

Author's response to reviews

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

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Version: 2 **Date:** 16 June 2008

Author's response to reviews: see over

Date: June 16, 2008

Editor-in-Chief,
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**Re: Revised Manuscript submission – Manuscript # MS: 1905360018189435
Occupational Exposures and Non-Hodgkin’s Lymphoma: Canadian Case-Control
Study**

Dear the Environmental Health Editorial Team,

Thank you for considering the manuscript “Occupational Exposures and Non-Hodgkin’s Lymphoma: Canadian Case-Control Study” for publication in your journal. We have considered and addressed the reviewers’ concerns. Please find enclosed:

- A response to the reviewers
- Revised version of the manuscript

Sincerely,

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Reviewer's report I

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

Version: 1 **Date:** 7 April 2008

Reviewer: Richard W. Clapp

Reviewer's report:

Major Compulsory Revision -

Reviewer's Comment:

The authors explain their finding of increased risk in machinists (OR=2.07) on p. 8 by saying "machinists may be exposed to solvents or engine exhaust" yet their study shows no increased risk from solvents and a lesser increase in risk from diesel exhaust (OR=1.33). From their data, the increase in machinists seems not to be driven by either of the risk factors they highlight in the manuscript.

Author's response:

The risk from diesel exhaust (OR=1.33) is based on the question "Have you ever been exposed at work to any of the following?" (see below).

-----Asbestos ----- Wood smoke
-----Used motor oil ----- Gasoline
-----Diesel exhaust fumes ----- Lubricants
----- Cutting Oils ----- Solvents
----- Cleaning Fluids -----Ether
-----Pelt, Fur or Hide preservatives ----- Mouldy grain or forage
----- Chlorine ----- Hair dyes
----- Hair permanent solution ----- Cyanide
----- Sour gas

Duration of exposure was not available for this question, however based on the long held job (Occupations defined as long held occupation if they had worked for 10 years or more in that occupation), machinists had increased risk (OR=2.07 in the original manuscript and OR=2.21 in revised version). It could be due to many years of working as a machinist (average number of years for cases=22.4 vs. 17.1 years for controls). It appears that the increased risk in machinist is driven by exposure to diesel because of the following reasons:

For subgroup of subjects who had long held job as a machinist, we conducted the bivariate analysis based on the cross-tabulation for (i) ever exposed to diesel and case/control status and (ii) ever exposed to solvents and case/controls status. These results showed that 2.99% cases (cases who had long held job machinist) were exposed to solvents compared to 2.91% controls (controls who had long held job machinist) who were exposed to solvents. In comparison to this, 3.83% cases (cases who had long held job machinist) were exposed to diesel compared to 1.94% controls (controls who had long held job machinist). These results indicate that the risk is driven by exposure to diesel.

Minor Essential Revisions –

Reviewer's Comment:

There are numerous grammatical errors and mis-spellings in the text and references. for example, on p. 6, line 4 the word "principle" should be principal; on p. 6, line 6 of the Results section, the word "difference" should be differences; on p. 7, line 12 the word "include" should be includes; p. 9, line 1 the words "a seed" should just be seed, etc. There are many more such minor changes needed in the final version.

Author's response:

The word "principle" changes to "principal", on p. 6, line 8 in the revised version. The word "'difference" changes to "differences" on p. 6, line 5 of the Results section in the revised version.

The word "include"" on p. 7, line 12. This sentence is changed in the revised version.

The word "a seed" p. 9, line 1. This line is removed from the paragraph.

We carefully proofread the revised version.

Reviewer's Comment:

On p. 9, the authors say "The mechanism of cancer induction by radiation shown in our study. . ." when no mechanism was shown at all - it may be more appropriate to say "suggested in our study. . ."

Author's response:

We agreed with the reviewers and have incorporated the suggested changes. Please see revised version page 9, para. 2, and line 1.

Reviewer's Comment:

In references 11 and 71, the word "nad" should be and; in reference 22, Adele Costantini's name is mis-spelled; in reference 33, Singleton is mis-spelled; in reference 54, "ration" should be radiation; in reference 64, Neil Maizlish's name is mis-spelled, etc.

Author's response:

We have made the following changes:

In reference 12 (original version reference 11) and 76 (original version 71): changes the word "nad" to "and".

In reference 23 (original version reference 22): "Constantini" to "Costantini".

In reference 34 (original version reference 33): "Sinleton" to "Singleton".

In reference 53 (original version reference 54): "ration" to "radiation".

In reference 34 (original version reference 64): "Malzlish" to "Maizlish".

Reviewer's Comment:

The section called "Strength and Limitations," beginning on p. 11 is poorly written and should be incorporated into the Discussion. The statement that "Women were excluded from the study due to financial reasons" is misleading. A better way of stating it might be "Due to budget constraints, the study was restricted to males."

Author's response:

We deleted the section heading "strengths and limitations" and made this paragraph a part of discussion and incorporated the suggested changes (page 10, para. 3 and 4).

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests.

Reviewer's report 2

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

Version: 1 **Date:** 11 April 2008

Reviewer: Pierluigi Cocco

Reviewer's report:

Several large multinational collaborative studies on lymphoma aetiology are currently under way, that only can achieve the statistical power necessary to test hypotheses related to rare disease entities or specific occupational and environmental exposures. However, it is this reviewer's opinion that local studies do maintain an important role, as long as they 1. suggest new hypotheses, and/or 2. are able to explore in detail associations that have been established, but not well defined for lack of detailed information in multicenter or pooled studies. Unfortunately, this paper, in its current version, does not comply with either requirement. The authors should make some additional effort to get the best from their potentially rich material. It is this reviewer's hope that the following suggestions and comments might help.

Major compulsory revisions

1. In their analysis, the authors consider two types of job entries in the individual work histories of study subjects: a. "longest" held jobs (those lasting one year or more), and b. short term employments, such as summer jobs and similar. Using the superlative adjective "longest" generates a linguistic misunderstanding that leads the reader to interpret it in relation to any other job entry in the work history of the same study subject. Such strategy might appear a non sense to the unaware reader, asking himself what convenience is out there in spending so much time and resources to conduct a questionnaire study to get complete work histories, when the longest held job during a lifetime may be more easily available from death certificates or other publicly available resources. Wording itself causes such a confusion. On the other hand, the authors should clearly explain in the methods section their rationale for analyzing short term employments as well. For instance, are these repeatedly held by the same subject over the years? If so, this reviewer sees a creative new feature in this study and encourages the authors to explain in the methods what were the minimum number of job entries to consider a short term employment for analysis. Alternatively, simply fix a minimum duration for considering a job entry (6 months – 1 year consistently with most literature) and cumulate years for the same job if repeated in the work history. Showing results for a summer job as chicken farmer that might have been held for three months as a student does not appear to convey much of a meaning. Once the criteria for selecting occupations are made clear (minimum duration, and minimum number of subjects), use an unique table to show number of cases and controls, and odds ratios for all the occupations. Negative and not significant results might be interesting for other scholars as comparison terms with the rest of the literature.

Author's response:

We redefined the “longest held job” to long held occupations (10 years or more). New variables were defined for ever held occupations (at least one year or more). See Table 2. We agreed with reviewer and decided not to include the short term employment in this paper since we do not have the duration of employment. The question for short-term occupations was “Have you ever worked at any of the following occupations less than one year at a time on a summer, casual or temporary basis?”. Here we do not know how long they have worked in a particular occupation or same job repeatedly over the years.

The occupations were selected for the analysis if they have worked in a particular occupation at least for one year and if at least 2% of cases for that occupational category. This information and definitions of “ever held” and “long held” occupations have been included in the methods section (please see page 5, para 2, lines 4-9).

2. Apparently, the authors used a very generic coding for occupations and did not code industries at all. Apart from the need of mentioning in the Methods what coding system, if any, was used to group the occupational titles, this is unfortunate, as the gain in statistical power is accompanied by a great loss in biological meaning of their findings. In this reviewer's view, it is preferable presenting results for a small number of well defined occupations rather than for a series of generic and bureaucratic definitions. For instance, starting from the hopefully commonly shared belief that our epidemiological work is meant for preventive purposes, how do the authors think the term “manager” can be interpreted? Bureaucratic definitions such as manager, labourer, or retired, might be helpful for socio-economic analyses, but, if alone, have not any occupational health significance. Under such perspective, even the definition of farmer and even pesticide, are too generic, but at least they can restrict the range for future studies investigating in more detail on risk factors within such broad categories. Broad definitions and variations in farming activities and type of pesticides should be discussed as sources of inconsistency across findings in different studies, which the authors address only on line 10-11 of the background section. Heterogeneity of work circumstances and exposures within such generic definitions implies that only conditions with high prevalence among subjects fitting them might account for the excess, and these are more likely to be socio-economic than occupational in nature. Alternatively, a number of different exposures/conditions might sum up their effects, which suggests the direction for future studies. To summarize: a. be more specific in defining occupations (4 digit codes are suitable); b. predefine in the methods the duration and number of study subjects criteria for considering an occupation worth of analysis; c. present odds ratios along with number of cases and controls for all occupations in one table divided in two sections: ever held (above the pre-defined minimum duration) and long held occupations (e.g. 10 years or more); and d. when and if applicable, use duration as a surrogate for cumulative exposure to calculate

trends, which are helpful in the inferential process.

Author's response:

- (a) Subjects (cases and controls) were asked to provide job title, types of business, industries or services, total number of years worked for each job that they held for at least one year or longer. Job titles coding was provided by Statistics Canada and long held jobs were analyzed in this manuscript. We have added job codes in Table 2 and also have added the reference (please see page 24 and page 18).

In this manuscript, the long held occupations were considered for analysis purposes and our focus was an exploratory analysis. However, in future work we plan to conduct intensive analysis of these data by using job exposure matrix approach, which is a cross-classification of job title, industry, and years of employment in a particular industry.

- (b) We predefine in the methods section the minimum duration and number of study subjects criteria for considering an occupation worth of analysis.
- (c) In Table 2 (new table in revised version, page 24) we presented the odds ratios along with number of cases and controls for all selected occupations in one table divided into two sections: [ever held (at least one year) and long held occupations (10 years or more)].
- (d) In Table 3 (new table in revised version, page 25) we presented the duration of exposure as a farmer and machinist and risk of NHL.

Minor essential revisions.

Reviewer's Comment:

1. First paragraph of introduction. A plateau in the incidence rates has been recently shown in the U.S. and some European countries. Is anything like that going on in Canada as well?

Author's response:

In Canada, for both males and females, incidence rates increased by about 50% between 1978 and late 1990s. Since that time the incidence rates have stabilized. Mortality rates have followed a similar pattern. We have included this information in the revised version of manuscript (Background section, page 3, para. 1, line 3).

“Canadian Cancer Society/National Cancer Institute of Canada: **Canadian Cancer Statistics 2007**, Toronto, Canada, 2007”.

Reviewer's Comment:

2. Defining “soil/field” as an exposure is awkward. Inorganic dust should be the proper term. Anyway, on page 10 (discussion) the authors do not mention dust

as the reported exposure in reference # 17, but the fact that “ Forest and the soil conservationists are often occupationally exposed from mixing and /or applying pesticides as a part of their regular duties [17]”. Organic dust including grain, wood and textile dust should be cited among the occupational exposures suspected of a role in lymphoma aetiology.

Author’s response:

Necessary changes and citations have been incorporated.

Reviewer’s Comment:

3. The classification criteria for diagnosis of non Hodgkin’s lymphoma need to be clarified in the Methods section. It seems clear that HL and MM cases were not included, but due to the frequent changes in Lymphoma classification, it would be suitable to be explicit about it to avoid confusion in the reader.

Author’s response:

More detail explanation of Lymphoma classification has been included in the methods section (please see page 4, para. 1, lines 7-10).

Reviewer’s Comment:

4. The response rates for cases and controls should be reported in the methods section. The low participation rate among controls was presumably expected, considering also that a postal questionnaire was administered, and the authors properly addressed it in the discussion. However, the participation rate seems low also among cases. Reasons for not participating (death, change of address, refusal, et cetera) should be highlighted in the discussion for either study groups..

Author’s response:

Data from postal questionnaires based on responses from 513 NHL cases (67.0% of those contacted) and 1506 control subjects (48.0% of those contacted) were analyzed. The most common reasons for not participating were death, change of address and refusal for both study groups. We have incorporated this information in the discussion (please see page 11, para. 1, lines 2-4).

Reviewer’s Comment:

5. What were the “Statistically significant ($p \leq 0.05$) variables and important explanatory variables [that] were considered for the final multivariate model”?

Author’s response:

We consider the long held occupations: farmer and machinist in this manuscript and our focus was an exploratory analysis. Table 5 shows the final multivariate model. For models for farmers and machinist the most important explanatory variables were personal history of another cancer, ever exposed to radium, ever exposed to diesel and duration of employment. Please see page 27 in revised version.

Reviewer's Comment:

6. *This reviewer was quite surprised in seeing that 12 cases and 12 controls reported exposure to radium. Can the authors explain in what occupation and industries, when and how long before lymphoma diagnosis?*

Author's response:

The following question was used to indentify the exposure to radium.

“ Have you ever been exposed at work to any of the following forms of radiation?

Ultra violet light

Radium

Uranium

X-rays

etc.

There were no questions about occupations and industries related to exposure to radium (Question # 12). There were 2.34% cases exposed to radium compared to 0.80% controls. The following table describes occupations and number of years in that occupation (in parenthesis) for 12 cases and 12 controls (obtained from question # 8: Please list all full-time jobs at which you have worked for at least one year, starting with your present or most recent job).

Observation	Cases : Occupation/industry (Number of years)	Controls: Occupation/industry (Number of years)
1	Administrator/hospital cardiology, radiology (24), Manager (5), Technician/hospital radiology (10)	Fireman (26)
2	Weigher-chem/ship yard (4), labourer (21)	Administrator/Telecommunication (6), computer programmer/nuclear research (1)
3	Painter (3), Miner (5), bricklayer (2)	Steel worker (46)
4	Factory worker/electric motors (47)	Surveyor (3), armed forces (30)
5	Accountant (1), Administrator (16)	Technician (22)
6	Machinist (28)	Engineer (12)
7	School Teacher (24)	Cook chef (16), oil industry (2), factory worker (2)
8	Dentist (41)	Factory worker (2), armed forces (34)
9	Mechanic/Transport (14), Mechanic/Mines (18), Farmer (15)	Nurse (40)
10	Technician (42)	Military (39)
11	Builder/construction (15), Area supervisor/ construction (5), contractor/construction (5),	Doctor (40)
12	Rail road/ Transportation (39)	Technician (1), Labourer (1), Driver (2), foreman (4)

Reviewer's Comment:

7. Discussion: avoid discussing together ionizing and non ionizing radiation. Update the references on UV light and lymphoma.

Author's response:

Ionizing and non ionizing radiation was separated into two separate paragraphs in the discussion. The references on UV light and lymphoma were updated. The references 56-58, and 60-63 were added to the text and reference list.

Reviewer's Comment:

8. Reorganization of the discussion, some rephrasing and some review of the typing is necessary. See for instance line 15 on page 10 "benzene exposure may increases the risk of NHL"; and lines 17-18 on page 7: "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".

Author's response:

Agreed with reviewer and discussion was reorganized (Please see pages: 8-11).

Line 15 on page 10 "benzene exposure may increases the risk of NHL". This sentence is rephrased (see page 10, para 2. line 3) in the revised version.

Lines 17-18 on page 7: "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". This sentence is rephrased (see page 7, para 3. line 21) in the revised version.

Minor discretionary revisions.

Reviewer's Comment:

9. Results. Please explain what a seed cleaner is and what exposures might be involved.

Author's response:

All short-term jobs were excluded from the analysis according to first comment. Therefore explanation was irrelevant.

Reviewer's Comment:

10. Odds ratio for ever exposure to cutting oils was significantly lower than unity. Unless authors have any reason to suspect a protective effect, it seems a chance finding, irrelevant, and pointless. The conclusion reports: "NHL was associated with personal history of cancer, exposure to cutting oils,..." However, Table 5

shows a negative risk; and on page 7 (Odds ratio of those who were ever exposed to cutting oils was significantly lower than those who were not exposed”) and page 8 (“Exposure to cutting oils at work independently was associated with decreased risk of developing NHL, the rationale for which is unclear”) a negative result is repeatedly reported.

Author’s response:

Agreed with the reviewer and it seems significance ever exposure to cutting oil a chance finding. We could not find any literature to support this. Therefore we removed ever exposure to cutting oil from the analysis.

Reviewer's Comment:

11. Second paragraph on page 10. Woodworkers are not mentioned in the results nor in the tables. Either cite the finding in the results as a negative one or drop the paragraph from the discussion.

Author’s response:

Removed this paragraph from the discussion and cite findings in the results section (see page 7, para. 2, line 3).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.