effects on the immune system [60]. Other occupations which might involve exposure to solvents or related chemicals have been reported as being at increased risk of NHL include those of highway workers [64], petroleum refinery employees [65-67], styrene workers [68], chemists [69-70], and chemical manufacturers [71-72]. In our study, exposure to solvents, cleaning fluids, preservatives were not showing any association with NHL.

## **Strength and Limitations**

A major strength of this study is the large number of cases and controls from residents of six Canadian provinces. Questions were designed to obtain a complete occupational history and extensive list of potential occupational exposures. A reference pathologist validated 84% of the NHL tumors.

There are several limitations in this study. One of the limitations of this study is the potential for recall bias and potential misclassification of pesticide exposures. Also, occupational exposures in this study were self-reported and this might also bias results. Women were excluded from the study due to financial reasons. The response rates of 67.1% for cases and 48% for controls represent another potential limitation that could lead to misleading conclusions if the non-respondents differ significantly from the respondents with respect to the variables under investigation. We compared non-respondents to respondents using postal codes as an indicator of rural residence and did not find a rural bias among respondents. Another limitation is the possibility of false-positive findings given the large number of jobs and exposures assessed.

## **Conclusions**

Our results support previous findings of an association between NHL and specific job titles and occupational exposures. In our final model with the long-term job titles, NHL was associated with personal history of cancer, exposure to cutting oils, exposure to radium and the job titles or occupations such as farmer, driver and machinist and short term employment

as seed cleaner. Also, we have supportive evidence of increased risk of NHL with longer duration of exposure.

### **List of Abbreviation**

Non-Hodgkin's Lymphoma (NHL), International Classification of Diseases (ICD), Soft Tissue Sarcoma (STS), Hodgkin's Disease (HD), Multiple Myeloma (MM).

### **Competing interests**

The authors declare no competing financial interests.

### **Author's contributions**

CPK analyzed data and prepared the manuscript. HHM designed, coordinated the study and collect the data. JAM participated in study design, coordination, data collection and manuscript preparation. JJS participated in the design of the study and data collection. PP designed, coordinated the study, collected and prepared the manuscript.

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**Table 1:** Cross Canada Study of Pesticides and Health: NHL

Characterization of study Participants Stratified by Case/ Control Status: Demographics and

	NHL (N=513)	Controls (N=1506)	OR <sup>b</sup> <sub>adj</sub> (95% CI)
<b>Demographics</b>			
Mean age ± SD (years)	57.7 ± 14.0	54.1 ± 16.0	
<b>Education Level<sup>a</sup></b>			
University and Vocational	28 (6.6)	96 (5.5)	1.23 (0.81, 1.88)
University	94 (18.5)	310 (20.8)	1.08 (0.68, 1.70)
Vocational	111 (21.9)	358 (24.1)	1.06 (0.67, 1.70)
Elementary/ High school	274 (54.0)	723 (48.6)	
<b>Ever lived/ worked on a farm</b>			
Yes n (%)	235 (45.8)	673 (44.7)	1.02 (0.82, 1.27)
No n (%)	278 (54.2)	833 (55.3)	
<b>Medical History</b>			
<b>Previous diagnosis of Cancer</b>			
Yes n (%)	74 (14.4)	87 (5.8)	<b>2.56 (1.81, 3.62)<sup>c</sup></b>
No n (%)	439 (85.6)	1419 (94.2)	
<b>selected Medical History</b>			

<sup>a</sup> 25 missing<sup>b</sup> Adjusted for age (5 year groups) and province<sup>c</sup> Statistically significant results are bold.

**Table 2:** Job Titles Reported Most Frequently as Being Held Longest Job during a Lifetime Stratified by NHL-control Status

Job Title <sup>#</sup>	NHL ( <i>N</i> =513)	Controls ( <i>N</i> =1506)
	n (%)	n (%)
Farmer	55 (11)	130 (9)
Manager	35 (7)	112 (7)
Salesman	29 (6)	63 (4)
Driver	30 (6)	58 (4)
School teacher	22 (4)	58 (4)
Accountant	22 (4)	52 (4)
Engineer	7 (1)	46 (3)
Mechanic	17 (3)	44 (3)
Clerk	7 (1)	39 (2)
Administrator	6 (1)	30 (2)
Labourer	12 (2)	30 (2)
Office Worker	10 (2)	29 (2)
Technician	11 (2)	27 (2)
Machinist	15 (3)	25 (2)
Armed Forces	6 (1)	25 (2)
Carpenter	12 (2)	22 (1)
Farm Labourer	3 (<1)	13 (<1)

n = Number of times reported the longest held jobs

<sup>#</sup> Statistics Canada. Standard occupational classification. Ottawa: Minister of Supply and Services, 1980.

**Table 3: Non-Hodgkin's Lymphoma and Longest Held Job Titles<sup>#</sup>**

	NHL ( <i>N</i> =513)	Control ( <i>N</i> =1506)	OR <sub>adj</sub> (95% CI)
	n (%)	n (%)	
<b>Longest Held Job Titles</b>			
Farmer	55 (10.7)	130 (8.6)	<b>1.45 (1.01,2.10)<sup>c</sup></b>
Driver	30 (5.8)	58 (3.8)	1.52 (0.95, 2.42)
Machinist	15 (2.9)	25 (1.7)	<b>2.07 (1.05,4.09)<sup>c</sup></b>
Manager	35 (6.8)	112 (7.4)	0.89 (0.59,1.35)
<b>Duration of exposure as the longest held job</b>			
No exposure	16 (3.1)	82 (5.4)	1.00
< 10 years	56 (10.9)	260 (17.3)	1.59 (0.81, 3.12)
10-20 years	110 (21.4)	356 (23.6)	1.51 (0.82, 2.81)
20-30 years	138 (26.9)	375 (25.0)	1.58 (0.87, 2.89)
> 30 years	193 (37.6)	433 (28.7)	<b>1.90 (1.05, 3.45)<sup>c</sup></b>
<b>Mean years worked in longest held job</b>			
	$\bar{X} \pm SE$	$\bar{X} \pm SE$	P value
			(H <sub>0</sub> : $\mu_1=\mu_2$ verse H <sub>1</sub> : $\mu_1\neq\mu_2$ )
Farmer	36.0 ± 2.5	32.3 ± 1.6	0.195
Driver	24.0 ± 2.1	22.5 ± 1.7	0.590
Machinist	22.4 ± 2.8	17.1 ± 2.5	0.188
Manager	21.8 ± 1.9	20.6 ± 1.0	0.580

<sup>c</sup> Statistically significant results are bold.

<sup>#</sup> Statistics Canada. Standard occupational classification. Ottawa: Minister of Supply and Services, 1980.

**Table 4:** Non-Hodgkin’s Lymphoma, Job Titles and Occupational Exposures.

	NHL ( <i>N</i> =513)		Control ( <i>N</i> =1506)		OR <sub>adj</sub> (95% CI) <sup>a</sup>
	n <sup>b</sup>	%	n <sup>b</sup>	%	
Diesel exhaust fumes	183	35.7	464	30.8	<b>1.33 (1.06,1.67)<sup>c</sup></b>
Chicken farmer	59	11.5	122	8.1	<b>1.51 (1.06, 2.13)<sup>c</sup></b>
Seed cleaner	16	3.1	22	1.5	<b>2.20 (1.11,4.35)<sup>c</sup></b>
Radium	12	2.34	12	0.80	<b>3.26 (1.38, 7.73)<sup>c</sup></b>

<sup>a</sup> all odds ratios were adjusted for age and province of residence.

<sup>b</sup> n and % are given for the “yes” responses.

<sup>c</sup> Statistically significant results are bold.

**Table 5:** Most parsimonious model: Conditional Logistic Regression analyses that contained the longest held jobs and important covariates

Variable	OR <sub>adj</sub> (95% CI) <sup>a</sup>
Personal history of another cancer (yes)	<b>2.66 (1.87, 3.78)<sup>c</sup></b>
Ever exposed to radium (yes)	<b>3.48 (1.44, 8.40)<sup>c</sup></b>
Farmer	<b>1.47 (1.00, 2.16)<sup>c</sup></b>
Driver	<b>1.64 (1.01, 2.65)<sup>c</sup></b>
Machinist	<b>2.33 (1.15, 4.72)<sup>c</sup></b>
Ever exposed to Cutting oils (Yes)	<b>0.74 (0.55, 1.00)<sup>c</sup></b>
Seed cleaner (< 1 year)	<b>2.05 (1.01, 4.13)<sup>c</sup></b>
Duration of exposure as the longest held job (reference to no exposure)	
< 10 years	1.39 (0.71, 2.75)
10-20 years	1.35 (0.73, 2.53)
20-30 years	1.48 (0.81, 2.71)
> 30 years	1.68 (0.92, 3.06) <sup>#</sup>

<sup>a</sup> all odds ratios were adjusted for age and province of residence.

<sup>c</sup> Statistically significant results are bold.

<sup>#</sup> Borderline significant at 5% level.