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Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces

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Pesticide exposures and immune suppression have been independently associated with the risk of non-Hodgkin lymphoma (NHL), but their joint effect has not been well explored. Data from a case–control study of men from six Canadian provinces were used to evaluate the potential effect modification of asthma, allergies, or asthma and allergies and hay fever combined on NHL risk from use of: (*i*) any pesticide; (*ii*) any organochlorine insecticide; (*iii*) any organophosphate insecticide; (*iv*) any phenoxy herbicide; (*v*) selected individual pesticides [1,1'-(2,2,2-trichloroethylidene)bis[4-chlorobenzene]; 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane (DDT), malathion, (4-chloro-2-methylphenoxy)acetic acid (MCPA), mecoprop, and (2,4-dichlorophenoxy)acetic acid (2,4-D); and (*vi*) from the number of potentially carcinogenic pesticides. Incident NHL cases (n = 513) diagnosed between 1991 and 1994 were recruited from provincial cancer registries and hospitalization records and compared to 1,506 controls. A stratified analysis was conducted to calculate odds ratios (ORs) adjusted for age, province, proxy respondent, and diesel oil exposure. Subjects with asthma, allergies, or hay fever had non-significantly elevated risks of NHL associated with use of MCPA (OR = 2.67, 95% confidence interval [CI]: 0.90–7.93) compared to subjects without any of these conditions (OR = 0.81, 95% CI: 0.39–1.70). Conversely, those with asthma, allergies, or hay fever who reported use of malathion had lower risks of NHL (OR = 1.25, 95% CI: 0.69–2.26) versus subjects with none of these conditions (OR = 2.44, 95% CI: 1.65–3.61). Similar effects were observed for asthma and allergies evaluated individually. Although there were some leads regarding effect modification by these immunologic conditions on the association between pesticide use and NHL, small numbers, measurement error and possible recall bias limit interpretation of these results.

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Key words: non-Hodgkin lymphoma, pesticides, immunologic conditions, case–control study

Abbreviations: CCSPH: Cross-Canada Study of Pesticides and Health; DDT: 1,1′-(2,2,2-trichloroethylidene)bis[4-chlorobenzene]; 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane; 2,4-D: (2,4-dichlorophenoxy)acetic acid; IARC: International Agency for Research on Cancer; MCPA: (4-chloro-2-methylphenoxy)acetic acid; NHL: non-Hodgkin lymphoma; US EPA IRIS: United States Environmental Protection Agency Integrated Risk Information System; US EPA OPP: United States Environmental Protection Agency Office of Pesticide Programs

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The incidence of non-Hodgkin lymphoma (NHL) showed a steady worldwide increase from 1950, but plateaued in the late 1990s.[1] In 2011, NHL was the fifth most frequently occurring cancer and the sixth leading cause of all cancer deaths in Canada.[2] The causes of NHL are not well-known.[1,3]

Immune suppression is the most clearly established risk factor for NHL [3–6] because of substantially elevated risks among individuals with autoimmune disease, primary or acquired immunodeficiencies, and organ transplant recipients.[1,3] Risk appears to increase with the degree of immune deficiency.[7] Factors that suppress the immune system, like chemical exposures, may facilitate the development of NHL.[3]

A number of occupational and environmental factors have been associated with NHL.[5,8] Farming has been linked to NHL[9] overall and for major NHL subtypes.[1] This observation has prompted research on agricultural chemicals, such as pesticides, solvents, fuels, oils, and other agents that are potentially carcinogenic.[10–12] Use of some specific pesticides may contribute to the increased incidence of NHL.[13–15] For example, occupational exposure to non-arsenical insecticides during spraying and application has been classified by the

International Agency for Research on Cancer (IARC) as a "probable human carcinogen" (group 2A) for NHL.[16]

Studies of the effect of immune conditions on pesticide exposure and NHL risk have generated inconsistent results.[17–19] Two population-based case–control investigations in the United States found that the relative risk of NHL from pesticide exposure was elevated among asthmatics compared to non-asthmatics.[17–18] Conversely, an Australian population-based case–control study found no effect of asthma and other immunologic conditions on the relationship between pesticide exposure and NHL risk.[19] The objective of this study was to further investigate the potential effect modification by immune conditions on the risk of NHL from self-reported pesticide use.

Material and Methods

Study population

Participants were from the Cross-Canada Study of Pesticides and Health (CCSPH), a population-based, case–control study of Canadian men aged 19 years and older in six provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia), that evaluated cancer risks from pesticide exposures and other factors.[14] The CCSPH included 2,019 subjects. There were 513 incident NHL cases diagnosed between September 1, 1991 and December 31, 1994 from cancer registries in all provinces except in Quebec, where cases were ascertained from hospitalization records. NHL diagnoses were pathologically confirmed. Population controls (n = 1506) were randomly selected from provincial health insurance records (Quebec, Manitoba, Saskatchewan, and Alberta), computerized telephone listings (Ontario), and voters' lists (British Columbia). Controls were frequency matched to cases by age ($\pm$2 years) and province of residence. There are four fewer cases of NHL in our analyses than in previous manuscripts [14] because of a subsequent pathology review.

Data collection

CCSPH data were obtained in a two-stage process. First, all subjects were mailed an informed consent form and asked to complete a postal questionnaire which included questions about demographic factors, medical history, lifetime occupational history and pesticide use, and other exposures. Second, subjects who reported 10 hours or more per year of exposure to pesticides (from any combination of compounds) and a 15% random sample of the remainder of the study participants were interviewed by telephone to elicit further details about use of individual pesticides, which included occupational or non-occupational use (home, garden, and hobby), duration of use, and method of application.[14] Both occupational and non-occupational pesticide uses were included in this study. We analyzed data from postal questionnaires based on responses from 513 NHL cases (67.1% of those contacted) and 1,506 controls (48.0% of those contacted). Non-respondents included people who did not personally receive the postal questionnaire due to inaccurate or out of date mailing information, and therefore, the true response rate was likely higher than the proportions observed. We were unable to evaluate the true response rate because in the original study, information was not collected on how many subjects personally received the postal questionnaire.

Categorization of immunologic conditions and pesticide use

Cases and controls reported whether they had ever been diagnosed with various immunologic conditions. To analyze the potential effect modification of immune conditions on NHL risk, we categorized these conditions into three groups: (*i*) asthma, allergies, or hay fever; (*ii*) asthma alone; and (*iii*) allergies alone. We also evaluated the effects of a group comprised of other immune conditions (hay fever, celiac disease, rheumatoid arthritis, or acne) in an exploratory fashion. These conditions were selected for analysis because they had been hypothesized to increase NHL risk,[7] were available in the CCSPH, and were relevant to earlier studies that explored the potential effect modification of asthma,[17–19] hay fever, eczema, and food allergy [19] on pesticide exposure and NHL risk. NHL risks were estimated from these groups of immunologic conditions and self-reported ever/never use of: (*i*) any pesticide; (*ii*) any organochlorine insecticide; (*iii*) any organophosphate insecticide; (*iv*) any phenoxy herbicide; (*v*) selected individual pesticides [1,1′-(2,2,2-trichloroethylidene)-bis[4-chlorobenzene]; 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane (DDT), malathion, (4-chloro-2-methylphenoxy)acetic acid (MCPA), mecoprop, and (2,4-dichlorophenoxy)acetic acid (2,4-D)]; and (*vi*) from the number of potentially carcinogenic pesticides reportedly used (see Appendix A for a complete list of pesticides in these six groups). A pesticide was considered "potentially carcinogenic" if it was classified as possibly carcinogenic to humans (group 2B) or higher by IARC,[20] a possible human carcinogen (group C) or higher by the United States Environmental Protection Agency Integrated Risk Information System (US EPA IRIS),[21] or at least suggestive evidence of carcinogenic potential by the United State Environmental Protection Agency Office of Pesticides Program (US EPA OPP).[22–23] Pesticide use groups 1, 2, 3, and 4 above were based on a study that demonstrated associations between these pesticides, asthma, and NHL [17] and groups 5 and 6 were developed according to previous CCSPH analyses that showed that NHL was associated with self-reported use of these pesticides.[14,23]

Statistical analysis

Multiple logistic regression was used to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) between the six pesticide use groups defined earlier and the risk of NHL using SAS software (SAS Institute, Cary, NC, Version 9.1). ORs were adjusted for age, province of residence, respondent type (self or proxy), and diesel oil exposure, which were found to be relevant confounders in the

Table 1. Characteristics of non-Hodgkin lymphoma cases and controls in the Cross-Canada Study of Pesticides and Health

	Cases	Controls	OR	95% CI
n	513	1,506		
Mean age ± SD (years)[1]	58 ± 14	54 ± 16		
Province of residence[2]				
Quebec	117 (23%)	291 (19%)		
Ontario	142 (28%)	585 (39%)		
Manitoba	34 (6.6%)	113 (7.5%)		
Saskatchewan	29 (5.7%)	91 (6.0%)		
Alberta	65 (13%)	196 (13%)		
British Columbia	126 (25%)	230 (15%)		
Respondent type				
Self-respondent	403 (79%)	1,286 (85%)	0.63	0.49–0.81
Proxy respondent	110 (21%)	220 (15%)		
Diesel oil exposure				
Yes	183 (36%)	464 (31%)	1.25	1.01–1.54
No	330 (64%)	1,042 (69%)		

[1]$t = -4.47$, $p < 0.0001$. [2]$X^2 = 34.81$ ($p < 0.0001$). All values in ( ) are percentage of *n* rounded up to two significant digits

Table 2. Risks of non-Hodgkin lymphoma by self-reported pesticide use

Self-reported pesticide use[1]	Cases ($n = 513$)	Controls ($n = 1,506$)	OR[2]	95% CI
Any pesticide	149 (29%)	380 (25%)	1.36	1.07–1.73
Organochlorine insecticides	106 (21%)	276 (18%)	1.29	0.99–1.67
DDT	33 (6.4%)	59 (3.9%)	1.69	1.07–2.67
Organophosphate insecticides	92 (18%)	169 (11%)	1.91	1.43–2.55
Malathion	72 (14%)	127 (8.4%)	1.96	1.42–2.70
Phenoxy herbicides	129 (25%)	318 (21%)	1.45	1.13–1.87
MCPA	17 (3.3%)	46 (3.1%)	1.12	0.62–2.03
Mecoprop	51 (9.9%)	81 (5.4%)	2.26	1.54–3.31
2,4-D	110 (21%)	293 (19%)	1.27	0.98–1.65
Number of potentially carcinogenic pesticides[3]			1.09	1.02–1.16

[1]Self-reported pesticide use as "yes" for each pesticide group or individual pesticide (Appendix A). [2]ORs adjusted for age, province of residence, respondent type, and diesel oil exposure. [3]Based on IARC, US EPA IRIS, and US EPA OPP classifications (17–20); is an ordinal variable. All values in ( ) are percentage of *n* rounded up to two significant digits.

literature.[14,17–19,24] A stratified analysis based on the *a priori* immunologic categories was conducted to estimate adjusted ORs for the association between pesticide use and risk of NHL. Afterwards, a formal test for statistical interaction for all combinations of immune condition and pesticide use categories was conducted by including an interaction term in the model using all data and calculating the Wald Chi-square test for interaction. *p*-Values less than or equal to 0.05 were considered to be statistically significant.

Ethics approval

Approval to conduct the present analysis was obtained in March 2010 from the Health Sciences Research Ethics Board at University of Toronto.

Results

Population characteristics

Table 1 summarizes the characteristics of cases and controls for age, province of residence, respondent type, and diesel oil exposure. The mean age of cases (58 ± 14 years) was slightly higher than controls (54 ± 16 years) because the analysis used all of the controls that were age-matched for all of the cancers in the CCSPH (NHL, Hodgkin lymphoma, soft tissue sarcoma, and multiple myeloma). Overall, 28% of cases were from Ontario, followed by British Columbia (25%), Quebec (23%), Alberta (13%), Manitoba (6.6%), and Saskatchewan (5.7%). Whereas the majority of cases (79%) and controls (85%) completed the postal questionnaire themselves, cases had a higher use of proxy respondents than controls (OR for self-respondents by case or control status was 0.63, 95% CI: 0.49–0.81). Additionally, subjects who were exposed to diesel oil had an increased risk of NHL compared to those who reported that they were not exposed (OR = 1.25, 95% CI: 1.01–1.54). The characteristics of NHL cases and controls stratified by immune condition diagnoses (Appendix B) were similar to that of all cases and controls (Table 1).

NHL risks

Non-stratified analysis. Table 2 summarizes the risks of NHL associated with various self-reported pesticide uses for all cases and controls (non-stratified analyses). These results are consistent with a previous CCSPH report [14] and slight differences in estimates are explained by the inclusion of different confounding variables in the models and that the dataset contained four fewer cases than the investigation completed by McDuffie et al.[14] For each additional potentially carcinogenic pesticide used, the risk of NHL increased by 1.09 (95% CI: 1.02–1.16).

Asthma, allergies, and hay fever. Table 3 shows ORs stratified by the presence or absence of asthma, allergies, or hay fever. The risk of NHL was higher among those without asthma, allergies, or hay fever than those with any of these immune conditions for use of malathion (OR = 2.44, 95% CI: 1.65–3.61 *vs.* OR = 1.25, 95% CI: 0.69–2.26), and for use of mecoprop (OR = 2.47, 95% CI: 1.55–3.94 *vs.* OR = 1.71; 95% CI: 0.86–3.40). In contrast, the odds of NHL associated with the use of MCPA was elevated for individuals with

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Table 3. Risks of non-Hodgkin lymphoma by self-reported pesticide use and asthma, allergies, or hay fever diagnosis

	Asthma, allergies, or hay fever				No asthma, allergies, or hay fever				
Self-reported pesticide use[1]	Cases ($n = 159$)	Controls ($n = 462$)	OR[3]	95% CI	Cases ($n = 354$)	Controls ($n = 1,044$)	OR[3]	95% CI	$p > X^2$
Any pesticide	52 (33%)	123 (27%)	1.46	0.97–2.22	97 (27%)	257 (25%)	1.32	0.99–1.77	0.61
Organochlorine insecticides	41 (26%)	93 (20%)	1.42	0.91–2.23	65 (18%)	183 (18%)	1.20	0.87–1.67	0.43
DDT	15 (9.4%)	16 (3.5%)	2.53	1.17–5.47	18 (5.1%)	43 (4.1%)	1.31	0.73–2.36	0.11
Organophosphate insecticides	24 (15%)	58 (13%)	1.33	0.78–2.29	68 (19%)	111 (11%)	2.26	1.60–3.20	0.11
Malathion	19 (12%)	47 (10%)	1.25	0.69–2.26	53 (15%)	80 (7.7%)	2.44	1.65–3.61	0.07
Phenoxy herbicides	44 (28%)	104 (23%)	1.49	0.95–2.33	85 (24%)	214 (20%)	1.44	1.06–1.97	0.85
MCPA	7 (4.4%)	9 (1.9%)	2.67	0.90–7.93	10 (2.8%)	37 (3.5%)	0.81	0.39–1.70	0.08
Mecoprop	16 (10%)	28 (6.1%)	1.71	0.86–3.40	35 (9.9%)	53 (5.1%)	2.47	1.55–3.94	0.47
2,4-D	39 (25%)	97 (21%)	1.36	0.86–2.16	71 (20%)	196 (19%)	1.23	0.89–1.70	0.67
Number of potentially carcinogenic pesticides[4]			1.16	1.04–1.29			1.06	0.97–1.14	0.15

[1]Self-reported pesticide use as "yes" for each pesticide group or individual pesticide (Appendix A). [2]Wald chi-square p value for pesticide use*asthma, allergies, or hay fever interaction term in multiple logistic regression model. [3]ORs adjusted for age, province of residence, respondent type, and diesel oil exposure. [4]Based on IARC, US EPA IRIS, and US EPA OPP classifications (17–20); is an ordinal variable. All values in ( ) are percentage of *n* rounded up to two significant digits.

asthma, allergies, or hay fever (OR = 2.67, 95% CI: 0.90–7.93) compared to those who were not diagnosed with any of these conditions (OR = 0.81, 95% CI: 0.39–1.70) and this was also observed for DDT (OR = 2.53, 95% CI: 1.17–5.47 *vs.* OR = 1.31, 95% CI: 0.73–2.36). For each increase in the number of potentially carcinogenic pesticides used, the risks of NHL increased in men with (OR = 1.16, 95% CI: 1.04–1.29) and without (OR = 1.06, 95% CI: 0.97–1.14) asthma, allergies, or hay fever. No interactions were statistically significant at $p = 0.05$, though the interactions of malathion and MCPA with asthma, allergies, or hay fever were nearly significant at $p = 0.07$ and $p = 0.08$, respectively.

Asthma. Table 4 presents adjusted ORs for NHL among subjects by asthma diagnosis and self-reported use of various pesticide groups and individual pesticides. Asthmatics had a higher risk of NHL for use of DDT (OR = 11.1, 95% CI: 1.59–78.1) compared to non-asthmatics (OR = 1.49, 95% CI: 0.92–2.40). An increase in risk was also observed for use of MCPA (OR = 6.57, 95% CI: 0.48–90.5 *vs.* OR = 0.99, 95% CI: 0.53–1.84). Similar patterns were observed for organochlorine insecticides and phenoxy herbicides including 2,4-D, but differences were smaller. Conversely, the odds of NHL for use of any organophosphate insecticide was higher for nonasthmatics (OR = 2.02, 95% CI: 1.50–2.72) compared to asthmatics (OR = 0.57, 95% CI: 0.11–2.96). This pattern was also seen for malathion, one of the organophosphate insecticides. Each additional potentially carcinogenic pesticide used was associated with an increased risk of NHL in asthmatics (OR = 1.31, 9% CI: 0.97–1.77) and nonasthmatics (OR = 1.08, 95% CI: 1.01–1.15). No interactions were statistically significant at $p = 0.05$.

Allergies. Based on the stratified analysis, the risks of NHL were greater among those without allergies for use of any organophosphate insecticide (OR = 2.25, 95% CI: 1.60–3.16 *vs.* OR = 1.27, 95% CI: 0.71–2.26), malathion (OR = 2.42, 95% CI: 1.65–3.56 *vs.* OR = 1.22, 95% CI: 0.65–2.29), and mecoprop (OR = 2.74, 95% CI: 1.75–4.28 *vs.* OR = 1.30, 95% CI: 0.59–2.88) (Table 5). However, subjects with allergies had higher risks of NHL for use of MCPA (OR = 2.83, 95% CI: 0.87–9.14 *vs.* OR = 0.84, 95% CI: 0.41–1.72) and DDT (OR = 2.70, 95% CI: 1.20–6.10 *vs.* OR = 1.38, 95% CI: 0.78–2.42). Odds of NHL were similar in both groups for use of any pesticide and any phenoxy herbicide. The risks of NHL from use of each additional potentially carcinogenic pesticide increased among those with allergies (OR = 1.15, 95% CI: 1.03–1.30) and without allergies (OR = 1.07, 95% CI: 0.99–1.15). Although interactions between all groups of pesticide used and allergies in multiple logistic regression models were not statistically significant at $p = 0.05$, the combination of malathion used and allergies diagnosis were borderline ($p = 0.06$).

Additional analyses. The exploratory analysis of diagnosis with hay fever, celiac disease, rheumatoid arthritis, or acne on the association between pesticide use and risk of NHL did not identify any differences in the magnitude of OR estimates and no interactions were statistically significant at $p = 0.05$.

Discussion

Although findings suggest that there may be differences in the risk of NHL from self-reported pesticide use by immunological status, the pattern of effect modification was complex and none were statistically significant. For organophosphate

Table 4. Risks of non-Hodgkin lymphoma by self-reported pesticide use and asthma diagnosis

	Asthma				No asthma				
Self-reported pesticide use[1]	Cases ($n = 32$)	Controls ($n = 107$)	OR[3]	95% CI	Cases ($n = 481$)	Controls ($n = 1,399$)	OR[3]	95% CI	$p > X^{22}$
Any pesticide	12 (38%)	24 (22%)	2.41	0.93–6.21	137 (28%)	356 (25%)	1.31	1.02–1.68	0.28
Organochlorine insecticides	10 (32%)	18 (17%)	2.80	0.98–7.95	96 (20%)	258 (18%)	1.23	0.93–1.62	0.25
DDT	4 (13%)	2 (1.9%)	11.1	1.59–78.1	29 (6.0%)	57 (4.1%)	1.49	0.92–2.40	0.10
Organophosphate insecticides	2 (6.3%)	12 (11%)	0.57	0.11–2.96	90 (19%)	157 (11%)	2.02	1.50–2.72	0.12
Malathion	2 (6.3%)	7 (6.5%)	1.07	0.18–6.38	70 (15%)	120 (8.6%)	2.01	1.44–2.80	0.37
Phenoxy herbicides	9 (28%)	21 (20%)	2.05	0.73–5.75	120 (25%)	297 (21%)	1.41	1.09–1.84	0.60
MCPA	2 (6.3%)	1 (0.9%)	6.57	0.48–90.5	15 (3.1%)	45 (3.2%)	0.99	0.53–1.84	0.14
Mecoprop	3 (9.4%)	7 (6.5%)	1.42	0.29–6.99	48 (10%)	74 (5.3%)	2.27	1.52–3.38	0.76
2,4-D	8 (25%)	18 (17%)	2.09	0.72–6.06	102 (21%)	275 (20%)	1.22	0.93–1.61	0.46
Number of potentially carcinogenic pesticides[4]			1.31	0.97–1.77			1.08	1.01–1.15	0.22

[1]Self-reported pesticide use as "yes" for each pesticide group or individual pesticide (Appendix A). [2]Wald chi-square p value for pesticide use*asthma interaction term in multiple logistic regression model. [3]ORs adjusted for age, province of residence, respondent type, and diesel oil exposure. [4]based on IARC, US EPA IRIS, and US EPA OPP classifications (17–20); is an ordinal variable. All values in ( ) are percentage of n rounded up to two significant digits.

insecticides (including malathion, the one individual organophosphate insecticide evaluated separately) and mecoprop, the ORs were larger among individuals without any of the immunologic conditions, or for asthma or allergies separately. Conversely, for DDT and MCPA, the ORs were larger among those with any of the immunologic conditions, or asthma or allergies separately. These patterns of NHL risk from possible pesticide exposure by the presence or absence of immunologic conditions do not follow chemical classes. DDT and MCPA associated with immunologic conditions are not in the same chemical class. Likewise, organophosphate insecticides and mecoprop, which show elevated ORs in the absence of immunologic conditions, are also in different chemical classes. These observations could represent new leads, or may simply be chance occurrences. Although the small numbers suggest these may be chance findings, evaluation in independent studies would be worthwhile.

We also analyzed the effect of immune conditions on NHL risk by the number of potentially carcinogenic pesticides used. For each additional potentially carcinogenic pesticide used, the risks of NHL increased in subjects with or without asthma, allergies, or hay fever, or for asthma or allergies separately. Odds were elevated in subjects who were diagnosed with any of these immune conditions compared to those who were not, but these differences were not statistically significant.

The literature regarding pesticide exposure, immunologic conditions, and NHL is not large and also somewhat contradictory. In combined data from studies in Iowa, Minnesota, and Nebraska,[17] the relative risk of NHL associated with exposure to organophosphate insecticides among non-asthmatic farmers was 1.4 (95% CI: 1.1–1.7); for asthmatic farmers, their risk was 2.0 (95% CI: 1.0–4.2). Similarly, non-asthmatic farmers exposed to malathion had a risk of NHL (OR = 1.5, 95% CI: 1.1–2.1) that was lower than the odds in asthmatic farmers exposed to malathion (OR = 1.9, 95% CI: 0.7–5.1). Our results showed the opposite effect (elevated risks among non-asthmatic subjects who reported use of these pesticides). Furthermore, this study [17] found an identical risk of NHL from DDT exposure for non-asthmatic farmers (OR = 1.2, 95% CI: 0.9–1.5) and asthmatic farmers (OR = 1.2, 95% CI: 0.6–2.4), whereas our analysis showed a higher risk of NHL among asthmatics who used DDT. Another study from Iowa, Los Angeles County, Seattle, and the Detroit Metropolitan Area [18] found that the odds of NHL associated with probable occupational exposure to pesticides was higher among asthmatics (OR = 1.7, 95% CI: 0.3–9.1) compared to non-asthmatics (OR = 0.9, 95% CI: 0.6–1.5), which is what we observed for overall pesticide use. Vajdic *et al.*,[19] in an evaluation of the effects of asthma, hay fever, eczema, and food allergy on the association between pesticide exposure and risk of NHL, observed that the odds of NHL with substantial pesticide exposure and any history of asthma was 3.07 (95% CI: 0.55–17.10); while for no asthma history, the risk was 4.23 (95% CI: 1.76–10.16).

Our study had several strengths. It provided the opportunity to evaluate immune status in relation to self-reported use of specific pesticides. Although CCSPH data were collected nearly two decades ago, many of the pesticides used then are still widely used today. DDT, although no longer used in North America, is still present in our environment because of the long half-life of its metabolites.[25] Our study included men in six Canadian provinces and, thus, has widespread relevance in Canada. We were able to control for

Table 5. Risks of non-Hodgkin lymphoma by self-reported pesticide use and allergies diagnosis

	Allergies				No allergies				
Self-reported pesticide use[1]	Cases ($n = 125$)	Controls ($n = 378$)	OR[3]	95% CI	Cases ($n = 388$)	Controls ($n = 1,128$)	OR[3]	95% CI	$p > X^{22}$
Any pesticide	40 (32%)	107 (28%)	1.38	0.87–2.21	109 (28%)	273 (24%)	1.39	1.05–1.83	0.94
Organochlorine insecticides	32 (26%)	79 (21%)	1.42	0.85–2.35	74 (19%)	197 (17%)	1.24	0.91–1.69	0.61
DDT	13 (10%)	15 (4.0%)	2.70	1.20–6.10	20 (5.2%)	44 (3.9%)	1.38	0.78–2.42	0.14
Organophosphate insecticides	21 (17%)	55 (15%)	1.27	0.71–2.26	71 (18%)	114 (10%)	2.25	1.60–3.16	0.09
Malathion	17 (14%)	45 (12%)	1.22	0.65–2.29	55 (14%)	82 (7.3%)	2.42	1.65–3.56	0.06
Phenoxy herbicides	35 (28%)	90 (24%)	1.50	0.91–2.46	94 (24%)	228 (20%)	1.48	1.10–1.99	0.92
MCPA	6 (4.8%)	8 (2.1%)	2.83	0.87–9.14	11 (2.8%)	38 (3.4%)	0.84	0.41–1.72	0.10
Mecoprop	11 (8.8%)	26 (6.9%)	1.30	0.59–2.88	40 (10%)	55 (4.9%)	2.74	1.75–4.28	0.13
2,4-D	32 (26%)	83 (22%)	1.46	0.88–2.42	78 (20%)	210 (19%)	1.24	0.91–1.69	0.69
Number of potentially carcinogenic pesticides[(4)]			1.15	1.03–1.30			1.07	0.99–1.15	0.29

[1]Self-reported pesticide use as "yes" for each pesticide group or individual pesticide (Appendix A). [2]Wald chi-square p value for pesticide use*allergies interaction term in multiple logistic regression model. [3]ORs adjusted for age, province of residence, respondent type, and diesel oil exposure. [4]Based on IARC, US EPA IRIS, and US EPA OPP classifications (17-20); is an ordinal variable. All values in ( ) are percentage of n rounded up to two significant digits

potential confounding from established and suspected NHL risk factors. Finally, NHL cases were histologically confirmed.

The study was limited, however, by the use of self-reported data for immunologic conditions and pesticide use. As in all case–control studies, recall bias is possible in the reporting of exposures. Cases or controls may have differentially recalled diagnoses with the immune conditions included in this analysis but because the study data had been previously collected, we were unable to validate the self-report of asthma, allergies, or hay fever with physician diagnosis of these conditions. Differential recall can bias risks toward or away from the null, depending on which group (*i.e.*, cases or controls) would be more likely to over report immune condition diagnoses. A similar study [18] collected information about asthma from participants by asking them if they had ever been hospitalized for asthma or took daily medication for asthma. This would have improved our analyses; however, we did not have the ability to obtain this information. While we did have data on the number of cases and controls who reported that they had positive skin prick and patch tests for allergies, the numbers were too small for analysis and thus, we decided to define allergies by self-reported diagnosis.

Differential and non-differential error in the reporting of pesticide use is a possible source of bias in this study, and even small amounts could have led to our observation of statistically non-significant interactions as demonstrated by a sensitivity and specificity analysis conducted by Blair *et al.*[26] However, in our study, much of the pesticide use was by farmers and methodological studies have demonstrated a high degree of reliability of such information obtained from farmers.[27–30] Analyses of differential reporting of pesticide exposure were conducted for case–control studies of pesticide exposure and risk of NHL in Iowa, Minnesota, Kansas, and Nebraska.[28] Investigators compared farmers' reported use of the number of pesticides and selected pesticides from open-ended questions and from probing questions. They found that the number of insecticides and herbicides reported, as well as the selected pesticides named, were similar among cases and controls for both open-ended and probing questions. These data suggest that non-differential misclassification, rather than differential misclassification, is a key challenge in evaluating past pesticide exposure based on information obtained from interviews. In addition, recall of pesticide use is not necessarily predictive of actual pesticide exposures or absorbed doses received. These exposure measurement errors would generally bias risk estimates toward the null, but the effects of measurement error, especially in the presence of confounding, is somewhat unpredictable. Moreover, when assessing interaction, the effect of these potential biases may be unpredictable.

Our analyses did not characterize pesticide use by duration, intensity, or frequency of use because there was limited information collected on these variables. This is perhaps the biggest limitation of the current analysis. A dichotomous classification of exposure into ever/never categories will not accurately reflect pesticide exposures over a lifetime. However, if strong and consistent associations are observed using these crude exposure classifications, they would be important leads for additional analyses using more sophisticated exposure measurement techniques. We did not consider simultaneous use of commonly used pesticide combinations [20] even though this represents realistic exposure scenarios where

subjects are likely to be exposed to more than one pesticide at once and/or experience exposures to a number of different pesticides over their lifetime.[6] This information was not collected for our study. Our analysis was also hampered by low statistical power because of the relatively small numbers of individuals reporting both the immunologic conditions and pesticides of interest. For example, only 32 out of 513 (6.2%) cases reported asthma diagnosis, and of these, two out of 32 (6.3%) asthmatic cases reported use of MCPA. Further investigation with a larger number of NHL cases or a pooled dataset will improve the power needed for testing this interaction hypothesis. Finally, we would have liked to perform some analyses by histologic type of NHL because they may have different etiologies,[1] but numbers were insufficient. Perhaps pooling of studies with appropriate information could accomplish this in the future.

In summary, the patterns of effect modification by immunologic conditions for risk of NHL from pesticide use were complex. Although there was some indication that individuals with and without certain immunologic conditions might experience different risks from certain pesticides or pesticide classes, interpretation of these findings may be limited by small numbers (*i.e.*, chance findings), measurement error, and possible recall bias. Nevertheless, this study adds valuable data to the small and inconsistent body of literature on this topic by assessing the effects of several immune conditions for commonly used groups of pesticides and individual substances, with widespread relevance across Canada. To better understand these associations, further efforts with larger numbers or pooled studies and better characterization of pesticide exposures and the immune conditions of interest are needed.

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Appendix A

Lists of pesticide names reportedly used by participants of the Cross-Canada Study of Pesticides and Health

Organochlorine insecticides

1. Aldrin
2. DDT (1,1′-(2,2,2-trichloroethylidene)bis[4-chlorobenzene]; 1,1,1- trichloro-2,2-bis(4-chlorophenyl) ethane)
3. Dieldrin
4. Endrin
5. Heptachlor
6. Lindane
7. Methoxychlor
8. Toxaphene
9. PCP (pentachlorophenol)
10. Rulene (DDT)
11. Thiodan
12. Chlordane

Organophosphate insecticides

1. Azinphosmethyl
2. Chlorpyrifos
3. Dimethoate
4. Malathion
5. Methidathion
6. Methamidophos
7. Trichlorfon
8. Co-ral (Coumaphos)
9. Diazinon
10. Fenthion
11. Metasystox (Oxydemeton-methyl)
12. Orthene (Acephate)
13. Systox (Demeton)
14. Triumph (Isazofos)

Phenoxy herbicides

1. 2,4-D (2,4-dichlorophenoxyacetic acid)
2. 2,4-DB (4-(2,4-dichlorophenoxy)butyric acid)
3. Dichlorprop
4. Diclofop methyl
5. Fenoprop
6. MCPA ((4-chloro-2-methylphenoxy)acetic acid)
7. MCPA-K (MCPA potassium salt)
8. MCPA ester
9. MCPB (4-(2-methyl-4-chlorophenoxy) butyric acid)
10. Mecoprop
11. 2,4,5-T (2,4,5-trichlorophenoxyacetic acid)
12. Acclaim (Fenoxaprop-P-ethyl)

All pesticides

1. Aldrin
2. DDT
3. Dieldrin
4. Endrin
5. Heptachlor
6. Lindane
7. Methoxychlor
8. Toxaphene
9. PCP
10. Rulene (DDT)
11. Thiodan
12. Chlordane
13. Azinphosmethyl
14. Chlorpyrifos
15. Dimethoate
16. Malathion
17. Methidathion
18. Methamidophos
19. Trichlorfon
20. Co-ral (Coumaphos)
21. Diazinon
22. Fenthion
23. Metasystox (Oxydemeton-methyl)
24. Orthene (Acephate)
25. Systox (Demeton)
26. Triumph (Isazofos)
27. 2,4-D
28. 2,4-DB
29. Dichlorprop
30. Diclofop methyl
31. Fenoprop
32. MCPA
33. MCPA-K
34. MCPA ester
35. MCPB
36. Mecoprop
37. 2,4,5-T
38. Acclaim (Fenoxaprop-P-ethyl)

Number of "potentially carcinogenic" pesticides

1. 2,4,5-T
2. 2,4-D
3. 2,4-DB

4. Arsenic
5. Asulam
6. Benomyl
7. Bromoxynil
8. Carbaryl
9. Cypermethrin
10. DDT
11. Dicamba
12. Diclofop-methyl
13. Dieldrin
14. Dimethoate
15. Dinoseb
16. Formaldehyde
17. Heptachlor
18. Lindane
19. Linuron
20. Mancozeb
21. MCPA
22. Mecoprop
23. Methidathion
24. Paraquat
25. Propoxur
26. Toxaphene
27. Triallate
28. Trichloroacetic acid
29. Trifluralin

Appendix B. Characteristics of non-Hodgkin lymphoma cases and controls stratified by immune condition diagnoses in the Cross-Canada Study of Pesticides and Health

	Asthma				Allergies				Asthma, allergies, or hay fever[1]			
	Yes		No		Yes		No		Yes		No	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
n	32	107	481	1399	125	378	388	1128	159	462	354	1044
Mean age ± SD (years)	59 ± 17	56 ± 16	58 ± 14	54 ± 16	58 ± 15	52 ± 16	58 ± 14	55 ± 16	59 ± 15	53 ± 17	57 ± 14	55 ± 16
Province of residence												
Quebec	10 (32%)	16 (15%)	107 (22%)	275 (20%)	23 (18%)	50 (13%)	94 (24%)	241 (21%)	33 (21%)	71 (15%)	84 (24%)	220 (21%)
Ontario	8 (25%)	39 (36%)	134 (28%)	546 (39%)	38 (30%)	158 (42%)	104 (27%)	427 (38%)	48 (30%)	184 (40%)	94 (27%)	401 (38%)
Manitoba	3 (9.4%)	8 (7.5%)	31 (6.4%)	105 (7.5%)	5 (4.0%)	33 (8.7%)	29 (7.5%)	80 (7.1%)	7 (4.4%)	35 (7.6%)	27 (7.6%)	78 (7.5%)
Saskatchewan	3 (9.4%)	6 (5.6%)	26 (5.4%)	85 (6.1%)	7 (5.6%)	24 (6.4%)	22 (5.7%)	67 (5.9%)	9 (5.7%)	29 (6.3%)	20 (5.7%)	62 (5.9%)
Alberta	4 (13%)	21 (20%)	61 (13%)	175 (13%)	22 (18%)	55 (15%)	43 (11%)	141 (13%)	23 (14%)	68 (15%)	42 (12%)	128 (12%)
British Columbia	4 (13%)	17 (16%)	122 (25%)	213 (15%)	30 (24%)	58 (15%)	96 (25%)	172 (15%)	39 (25%)	75 (16%)	87 (25%)	155 (15%)
Respondent type												
Self-respondent	23 (72%)	89 (83%)	380 (79%)	1197 (86%)	102 (82%)	322 (85%)	301 (78%)	964 (85%)	125 (79%)	395 (86%)	278 (79%)	891 (85%)
Proxy respondent	9 (28%)	18 (17%)	101 (21%)	202 (14%)	23 (18%)	56 (15%)	87 (22%)	164 (15%)	34 (21%)	67 (14%)	76 (21%)	153 (15%)
Diesel oil exposure												
Yes	14 (44%)	42 (39%)	169 (35%)	422 (30%)	52 (42%)	128 (34%)	131 (34%)	336 (30%)	68 (43%)	152 (33%)	115 (32%)	312 (30%)
No	18 (56%)	65 (61%)	312 (65%)	977 (70%)	73 (58%)	250 (66%)	257 (66%)	792 (70%)	91 (57%)	310 (67%)	239 (68%)	732 (70%)

[1]Self-reported diagnosis with any one of asthma, allergies, or hay fever. All values in ( ) are percentage of *n* rounded up to two significant digits.