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Multiple pesticide exposures and the risk of multiple myeloma in Canadian men

Linda Kachuri[1,2,3], Paul A Demers[1,2,3], Aaron Blair[1], John J Spinelli[4,5], Manisha Pahwa[1], John R McLaughlin[1,2,6], Punam Pahwa[7], James A Dosman[8] and Shelley A Harris[1,2,3]

[1] Occupational Cancer Research Centre, Toronto, ON, Canada
[2] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[3] Cancer Care Ontario, Toronto, ON, Canada
[4] BC Cancer Agency, Vancouver, BC, Canada
[5] School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
[6] Samuel Lunenfeld Research Institute, Toronto, ON, Canada
[7] Department of Community Health and Epidemiology, University of Saskatchewan, Saskatoon, SK, Canada
[8] Canadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Saskatoon, SK, Canada

Multiple myeloma (MM) has been linked to certain agricultural exposures, including pesticides. This analysis aimed to investigate the association between lifetime use of multiple pesticides and MM risk using two exposure metrics: number of pesticides used and days per year of pesticide use. A frequency-matched, population-based case-control study was conducted among men in six Canadian provinces between 1991 and 1994. Data from 342 MM cases and 1,357 controls were analyzed using logistic regression to calculate odds ratios (OR) and 95% confidence intervals. Pesticides were grouped by type, chemical class and carcinogenic potential, using a composite carcinogenic probability score. Selected individual pesticides were also examined. Regression models were adjusted for age, province of residence, use of proxy respondents, smoking and selected medical history variables. The overall pattern of results was complex. Positive trends in risk were observed for fungicides (p_{trend}=0.04) and pesticides classified as probably carcinogenic or higher (p_{trend}=0.03). Excess risks of MM were observed among men who reported using at least one carbamate pesticide (OR=1.94, 1.16–3.25), one phenoxy herbicide (OR=1.56, 1.09–2.25) and ≥3 organochlorines (OR=2.21, 1.05–4.66). Significantly higher odds of MM were seen for exposure to carbaryl (OR=2.71, 1.47–5.00) and captan (OR=2.96, 1.40–6.24). Use of mecoprop for >2 days per year was also significantly associated with MM (OR=2.15, 1.03–4.48). Focusing on multiple pesticide exposures is important because this more accurately reflects how exposures occur in occupational settings. Significant associations observed for certain chemical classes and individual pesticides suggest that these may be MM risk factors.

Epidemiology

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for ~10% of all blood malignancies.[1,2] Most patients with MM evolve from an asymptomatic premalignant condition termed monoclonal gammopathy of undetermined significance (MGUS).[3,4] The median age at MM diagnosis is about 62 years, with only 2% of patients younger than 40 years.[4] Established risk factors for this disease include the male gender, African American ethnicity, advanced age and antigenic stimulation.[4,5] Familial clustering of MM and MGUS has also been reported,[3] which implicates genetic susceptibility factors in MM etiology, although,

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Abbreviations: Captan: N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide; Carbaryl: 1-naphthyl methylcarbamate; CCSPH: Cross-Canada Study of Pesticides and Health; HL: Hodgkin lymphoma; IARC: International Agency for Research on Cancer; ICD, International Classification of Diseases; Mecoprop: (RS)-2-(4-chloro-2-methylphenoxy)propanoic acid; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; STS: soft tissue sarcoma; US EPA OPP: United States Environmental Protection Agency Office of Pesticides Program; US EPA IRIS: United States Environmental Protection Agency Integrated Risk Information System; 2,4-D: ((2,4-dichlorophenoxy)acetic acid)

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Correspondence to: Shelley A Harris, Cancer Care Ontario, 505 University Avenue, Toronto, Ontario, Canada, M5G 1X3, Tel.: 416-971-9800 × 3234; Fax: 416-971-6888, E-mail: Shelley.Harris@cancercare.on.ca

What's new?
This study is the first to investigate the risk of multiple myeloma from exposure to multiple pesticides using two distinct metrics: number of pesticides and days per year of pesticide use. Focusing on multiple pesticide exposures is important because it more accurately reflects how exposures occur in agricultural settings. Although the overall pattern was complex, increased risks observed for certain pesticide groups and individual compounds suggest that these may be risk factors for multiple myeloma.

shared environmental influences or a combination of the two cannot be discounted. In addition to these established risk factors, many epidemiological studies have focused on occupational or environmental exposures that might be linked to the development of MM.

Numerous studies have observed elevated risks of MM among individuals employed in agriculture, which has brought attention to pesticides as potentially relevant exposures.[6–11] Positive associations with MM have been observed for certain herbicides[7,11,12] as well as organochlorine and carbamate insecticides.[8,11,12] A recent analysis of the Cross-Canada Study of Pesticides and Health (CCSPH) showed that men who reported use of the insecticide carbaryl and the fungicide captan had significantly elevated risks of MM.[12] Most studies have focused on risks for individual pesticides, but farmers are typically exposed to a number of different pesticides over their lifetime. Multiple pesticides could be used simultaneously or during the same growing season, but not necessarily during the same application. For this reason, it is important to distinguish individual from combined effects. Studies have examined the effect of exposure to multiple pesticides on the risk of non-Hodgkin lymphoma (NHL),[13,14] but this approach has not yet been extended to MM.

The focus of this report is the association between lifetime pesticide exposure and risk of MM. We investigated exposure to multiple pesticides grouped by pesticide type, chemical class and carcinogenic potential. We also examined exposure to selected individual pesticides within each group.

Material and Methods

Study population and recruitment

The data used in these analyses were previously collected for the CCSPH and details of the design and methodology have been published.[15] Briefly, the CCSPH was a population-based, case-control study of men residing in six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Québec) that was conducted to explore associations between pesticide exposure and four different types of cancer: MM, Hodgkin lymphoma (HL), NHL and soft tissue sarcoma (STS).

Incident MM cases (International Classification of Diseases [ICD]-9 203) among men aged 19 years or older who were diagnosed between September 1, 1991 and December 31, 1994, were eligible and were ascertained from provincial cancer registries except in Quebec, where cases were ascertained from hospitals.[15] A reference pathologist reviewed pathology and tumor tissue slides for 125 out of 342 (36.55%) MM cases. Because of a mid-study change in some hospitals' policies regarding supplying pathological material without charge, samples could not be obtained for all cases due to limited funding. Potential controls were men aged 19 years or older who were selected randomly using provincial health insurance records, random digit dialing, or voters' lists.[15] These sampling frames were used because their efficiency and high coverage produced a sample that was sufficiently representative and minimally biased for the purposes of the study.[16] Control subjects were frequency-matched to cases by age ($\pm$2 years) and province of residence. Deceased subjects were ineligible as either cases or controls and proxy respondents for deceased participants were also ineligible.

Information on pesticides used, demographic characteristics, medical and occupational history, exposure to selected chemical substances and other variables was obtained from all participants using the postal questionnaire. A subsequent telephone interview was used to gather detailed information about individual pesticide use for subjects who reported $\geq$10 hr/year of pesticide use in the postal questionnaire and a 15% random sample of the remainder. These participants were mailed a list of pesticides (both chemical and trade names) and an information letter a week before the telephone interview. This analysis used merged data from the postal and the telephone questionnaires.

Pesticides were selected for inclusion if: (1) the compound was ever registered for use in Canada and reviewed by the International Agency for Research on Cancer (IARC); (2) the pesticide was recently banned or restricted in Canada by the federal licensing agency; or, (3) the pesticide was commonly used in Canada for specific purposes (see Appendix A for a list of all pesticides evaluated).[15]

Exposure to multiple pesticides

Use of multiple pesticides, as a proxy for exposure, was classified in two different ways: total number of pesticides used and the self-reported days per year (days/year) of pesticide use. Basic descriptive calculations, such as frequencies and ranges, were used to determine the most appropriate exposure categories.

The first set of analyses focused on the total number of pesticides used. Exposure categories were created for the use of 1, 2-4 and $\geq$5 pesticides. A binary variable (ever/never pesticide use) was used to derive each exposure category.

Similar exposure variables were constructed for herbicides and insecticides. Fewer participants reported using multiple fungicides, so self-reported use was categorized as exposure to 1 and ≥2 fungicides. For these analyses the unexposed category was specific to the pesticide type or class.

We also examined the effects of exposure to multiple pesticides with different levels of known carcinogenicity. A composite carcinogenicity score was created using assessments from the IARC Monographs, U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) and the U.S. EPA Office of Pesticides Program (OPP): 1.0 = classified as a human carcinogen in any assessment; 0.9 = probable human carcinogen in all assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in another assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable (or not assessed) in the others; 0.5 = possible human carcinogen in all assessments, or possible human carcinogen in one assessment and unclassifiable (or not assessed) by the others. Using this composite score we created two exposure groups: one for pesticides rated as possibly carcinogenic or higher (score of ≥0.5), and another for pesticides rated as probably carcinogenic or higher (score of ≥0.6). For pesticides classified as possibly carcinogenic or higher (score of ≥0.5), exposure was categorized as use of 1, 2-4 and ≥5 pesticides. For pesticides rated as probably carcinogenic or higher (score of ≥0.6), exposure was grouped as use of 1, 2 and ≥3 pesticides.

Last, we examined exposure to multiple pesticides classified by major chemical class. We created categorical variables for the use of 1, 2 and ≥3 phenoxy herbicides and the use of 1, 2 and ≥3 organochlorines. Within the organophosphate class, exposure was categorized as the use of 1 and ≥2 organophosphate pesticides. For carbamates, exposure was categorized as the use of ≥1 carbamate pesticides.

The second set of analyses used days/year of pesticide use as the exposure metric. In the telephone questionnaire, participants were asked to indicate how many days each year they personally mixed or applied specific herbicides, insecticides, or fungicides. For pesticides rated as possibly carcinogenic or higher (score of ≥0.5), exposure groups were created for >0 and ≤2 days/year, >2 and ≤5 days/year, >5 and ≤15 days/year and >15 days/year of pesticide use. For pesticides rated as probably carcinogenic or higher (score of ≥0.6), phenoxy herbicides, organochlorines and organophosphates, exposure was categorized as >0 and ≤2 days/year, >2 and ≤5 days/year and >5 days/year of pesticide use. For carbamate pesticides, two exposure groups were created: >0 and ≤2 days/year and >2 days/year of pesticide use.

Individual pesticides

The third set of analyses focused on the most frequently used individual herbicides, insecticides and fungicides. Similar to the other analyses, two exposure metrics were used: a binary variable (ever/never exposed) and days/year of individual pesticide use.

Statistical analyses

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for categorical pesticide exposure variables using unconditional logistic regression since cases and controls were not individually matched on age and province of residence.[17] Descriptive analyses were conducted and potentially confounding variables suggested by the literature and by previous analyses of CCSPH data were investigated. We calculated odds ratios adjusted for age and province of residence, use of a proxy respondent, personal and family medical history and smoking history. Variables that were significantly ($p < 0.05$) associated with MM in these bivariate analyses were retained in the multivariate models estimating the effects of exposure to multiple pesticides and selected individual pesticides.

Trends were examined using multiple logistic regression. Categorical variables indicating the number of pesticides that participants used or the number of days/year of pesticide use were treated as continuous in the regression model to obtain the slope estimate and associated p-value for trend (p_{trend}).

All analyses were conducted using SAS version 9.3 (Cary, N.C.).

The University of Toronto Health Sciences Research Ethics Board reviewed and approved the protocol for these analyses.

Results

A total of 342 MM cases (58% of those contacted) and 1506 frequency age-matched controls (48% of those contacted) participated in the CCSPH. A summary of relevant demographic characteristics, including personal and family medical history and cigarette smoking history, is presented in Table 1. The control group was matched to the overall age distribution for all cancer cases in the CCSPH (HL, NHL, STS and MM), but because MM typically occurs at a more advanced age, MM cases were significantly older than controls. In order to account for this, 52 controls aged younger than 25 years and 97 controls aged 25 to 29 years with no matching MM cases were excluded. Hence, this analysis used data from 342 MM cases and 1,357 controls.

Proxy respondents were used for 14.89% of controls and 30.12% of cases, and this was significantly associated with MM (OR: 2.09, 95% CI: 1.57–2.89). All regression models were adjusted for the use of proxy respondents. In addition, sensitivity analyses were conducted excluding information that was not directly reported by the participant, in order to fully evaluate the effect of potential misclassification arising from the use of proxy respondents.

Participants who reported that they never smoked or smoked less than 400 cigarettes in their lifetime were classified as non-smokers. Compared to non-smokers, both current smokers (OR: 1.29, 0.88–1.90) and former smokers (OR:

Table 1. Characteristics of multiple myeloma cases and controls in the Cross-Canada Study of Pesticides and Health (CCSPH)

	Cases ($N = 342$)		Controls ($N = 1357$)		
	Mean	SD	Mean	SD	OR[1] (95% CI)
Age (years)[2]	64.70	11.08	57.17	14.14	
	N	%	*N*	%	
30-39	9	2.63	207	15.25	
40-49	30	8.77	255	18.79	
50-59	62	18.13	238	17.54	
60-69	118	34.50	370	27.27	
70-79	101	29.53	252	18.57	
80 and older	22	6.43	35	2.58	
Province[3]					
Alberta	58	16.96	177	13.04	
Saskatchewan	28	8.19	84	6.19	
Manitoba	25	7.31	100	7.37	
Ontario	103	30.12	522	38.47	
Quebec	37	10.82	256	18.87	
British Columbia	91	26.61	218	16.06	
Respondent type					
Subject (self)	239	69.88	1155	85.11	1.00
Other	103	30.12	202	14.89	2.09 (1.57, 2.78)
Smoking status[4]					
Never smoked cigarettes	92	26.90	473	34.86	1.00
Former smoker	197	57.60	627	46.20	1.36 (1.02, 1.80)
Current smoker	53	15.50	257	18.94	1.29 (0.88, 1.90)
Ever diagnosed with the following conditions[5]					
Allergies (yes)	60	17.54	337	24.83	0.67 (0.49, 0.91)
Measles (yes)	166	48.54	831	61.24	0.57 (0.44, 0.73)
Rheumatoid arthritis (yes)	16	4.68	85	6.26	0.54 (0.31, 0.94)
Shingles (yes)	49	14.33	83	6.12	2.08 (1.41, 3.08)
Cancer (yes)	61	17.84	86	6.34	2.39 (1.65, 3.45)
Cancer in first-degree relatives					
Any cancer (yes)	164	47.95	480	35.37	1.42 (1.10, 1.81)
Hematologic cancer[6] (yes)	28	8.19	67	4.94	1.40 (0.87, 2.25)
Multiple myeloma (yes)	9	2.63	5	0.37	9.15 (2.90, 28.80)
Ever lived or worked on a farm					
No	166	48.54	725	53.43	1.00
Yes	176	51.46	632	45.57	1.00 (0.77, 1.29)
Longest-held job as a farmer					
No	256	74.85	1134	83.57	1.00
Yes	86	25.15	223	16.43	1.25 (0.92, 1.72)

[1]Adjusted for matching variables: age and province of residence
[2]$t = -10.59$, $p < 0.0001$
[3]$X^2 = 36.81$, $p < 0.0001$
[4]Individuals who smoked 400 cigarettes or less during their lifetime were considered non-smokers
[5]Also tested and found not to be associated: acne, asthma, mumps, celiac disease, chickenpox, diabetes, hay fever, mononucleosis, rheumatic fever, ringworm, syphilis, urinary tract infections, whooping cough, treatment for overactive thyroid, drug treatment for lice or scabies, medical implants, drug treatment for epilepsy, tonsillectomy
[6]Cancer other than non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma or soft-tissue sarcoma
[7]This includes non-Hodgkin lymphoma, Hodgkin lymphoma, all types of leukemia and multiple myeloma

1.36, 1.02–2.78) were more likely to be diagnosed with MM. A comparison of the participants' personal medical history revealed that certain immune and inflammatory conditions and infectious diseases were significantly associated with MM (Table 1). Compared with controls, cases with a history of allergies (OR: 0.67, 0.49–0.91), measles (OR: 0.57, 0.44–73) and rheumatoid arthritis (OR: 0.54, 0.31–0.94) had significantly lower odds of MM. On the other hand, a previous diagnosis of shingles (OR: 2.08, 1.41–3.08) or personal history of cancer (OR: 2.39, 1.65–3.45) was associated with higher likelihood of MM.

A significantly higher proportion of cases than controls reported a positive family history of cancer. Family history of cancer can be an indicator of inherited genetic susceptibility to cancer and was included as a covariate in logistic regression models. Cancer of any type in a first-degree relative was associated with a significantly higher risk of MM (OR: 1.42, 1.10–1.81). The odds of MM observed for diagnosis of any hematologic cancer in a first-degree relative was similar (OR: 1.40, 0.87–2.25), but when the type of cancer was restricted to MM, much higher odds were observed (OR: 9.15, 2.90–28.80).

Approximately half of cases (51.46%) and controls (45.57%) had ever lived or worked on a farm, but this was not significantly related to MM. Compared with controls, cases were more likely to report farming as their longest-held occupation and this was associated with higher odds of MM (OR: 1.25, 0.92–1.72).

Exposure to multiple pesticides

The risk of MM tended to be higher with an increasing number of pesticides used, but the trend did not increase monotonically in most analyses (Table 2). Overall, the use of an increasing number of any pesticide was associated with a non-significant positive trend in risk ($p_{trend} = 0.11$). When pesticides were grouped by type, a positive trend in risk was observed for the use of multiple insecticides ($p_{trend} = 0.10$). This association became stronger after the exclusion of information provided by proxy respondents, whereby the use of $\geq$5 insecticides was significantly associated with MM (OR: 2.17, 1.02–4.63; ($p_{trend} = 0.07$). The use of multiple fungicides appeared to be less common, and despite a positive trend in risk ($p_{trend} = 0.04$), the likelihood of MM was significantly higher only among men who reported use of 1 fungicide (OR: 1.73, 1.00–3.00).

When trends in risk were examined for pesticides grouped according to their carcinogenic potential (Table 2), this revealed differences in the pattern of risk between pesticides rated as possibly carcinogenic or higher compared to those classified as probably carcinogenic or higher. Although a positive association was observed for pesticides with a composite carcinogenicity score of $\geq$0.5 (p_{trend}=0.11), limiting the analysis to pesticides with carcinogenicity scores of $\geq$0.6 revealed a stronger trend in risk with increasing numbers of pesticides used ($p_{trend} = 0.04$). Restricting the analysis to information reported directly by the participants yielded slightly higher estimates (OR for $\geq$3 pesticides: 2.24, 0.94–5.34; $p_{trend} = 0.03$).

Some significant associations were also observed when pesticides were examined by major chemical class, but no clear exposure-response patterns were identified (Table 3). A significantly increased MM risk was observed for exposure to $\geq$3 organochlorine pesticides (OR: 2.21, 1.05–4.66), but the trend was not significant ($p_{trend} = 0.13$). The use of $\geq$1 carbamate pesticides appeared to significantly increase the likelihood of MM (OR: 1.94, 1.16–3.25). An excess of MM also occurred from the use of any single phenoxy herbicide (OR: 1.56, 1.09–2.25), but not for use of more than one phenoxy herbicides. Similarly to the analyses of pesticides grouped by type (Table 2), the observed associations were strengthened with the exclusion of information provided by proxy respondents.

The next set of analyses examined MM risk in association with the number of days/year mixing or applying pesticides, grouped by carcinogenic potential and major chemical class (Table 4). After excluding information reported by proxy respondents, a significant positive trend in risk (p_{trend}=0.03) was observed for pesticides classified as probably carcinogenic or higher (score of $\geq$0.6), but not for pesticides classified as possibly carcinogenic or higher (score of $\geq$0.5) (p_{trend}=0.15). Although the overall trend in risk was significant for carbamates (p_{trend}=0.02), men who directly reported using these pesticides for $\leq$2 days/year (OR: 2.17, 0.98–4.81) had a higher likelihood of MM than those who self-reported >2 days/year of use (OR: 2.02, 0.89–4.60). After excluding proxy responses, a borderline significant association was observed for men who reported mixing or applying organophosphate pesticides for >5 days/year (OR: 1.87, 0.99–3.50; $p_{trend} = 0.17$).

Individual pesticides

The ORs for some of the most frequently used herbicides, insecticides and fungicides are presented in Table 5. Mecoprop was the only herbicide significantly associated with MM (OR: 1.94, 1.19–3.19). 2,4-D was the most commonly used herbicide, but the observed excess risk of MM was not statistically significant (OR: 1.30, 0.95-1.78). Among insecticides, the most notable associations were observed for carbaryl (OR: 2.71, 1.47-5.00) and lindane (OR: 2.37, 1.08-5.16). A non-significant, increased risk was also observed for DDT (OR: 1.64, 0.97–2.79). For fungicides, only exposure to captan was associated with a significantly higher likelihood of MM (OR: 2.96, 1.40–6.24). Excluding proxy responses revealed stronger positive associations for mercury dust, mecoprop, DDT and captan.

Several positive associations were observed when these individual pesticides were assessed by days/year of pesticide use (Table 6). Men who directly self-reported using mecoprop for >2 days/year had significantly higher odds of MM (OR: 2.56, 1.17–5.64), and this effect was larger than what was observed for $\leq$2 days/year of mecoprop use (OR: 1.82,

Table 2. Adjusted odds ratios for multiple myeloma in relation to the number of pesticides used grouped by pesticide type and carcinogenic potential, defined using a composite carcinogenic probability score[1]

				Proxy responses excluded		
Number of pesticides used	**Cases**	**Controls**	**OR[2] (95% CI)**	**Cases**	**Controls**	**OR[3] (95% CI)**
All pesticides						
0	240	976	1.00	162	821	1.00
1	6	55	0.52 (0.21, 1.28)	5	49	0.64 (0.24, 1.71)
2-4	47	157	1.40 (0.95, 2.06)	32	137	1.28 (0.82, 2.01)
≥5	49	169	1.26 (0.85, 1.86)	50	148	1.43 (0.92, 2.21)
			$p_{trend}^2 = 0.11$			$p_{trend}^3 = 0.09$
Herbicides						
0	248	1023	1.00	168	862	1.00
1	43	138	1.41 (0.95, 2.11)	32	121	1.39 (0.88, 2.18)
2-4	34	136	1.07 (0.69, 1.66)	26	121	1.09 (0.67, 1.79)
≥5	17	60	1.47 (0.79, 2.72)	13	51	1.68 (0.84, 3.39)
			$p_{trend}^2 = 0.18$			$p_{trend}^3 = 0.16$
Insecticides						
0	248	1027	1.00	168	867	1.00
1	38	113	1.52 (0.99, 2.34)	24	95	1.45 (0.87, 2.42)
2-4	43	182	1.09 (0.73, 1.61)	35	163	1.16 (0.75, 1.79)
≥5	13	35	1.91 (0.95, 3.85)	12	30	2.17 (1.02, 4.63)
			$p_{trend}^2 = 0.10$			$p_{trend}^3 = 0.07$
Fungicides						
0	295	1217	1.00	202	1034	1.00
1	25	85	1.27 (0.77, 2.11)	21	69	1.73 (1.00, 3.00)
≥2	22	55	1.70 (0.96, 3.00)	16	52	1.59 (0.83, 3.03)
			$p_{trend}^2 = 0.05$			$p_{trend}^3 = 0.04$
Pesticides rated as possibly carcinogenic or higher (score of ≥0.5)						
0	248	1035	1.00	167	874	1.00
1	29	99	1.43 (0.89, 2.29)	22	84	1.54 (0.91, 2.63)
2-4	46	157	1.26 (0.85, 1.87)	35	137	1.33 (0.85, 2.08)
≥5	19	66	1.34 (0.75, 2.39)	15	60	1.37 (0.72, 2.61)
			$p_{trend}^2 = 0.11$			$p_{trend}^3 = 0.11$
Pesticides rated as probably carcinogenic or higher (score of ≥0.6)						
0	279	1177	1.00	190	995	1.00
1	37	104	1.66 (1.08, 2.56)	27	95	1.57 (0.96, 2.56)
2	16	53	1.04 (0.55, 1.95)	13	43	1.26 (0.63, 2.56)
≥3	10	23	2.18 (0.97, 4.93)	9	22	2.24 (0.94, 5.34)
			$p_{trend}^2 = 0.04$			$p_{trend}^3 = 0.03$

[1]Carcinogenic probability values created by integrating IARC, US EPA IRIS, US EPA OPP assessments: 1.0 = classified as a human carcinogen in either assessment; 0.9 = probable human carcinogen in all assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in another assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable (or not assessed) in the others; 0.5 = possible human carcinogen in all assessments, or possible human carcinogen in one assessment and unclassifiable (or not assessed) by the others; 0.3 = not assessed, or deemed unclassifiable in one or all three assessments; 0.1= evidence for non-carcinogenicity in any assessment
[2]Adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer.
[3]Adjusted for age, province of residence, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer.

Table 3. Adjusted odds ratios for multiple myeloma in relation to the number of pesticides used, grouped by major chemical class

				Proxy responses excluded		
Number of pesticides used	Cases	Controls	OR[1] (95% CI)	Cases	Controls	OR[2] (95% CI)
Phenoxy herbicides						
0	255	1058	1.00	173	893	1.00
1	56	170	1.56 (1.09, 2.25)	40	148	1.54 (1.01, 2.34)
2	16	80	0.90 (0.50, 1.64)	13	70	1.03 (0.54, 1.99)
≥3	15	49	1.50 (0.78, 2.87)	13	44	1.72 (0.85, 3.49)
			p_{trend}^1 =0.16			p_{trend}^2 =0.09
Organochlorines						
0	274	1098	1.00	184	926	1.00
1	41	158	1.17 (0.79, 1.74)	33	137	1.25 (0.81, 1.94)
2	15	74	0.96 (0.52, 1.78)	11	68	0.90 (0.45, 1.82)
≥3	12	27	2.21 (1.05, 4.66)	11	24	2.46 (1.10, 5.48)
			p_{trend}^1 =0.13			p_{trend}^2 =0.11
Organophosphates						
0	287	1139	1.00	196	963	1.00
1	31	120	1.16 (0.75, 1.81)	23	105	1.10 (0.66, 1.83)
≥2	24	98	1.07 (0.64, 1.77)	20	87	1.13 (0.64, 1.98)
			p_{trend}^1 = 0.63			p_{trend}^2 = 0.61
Carbamates						
0	315	1298	1.00	217	1104	1.00
≥1	27	59	1.94 (1.16, 3.25)	22	51	2.09 (1.19, 3.70)

[1]Adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer
[2]Adjusted for age, province of residence, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer

0.89–3.70). Although the herbicide glyphosate did not appear to be significantly associated with MM in the previous analysis using binary exposure variables (Table 5), a nearly significant association was observed for >2 days/year of glyphosate use (OR: 2.11, 0.95–4.70). Self-reported use of DDT for ≤2 days/year was significantly related to MM (OR: 3.09, 1.15–8.31), but the magnitude of risk was lower for >2 days/year of exposure (OR: 1.40, 0.62–3.18). Likewise, the risk of MM was significantly elevated among men who self-reported using of captan for ≤2 days/year (OR: 6.84, 1.95–23.96) but not for >2 days/year (OR: 1.95, 0.51–7.45).

On the other hand, participants who directly reported using mecoprop for >2 days/year had significantly higher odds of MM (OR: 2.56, 1.17–5.64) and this effect was larger than what was observed for ≤2 days/year of mecoprop use (OR: 1.82, 0.89–3.70). For carbaryl higher odds of MM were also observed for >2 days/year (OR: 3.33, 1.24–8.97) than shorter duration of exposure (OR for ≤2 days/year: 2.47, 0.99–6.15). A similar pattern of increasing risk with progressively more days/year of pesticide use was also observed for mercury dust (OR for >2 days/year: 2.35, 0.98–5.64), as well as formaldehyde (OR for >2 days/year: 3.41, 0.84–13.77), but only after the exclusion of proxy responses.

Discussion

The hypothesis that farming and other agricultural activities are associated with MM has been raised previously,[18,19] but only a few studies of farmers have focused specifically on pesticides.[6–11,20] Analyses of multiple pesticide exposures in the CCSPH found that the risk of NHL also increased with greater numbers of pesticides used and even more strikingly with pesticides that were suspected carcinogens.[14] In the present analysis, there was a significant trend in risk for self-reported use of increasing numbers of pesticides classified as probably carcinogenic or higher (score of ≥0.6). A significantly higher risk of MM was also observed for exposure to ≥3 organochlorines, although the trend was not statistically significant. In addition, use of carbamate pesticides was significantly associated with an excess risk of MM. Investigating MM risk from exposure to multiple pesticides using days/year as the exposure metric also revealed a significant trend in risk for pesticides classified as probable carcinogens or higher (p_{trend}=0.03) and for carbamates (p_{trend} = 0.02). We also observed an increased likelihood of MM among men who directly reported mixing or applying organophosphate pesticides for >5 days/year. This is in contrast to the results obtained using the total number of organophosphates as the

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Table 4. Adjusted odds ratios for multiple myeloma in relation to the days/year of mixing or applying pesticides, grouped by chemical class and carcinogenic potential, defined using a composite carcinogenic probability score[1]

				Proxy responses excluded		
Days/year	Cases	Controls	OR[2] (95% CI)	Cases	Controls	OR[3] (95% CI)
Pesticides rated as possibly carcinogenic or higher (score of ≥0.5)						
Unexposed	250	1039	1.00	168	877	1.00
>0 and ≤2	24	72	1.56 (0.92, 2.64)	17	60	1.65 (0.89, 3.05)
>2 and ≤5	22	66	1.47 (0.85, 2.53)	14	56	1.30 (0.67, 2.50)
>5 and ≤15	22	96	1.18 (0.70, 1.99)	20	86	1.44 (0.83, 2.51)
15>	24	84	1.14 (0.68, 1.92)	20	76	1.25 (0.71, 2.19)
			$p_{trend}^2 = 0.26$			$p_{trend}^3 = 0.15$
Pesticides rated as probably carcinogenic or higher (score of ≥0.6)						
Unexposed	283	1189	1.00	191	1006	1.00
>0 and ≤2	25	62	1.89 (1.12, 3.21)	19	57	1.75 (0.96, 3.17)
>2 and ≤5	13	47	1.52 (0.78, 2.96)	10	40	1.76 (0.83, 3.74)
>5	21	59	1.26 (0.71, 2.22)	19	52	1.58 (0.87, 2.85)
			$p_{trend}^2 = 0.10$			$p_{trend}^3 = 0.03$
Phenoxy herbicides						
Unexposed	258	1064	1.00	175	898	1.00
>0 and ≤2	35	111	1.47 (0.95, 2.28)	23	95	1.42 (0.84, 2.39)
>2 and ≤5	23	86	1.33 (0.80, 2.23)	19	73	1.48 (0.84, 2.61)
>5	26	96	1.23 (0.75, 2.02)	22	89	1.34 (0.78, 2.29)
			$p_{trend}^2 = 0.16$			$p_{trend}^3 = 0.11$
Organochlorines						
Unexposed	281	1120	1.00	188	945	1.00
>0 and ≤2	20	77	1.19 (0.69, 2.05)	14	71	1.07 (0.57, 2.01)
>2 and ≤5	17	61	1.55 (0.85, 2.81)	14	54	1.64 (0.85, 3.19)
>5	24	99	1.11 (0.67, 1.85)	23	85	1.37 (0.81, 2.31)
			$p_{trend}^2 = 0.30$			$p_{trend}^3 = 0.11$
Organophosphates						
Unexposed	291	1148	1.00	197	972	1.00
>0 and ≤2	21	100	0.90 (0.53, 1.51)	16	86	0.92 (0.51, 1.67)
>2 and ≤5	11	56	0.87 (0.43, 1.76)	9	51	0.90 (0.42, 1.94)
>5	19	53	1.67 (0.93, 2.98)	17	46	1.87 (0.99, 3.50)
			$p_{trend}^2 = 0.27$			$p_{trend}^3 = 0.17$
Carbamates						
Unexposed	317	1302	1.00	218	1106	1.00
>0 and ≤2	14	26	2.26 (1.10, 4.67)	11	24	2.17 (0.98, 4.81)
>2	11	29	1.74 (0.81, 3.73)	10	25	2.02 (0.89, 4.60)
			$p_{trend}^2 = 0.03$			$p_{trend}^3 = 0.02$

[1]Carcinogenic probability values created by integrating IARC, US EPA IRIS, US EPA OPP assessments: 1.0 = classified as a human carcinogen in either assessment; 0.9 = probable human carcinogen in all assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in another assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable (or not assessed) in the others; 0.5 = possible human carcinogen in all assessments, or possible human carcinogen in one assessment and unclassifiable (or not assessed) by the others; 0.3 = not assessed, or deemed unclassifiable in one or all three assessments; 0.1= evidence for non-carcinogenicity in any assessment
[2]Adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer
[3]Adjusted for age, province of residence, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer.

Table 5. Adjusted odds ratios for multiple myeloma in relation to exposure to selected herbicides, insecticides and fungicides

Individual Pesticides (Carcinogenic Probability Score[1])	Number Exposed			Proxy responses excluded		
	Cases	Controls	OR[2] (95% CI)	Number Exposed Cases	Controls	OR[3] (95% CI)
Herbicides						
2,4-D (0.5)	80	278	1.30 (0.95, 1.78)	61	244	1.36 (0.95, 1.95)
Glyphosate (0.3)	32	121	1.19 (0.76, 1.87)	23	108	1.11 (0.66, 1.86)
Mecoprop (0.5)	27	74	1.94 (1.19, 3.19)	23	68	1.97 (1.16, 3.37)
Insecticides						
Methoxychlor (0.3)	43	187	1.17 (0.80, 1.72)	35	157	1.18 (0.77, 1.80)
Malathion (0.3)	32	124	1.12 (0.71, 1.74)	29	110	1.28 (0.79, 2.07)
Chlordane (0.8)	25	100	1.18 (0.72, 1.93)	22	89	1.27 (0.75, 2.17)
DDT (0.8)	25	57	1.64 (0.97, 2.79)	21	51	1.68 (0.94, 3.01)
Carbaryl (0.6)	21	33	2.71 (1.47, 5.00)	17	30	2.69 (1.37, 5.28)
Lindane (0.5)	12	23	2.37 (1.08, 5.16)	8	21	2.35 (0.96, 5.73)
Fungicides						
Mercury dust (0.3)	17	39	1.57 (0.82, 2.99)	15	35	1.91 (0.95, 3.83)
Captan (0.3)	14	24	2.96 (1.40, 6.24)	10	19	3.03 (1.27, 7.22)
Formaldehyde (1.0)	12	25	1.24 (0.56, 2.74)	8	20	1.52 (0.59, 3.87)

[1]Carcinogenic probability values created by integrating IARC, US EPA IRIS, US EPA OPP assessments: 1.0 = classified as a human carcinogen in either assessment; 0.9 = probable human carcinogen in all assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in another assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable (or not assessed) in the others; 0.5 = possible human carcinogen in all assessments, or possible human carcinogen in one assessment and unclassifiable (or not assessed) by the others; 0.3 = not assessed, or deemed unclassifiable in one or all three assessments; 0.1= evidence for non-carcinogenicity in any assessment
[2]Adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer
[3]Adjusted for age, province of residence, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer

exposure metric, where no notable excesses in risk were observed.

Despite several statistically significant trends, the overall pattern of MM risk was complex. There are a number of explanations for the lack of clear exposure-response patterns. It is possible that the observed associations were due to chance. The numbers, although adequate, were not large and a number of comparisons were made. Exposure measurement error may have also influenced results. Non-differential exposure misclassification can obscure even moderate excesses in risk. In addition, combining different individual pesticides into a single category was challenging because the chemicals have different structures, modes of action in target species and may have different mechanisms of suspected carcinogenic action. Pesticides are a heterogeneous group of chemicals with diverse functions and formulations. Little is known about the mechanisms by which several pesticides could influence cancer risk, and even less is known about the possible interactions involving adjuvant ingredients typically contained in commercial formulations. Any increase in MM risk associated with the use of broad types of pesticides or chemical classes could likely be attributed to the action of only a few compounds with non-carcinogens tending to attenuate associations.

Examination of individual pesticides provided some insight as to what specific compounds might be driving the increased risks observed in the analyses of multiple pesticide use. Risk of MM in relation to self-reported use of individual pesticides has also been reported by Pahwa *et al.*[12] in a previous analysis of CCSPH data. Our findings extend these analyses, while also examining the impact of excluding information provided by proxy respondents on effect estimates. The significant trend in risk observed for fungicides may reflect the three-fold risk of MM observed for exposure to captan, a broad-spectrum fungicide used on a variety of crops, ornamental plants, seeds and post-harvest fruit for cosmetic purposes. The carcinogenic potential of captan remains controversial. It has been shown to disrupt the inactivation of caspases, a group of intracellular cysteine enzymes that lead to apoptosis when activated.[21] The increased apoptosis of human erythrocytes stimulates the production of replacement cells within the bone marrow and this increased cell division may increase the potential for genetic error in replication, leading to neoplastic transformation. However, results of mutagenicity studies have been contradictory, with only *in-vitro* but not *in-vivo* studies showing positive results.[22] The U.S. EPA has recently downgraded its classification of captan to not likely to be carcinogenic to humans,

Table 6. Adjusted odds ratios for multiple myeloma in relation to days per year of mixing or applying selected herbicides, insecticides and fungicides

Individual Pesticides (Carcinogenic Probability Score[1])	Number Exposed			Proxy responses excluded: Number Exposed		
Days/year	Cases	Controls	OR[2] (95% CI)	Cases	Controls	OR[3] (95% CI)
Herbicides						
2,4-D (0.5)						
>0 and ≤2	35	144	1.13 (0.74, 1.74)	25	123	1.19 (0.72, 1.94)
>2 and ≤5	23	77	1.36 (0.80, 2.31)	19	70	1.41 (0.79, 2.51)
≥5	17	49	1.46 (0.79, 2.70)	14	44	1.59 (0.82, 3.09)
Glyphosate (0.3)						
>0 and ≤2	15	88	0.72 (0.39, 1.32)	11	78	0.70 (0.35, 1.40)
>2	12	29	2.04 (0.98, 4.23)	10	26	2.11 (0.95, 4.70)
Mecoprop (0.5)						
>0 and ≤2	14	40	1.87 (0.96, 3.61)	12	37	1.82 (0.89, 3.70)
>2	12	31	2.15 (1.03, 4.48)	11	28	2.56 (1.17, 5.64)
Insecticides						
Methoxychlor (0.3)						
>0 and ≤2	14	67	0.96 (0.51, 1.81)	11	63	0.90 (0.45, 1.82)
>2 and ≤5	11	39	1.85 (0.88, 3.88)	8	36	1.53 (0.65, 3.59)
≥5	12	57	1.16 (0.60, 2.27)	12	48	1.37 (0.68, 2.74)
Malathion (0.3)						
>0 and ≤2	17	74	1.04 (0.58, 1.88)	16	67	1.21 (0.65, 2.26)
>2	12	38	1.37 (0.68, 2.77)	11	32	1.59 (0.75, 3.39)
Chlordane (0.8)						
>0 and ≤2	11	52	1.07 (0.53, 2.16)	10	48	1.10 (0.52, 2.34)
>2	10	42	1.09 (0.51, 2.34)	9	37	1.24 (0.55, 2.76)
DDT (0.8)						
>0 and ≤2	9	17	2.53 (1.05, 6.06)	7	14	3.09 (1.15, 8.31)
>2	10	27	1.16 (0.52, 2.59)	10	24	1.40 (0.62, 3.18)
Carbaryl (0.6)						
>0 and ≤2	11	18	2.61 (1.13, 6.01)	9	17	2.47 (0.99, 6.15)
>2	9	14	2.74 (1.10, 6.83)	8	12	3.33 (1.24, 8.97)
Lindane (0.5)						
>0 and ≤2	7	12	2.37 (0.85, 6.61)	4	11	2.05 (0.59, 7.17)
>2	3	11	1.27 (0.30, 5.30)	3	10	1.96 (0.50, 7.76)
Fungicides						
Mercury dust (0.3)						
>0 and ≤2	5	13	1.29 (0.43, 3.87)	5	11	1.90 (0.59, 6.11)
>2	10	20	2.14 (0.94, 4.88)	9	19	2.35 (0.98, 5.64)
Captan (0.3)						
>0 and ≤2	8	9	4.50 (1.60, 12.63)	6	5	6.84 (1.95, 23.96)
>2	5	12	2.00 (0.60, 6.67)	4	11	1.95 (0.51, 7.45)
Formaldehyde (1.0)						
>0 and ≤2	5	10	1.68 (0.52, 5.43)	4	8	1.84 (0.48, 7.16)
>2	5	8	1.13 (0.31, 4.15)	4	5	3.41 (0.84, 13.77)

[1]Carcinogenic probability values created by integrating IARC, US EPA IRIS, US EPA OPP assessments: 1.0 = classified as a human carcinogen in either assessment; 0.9 = probable human carcinogen in all assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in another assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable (or not assessed) in the others; 0.5 = possible human carcinogen in all assessments, or possible human carcinogen in one assessment and unclassifiable (or not assessed) by the others; 0.3 = not assessed, or deemed unclassifiable in one or all three assessments; 0.1= evidence for non-carcinogenicity in any assessment
[2]Adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer
[3]Adjusted for age, province of residence, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer.

except following prolonged, high-level exposures, which are above those likely to be encountered in occupational or residential settings.[23] This is consistent with the findings of the Agricultural Health Study, where no association was observed between the highest level of captan exposure and development of cancer at any site.[24]

Within the phenoxy herbicide class, 92% of exposed cases reported use of 2,4-D and 31% had used mecoprop. Although only mecoprop was significantly related to MM, the odds associated with 2,4-D exposure were also elevated. When days/year of pesticide use were examined, the odds of MM increased with a greater number of days spent mixing or applying these herbicides. All chlorophenoxy herbicides, as a group, have been classified by IARC as possibly carcinogenic to humans (Group 2B).[25] An increased risk of MM with exposure to phenoxy herbicides has also been reported in a Swedish population-based case-control study.[11] There is potential for 2,4-D to promote cancer by inducing DNA damage, compromising the ability of cells to eliminate reactive oxygen species and enhancing the lymphocyte replication index.[26] However, most of experimental the literature on the carcinogenicity of 2,4-D has been negative.[27,28] 2,4-D has been more consistently associated with NHL than MM, both in the CCSPH and in other studies.[29–32] Mecoprop was previously found to be associated with MM in the CCSPH dataset.[12] Mutagenicity assays in bacteria have been negative, but a dose-dependent increase in chromosomal aberrations in the bone marrow of Chinese hamsters was noted following oral administration of mecoprop.[33]

The association between MM and carbamate pesticides can be mostly attributed to carbaryl. Carbaryl was responsible for 78% (21 out of 27) of carbamate exposure among cases and 55% (34 out of 62) of exposure among controls in this category. Carbaryl is an N-methylcarbamate insecticide used in agriculture to control pests on terrestrial food crops and other locations like golf courses and oyster beds. The genotoxicity of N-methylcarbamate insecticides has been studied extensively; however, results from different endpoints are often contradictory. A study found much higher levels of chromosomal damage in the sperm of carbaryl-exposed Chinese factory workers.[34] Carbaryl has been found to increase sister chromatid exchange in human cells.[35] The U.S. EPA classifies carbaryl as "likely to be carcinogenic to humans" based on evidence of liver tumors in rats[36] and vascular tumors in mice,[37,38] whereas IARC has not assessed carbaryl since 1987, when the human evidence was deemed to be inadequate which resulted in a Group 3 classification.[25]

The increasing risk of MM with the number of organochlorine pesticides used is noteworthy. The most frequently used organochlorines used in the CCSPH were methoxychlor, chlordane, DDT and lindane. DDT exposure has been found to increase MM risk in some studies[8,11] and we also observed this in our analysis. DDT is classified by IARC as a possible human carcinogen (Group 2B), and the U.S. EPA considers it a probable carcinogen (Group B2).[39,40] Similarly, the U.S. EPA categorizes chlordane as a probable human carcinogen (Group B2), while IARC considers it to be possibly carcinogenic to humans (Group 2B).[39,41] Chlordane did not appear to be significantly linked to MM in our analysis. Exposure to lindane, on the other hand, was associated with a significantly higher likelihood of MM, and this is consistent with a previous CCSPH analysis by Pahwa *et al.*[12]

In addition to the investigations of multiple pesticide exposures and selected individual compounds, a unique feature of this study is the sensitivity analysis that evaluated the effects of using proxy respondents. Inclusion of proxy respondents increases sample size and improves the representativeness of the case group, though this may be at the expense of non-response bias and potential misclassification of exposure.[42] The results of our sensitivity analysis showed that for certain pesticide groups and individual compounds the estimates of effect actually increased, despite the apparent loss of power resulting from the exclusion of 30% of cases and 15% of controls who required the use of proxy respondents. This supports our hypothesis that the use of proxy respondents introduced exposure misclassification that biased the observed odds ratios towards the null. A recent investigation of the accuracy of proxy respondents in population-based case-control studies found that for pesticide exposure, 26% of proxy responses were missing, compared to 9% for index cases.[42] Although proxies such as spouses of farmers can provide some useful information regarding a farmer's pesticide use, proxies are less aware of specific pesticides used and details about pesticide use than the farmers themselves.[43]

Although not the primary objective of this analysis, the finding that smoking was positively associated with MM is interesting because this link has only been reported in a few studies.[44,45] Smoking may be related to MM and occupational pesticide exposures,[46] and it can also directly influence exposures from hand-mouth contact.[47] Smoking could also modify cancer risk from pesticide exposure because carcinogens found in cigarette smoke may potentiate the genotoxic effects of pesticide exposures.[47] The observation that former smokers appeared to be at a slightly higher risk than current smokers may be explained by the older age of former smokers and the resulting longer lifetime exposure to cigarette smoke. In addition, smoking may reduce the use of personal protective equipment (PPE), increasing the likelihood of oral and dermal exposure to pesticide residues.[46,47] A Danish study found that greenhouse workers who had not used PPE and were current smokers had higher ratios of chromatid gaps compared to non-smokers.[47]

One of the main limitations of this study is the low response rates observed for cases and controls. To minimize selection bias, extensive follow-up efforts were made to contact all living cases.[12] The postal codes for responders and non-responders in the CCSPH were available and these were used as an indicator of urban vs. rural residence. Despite the low response rate, a comparison of the postal codes for participants and non-participants did not indicate the presence of a rural bias.[15] A comparison of the postal codes also

confirmed that the main reasons for non-participation were due to death or a change of address.[48]

Recall bias is a concern in case-control studies because cases may be more prone than controls to reflect on past exposures after diagnosis of cancer, which may result in false positive associations or inflated OR estimates. Investigations of self-reported pesticide use among farmers in studies with comparable methods of exposure ascertainment to those used in the CCSPH found that cases and controls reported similar numbers of specific pesticides used when this information was volunteered and when it was reported after probing.[49] If recall bias occurred, cases would be expected to volunteer a larger proportion of use than controls because they had been thinking about possible exposures that may have caused their cancer.[49] Furthermore, farmers have demonstrated reliable recall of pesticide use that is comparable in accuracy to their recall of other standard epidemiological variables.[49,50]

This analysis has several important strengths, including the relatively large number of incident MM cases and controls and the population-based nature of the CCSPH, which ensured that cancer cases and controls were representative of the Canadian population. The considerable variation in pesticide use reported by the participants made it possible to investigate the effects of multiple pesticide use. This also allowed us to create unique ways of grouping multiple pesticide use, such as by integrating carcinogenicity ratings from different regulatory agencies into a single composite carcinogenicity score.

The detailed information on pesticide exposure that was collected in the CCSPH is another important strength of this study because it allowed us to construct two different metrics in order to assess the effects of exposure to multiple pesticides in a more comprehensive manner. The use of multiple pesticides is not a surrogate for total days of pesticide use but rather a distinct metric designed to capture the effects of lifetime exposure to a number of different chemical compounds. For a particular combination of crops and pests, several pesticides may be used to achieve optimal results, therefore multiple pesticide use more accurately captures how exposures occur in agricultural settings. Pesticide mixtures involving up to 3 chemicals are also common; therefore, focusing solely on risk from individual compounds might miss some of the joint effects arising from exposure to several pesticides.

The etiology of MM remains obscure. Although we did not uncover any large risks associated with pesticide use, there are some important leads. The use of carbamate pesticides, specifically carbaryl, was associated with a twofold risk of MM. Exposure to increasing numbers of organochlorine pesticides, fungicides and pesticides that have been classified as probably carcinogenic or higher on our composite scale, also appeared to be significant risk factors for MM. The larger risk of MM for pesticides classified as probably carcinogenic compared to those classified as possibly carcinogenic, highlight the importance of using this approach in future epidemiological studies to evaluate combined effects from use of multiple pesticides. Although the overall pattern of risk appears to be complex, the associations observed for certain chemical classes and individual pesticides suggest that these may be risk factors for MM. Additional research that accounts for other determinants of pesticide exposure, such as timing, intensity and use of PPE, is needed to further evaluate these associations.

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References

1. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004;351:1860–73.
2. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2005;80: 1371–82.
3. Greenberg AJ, Rajkumar SV, Vachon CM. Familial monoclonal gammopathy of undetermined significance and multiple myeloma: epidemiology, risk factors, and biological characteristics. *Blood* 2012;119: 5359–66.
4. Raab MS, Podar K, Breitkreutz I, et al. Multiple myeloma. *Lancet* 2009;374:324–39.
5. Lope V, Perez-Gomez B, Aragones N, et al. Occupation, exposure to chemicals, sensitizing agents, and risk of multiple myeloma in Sweden. *Cancer Epidemiol Biomarkers Prev* 2008;17: 3123–7.
6. Brown LM, Burmeister LF, Everett GD, et al. Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes Control* 1993;4: 153–6.
7. Baris D, Silverman DT, Brown LM, et al. Occupation, pesticide exposure and risk of multiple myeloma. *Scand J Work Environ Health* 2004;30:215–22.
8. Nanni O, Falcini F, Buiatti E, et al. Multiple myeloma and work in agriculture: results of a case-control study in Forli, Italy. *Cancer Causes Control* 1998;9:277–83.
9. Pasqualetti P, Casale R, Collacciani A, et al. Work activities and the risk of multiple myeloma. A case-control study. *Med Lav* 1990;81:308–19.
10. Demers PA, Vaughan TL, Koepsell TD, et al. A case-control study of multiple myeloma and occupation. *Am J Ind Med* 1993;23:629–39.
11. Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: a population based case-control study. *Br J Ind Med* 1992;49:95–103.
12. Pahwa P, Karunanayake CP, Dosman JA, et al. Multiple myeloma and exposure to pesticides: a Canadian case-control study. *J Agromed* 2012;17: 40–50.
13. De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003;60:E11.
14. Hohenadel K, Harris SA, McLaughlin JR, et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health* 2011;8: 2320–30.
15. McDuffie HH, Pahwa P, McLaughlin JR, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001;10:1155–63.
16. Wang PP, Dicks E, Gong X, et al. Validity of random-digit-dialing in recruiting controls in a case-control study. *Am J Health Behav* 2009;33: 513–20.
17. Szklo M, Nieto J. Epidemiology: beyond the basics. 2nd Ed. Sudbury, Massachusetts: Jones and Bartlett Publishers, 2007.

18. Blair A, McDuffie HH, Dosman JA. Cancer in rural areas. *CMAJ* 1987;136:924–5.
19. Blair A, Zahm SH, Pearce NE, et al. Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 1992;18:209–15.
20. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma cell and lymphoproliferative disorders among 14621 first-degree relatives of 4458 patients with monoclonal gammopathy of undetermined significance in Sweden. *Blood* 2009; 114:791–5.
21. Lavrik IN, Golks A, Krammer PH. Caspases: pharmacological manipulation of cell death. *J Clin Invest* 2005;115:2665–72.
22. Gordon E. Captan: transition from 'B2' to 'not likely'. How pesticide registrants affected the EPA Cancer Classification Update. *J Appl Toxicol* 2007;27:519–26.
23. Agency UEP, Captan: Cancer Reclassification; Amendment of Reregistration Eligibility Decision; Notice of Availability. Reg. 68357–68360 2004.
24. Greenburg DL, Rusiecki J, Koutros S, 2004. Cancer incidence among pesticide applicators exposed to captan in the Agricultural Health Study. *Cancer Causes Control* 2008;19:1401–7.
25. International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. World Health Organization, 1987.
26. Figgs LW, Holland NT, Rothmann N, et al. Increased lymphocyte replicative index following 2,4-dichlorophenoxyacetic acid herbicide exposure. *Cancer Causes Control* 2000;11:373–80.
27. Gollapudi BB, Charles JM, Linscombe VA, et al. Evaluation of the genotoxicity of 2,4-dichlorophenoxyacetic acid and its derivatives in mammalian cell cultures. *Mutat Res* 1999;444: 217–25.
28. Munro IC, Carlo GL, Orr JC, et al. A comprehensive, integrated review and evaluation of the scientific evidence relating to the safety of the herbicide 2,4-D. *J Am Coll Toxicol* 1992;11: 559–664.
29. Pahwa P, McDuffie HH, Dosman JA, et al. Hodgkin lymphoma, multiple myeloma, soft tissue sarcomas, insect repellents, and phenoxyherbicides. *J Occup Environ Med* 2006;48: 264–74.
30. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 1986;256:1141–7.
31. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447–55.
32. Zahm SH, Weisenburger DD, Babbitt PA, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1990;1: 349–56.
33. California Environmental Protection Agency (EPA), Summary of toxicology data: MCPP. Department of Pesticide Regulation, 1999.
34. Xia Y, Cheng S, Bian Q, et al. Genotoxic effects on spermatozoa of carbaryl-exposed workers. *Toxicol Sci* 2005;85:615–23.
35. Onfelt A, Klasterska I. Sister-chromatid exchanges and thioguanine resistance in V79 Chinese hamster cells after treatment with the aneuploidy-inducing agent carbaryl +/- S9 mix. *Mutat Res* 1984;125:269–74.
36. National Institutes of Health, Toxicology and carcinogenesis studies of methyl carbamate in F344/N rats and B6C3F1 mice., 1987.
37. US Environmental Protection Agency, Amended reregistration eligibility decision (RED) for Carbaryl. Office of Prevention, Pesticides, and Toxic Substances, 2008.
38. Hamada N, Combined chronic toxicity and oncogenicity study with carbaryl technical in CD-1 mice. Study No. 656-138 (Unpublished), 1993.
39. International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 53: Occupational Exposures in Insecticide Application, and Some Pesticides. World Health Organization, 1991.
40. US Environmental Protection Agency, DDT. General Fact Sheet. National Pesticide Information Center, 1999.
41. US Environmental Protection Agency, Chlordane. General Fact Sheet. National Pesticide Information Center, 2001.
42. Campbell PT, Sloan M, Kreiger N. Utility of proxy versus index respondent information in a population-based case-control study of rapidly fatal cancers. *Ann Epidemiol* 2007;17:253–7.
43. Brown LM, Dosemeci M, Blair A, et al. Comparability of data obtained from farmers and surrogate respondents on use of agricultural pesticides. *Am J Epidemiol* 1991;134:348–55.
44. Mills PK, Newell GR, Beeson WL, et al. History of cigarette smoking and risk of leukemia and myeloma: results from the Adventist health study. *J Natl Cancer Inst* 1990;82:1832–6.
45. Nieters A, Deeg E, Becker N. Tobacco and alcohol consumption and risk of lymphoma: results of a population-based case-control study in Germany. *Int J Cancer* 2006;118:422–30.
46. Harris SA, Sass-Kortsak AM, Corey PN, et al. Development of models to predict dose of pesticides in professional turf applicators. *J Expo Anal Environ Epidemiol* 2002;12:130–44.
47. Lander BF, Knudsen LE, Gamborg MO, et al. Chromosome aberrations in pesticide-exposed greenhouse workers. *Scand J Work Environ Health* 2000;26:436–42.
48. Ghosh S, McLaughlin JR, Spinelli JJ, et al. Multiple myeloma and occupational exposures: a population-based case-control study. *J Occup Environ Med* 2011;53:641–6.
49. Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993;4:55–62.
50. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. *Epidemiology* 2002;13: 94–9.