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Original Contribution

Occupational Exposure to Pesticides and Risk of Non-Hodgkin's Lymphoma

L. Fritschi[1], G. Benke[2], A. M. Hughes[3], A. Kricker[3], J. Turner[4], C. M. Vajdic[5], A. Grulich[5], S. Milliken[4], J. Kaldor[5], and B. K. Armstrong[3]

[1] Viertel Centre for Research, Queensland Cancer Fund, Brisbane, Queensland, Australia.
[2] Department of Epidemiology and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia.
[3] School of Public Health, University of Sydney, Sydney, New South Wales, Australia.
[4] St. Vincent's Hospital, Sydney, New South Wales, Australia.
[5] National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, New South Wales, Australia.

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Pesticide exposure may be a risk factor for non-Hodgkin's lymphoma, but it is not certain which types of pesticides are involved. A population-based case-control study was undertaken in 2000–2001 using detailed methods of assessing occupational pesticide exposure. Cases with incident non-Hodgkin's lymphoma in two Australian states ($n = 694$) and controls ($n = 694$) were chosen from Australian electoral rolls. Logistic regression was used to estimate the risks of non-Hodgkin's lymphoma associated with exposure to subgroups of pesticides after adjustment for age, sex, ethnic origin, and residence. Approximately 10% of cases and controls had incurred pesticide exposure. Substantial exposure to any pesticide was associated with a trebling of the risk of non-Hodgkin's lymphoma (odds ratio = 3.09, 95% confidence interval: 1.42, 6.70). Subjects with substantial exposure to organochlorines, organophosphates, and "other pesticides" (all other pesticides excluding herbicides) and herbicides other than phenoxy herbicides had similarly increased risks, although the increase was statistically significant only for "other pesticides." None of the exposure metrics (probability, level, frequency, duration, or years of exposure) were associated with non-Hodgkin's lymphoma. Analyses of the major World Health Organization subtypes of non-Hodgkin's lymphoma suggested a stronger effect for follicular lymphoma. These increases in risk of non-Hodgkin's lymphoma with substantial occupational pesticide exposure are consistent with previous work.

case-control studies; herbicides; lymphoma, non-Hodgkin; occupational exposure; pesticides

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; OR, odds ratio.

There has been considerable interest in the question of whether exposure to pesticides causes non-Hodgkin's lymphoma, with recent reviews highlighting pesticide exposure as one of the likely occupational risk factors for this cancer (1, 2). This hypothesis was originally derived from studies suggesting that farmers had increased rates of non-Hodgkin's lymphoma (3, 4). Although farmers are exposed to a number of potential carcinogens (diesel exhaust, animal viruses, etc.), researchers have concentrated on their occupational exposure to pesticides. There are hundreds of different types of pesticides in common use in developed countries, and many more have been banned or have had their use discontinued in the past 30 years.

Importantly, "pesticides" is a generic term that includes substances with a variety of different chemical structures and mechanisms of action. Only particular types of pesticides

Correspondence to Dr. Jacqueline Fritschi, Viertel Centre for Research, Queensland Cancer Fund, 553 Gregory Terrace, Fortitude Valley, Queensland 4006, Australia (e-mail: lfritschi@qldcancer.com.au).

or specific chemicals might be related to non-Hodgkin's lymphoma. There has been interest recently in trying to determine which of the many pesticides in use may be responsible for the reported association with non-Hodgkin's lymphoma. Interest has focused on three groups of substances:

- phenoxy herbicides—general-use herbicides (chemicals that kill weeds) which include known animal carcinogens such as 2,4-dichlorophenoxyacetic acid;
- organophosphates—primarily insecticides which work by inhibiting acetylcholinesterase, resulting in neurotoxicity and paralysis (e.g., diazinon, parathion); and
- organochlorines—primarily insecticides and fungicides (e.g., chlordane, lindane) which include some substances known to persist for very long periods in the environment (e.g., dichlorodiphenyltrichloroethane (DDT)).

In addition, there is a wide range of other herbicides (e.g., triazines, dipyridyls (diquat, paraquat), chlorates) and pesticides (e.g., carbamates, pyrethroids) that are commonly used in farming.

In a case-control study of non-Hodgkin's lymphoma, we examined exposure to each of the above groups of pesticides using detailed methods of assessing pesticide exposure.

MATERIALS AND METHODS

Case and control recruitment

Details on case and control ascertainment for this study can be found in related articles (5, 6). Briefly, cases were persons with incident non-Hodgkin's lymphoma that was first diagnosed between January 1, 2000, and August 31, 2001, and reported to the Central Cancer Registry of New South Wales, Australia. Patients were 20–74 years of age and resident in New South Wales or the Australian Capital Territory. Ineligibility criteria included a history of organ transplantation or human immunodeficiency virus infection, poor English language skills, inability to complete a telephone interview, or a diagnosis of chronic lymphocytic leukemia, plasma cell myeloma, or B- or T-cell lymphoblastic leukemia. An anatomic pathologist reviewed all relevant pathology reports for all consenting patients. The pathologist reviewed diagnostic histopathology sections for all consenting patients judged to be less than 90 percent certain to have an eligible diagnosis of non-Hodgkin's lymphoma in the report review. The aim of this review was to assure the correct diagnosis and to obtain, where possible, a World Health Organization classification category (7) and the corresponding *International Classification of Diseases for Oncology*, Third Edition, code (8).

Controls were randomly selected from the New South Wales and Australian Capital Territory electoral rolls to approximately match the expected distributions of cases with regard to age, sex, and region of residence (New South Wales or Australian Capital Territory). Electoral registration is compulsory for Australian citizens aged 18 years or over. Similar eligibility criteria were used as for cases, except for human immunodeficiency virus infection, which was expected to be rare in the general population.

Cases and controls were mailed an introductory letter and an information leaflet, followed by a self-administered questionnaire to each consenting subject. The questionnaire included a diary with a detailed lifetime history of each job the subject had held for 1 year or more. Information obtained on each job included job title, employer, industry, start and finish years, number of hours worked per day, and number of days worked per week.

The final data set consisted of 694 cases (of 1,230 ascertained cases, 842 were apparently eligible and contactable) and 694 controls (of 1,687 controls selected, 1,136 were apparently eligible and contactable). Further details on response fractions are available in previous articles (5, 6). Twenty-three cases were excluded after the pathology reviews because the pathologist considered them not to have an eligible diagnosis. Ten of these cases were removed after review of the pathology sections; these 10 cases were included in an earlier report (5).

Exposure allocation

A total of 28 jobs and 16 industries were identified as being of particular interest because of the possibility of exposure to the substances evaluated in this study (6). For these 44 jobs and industries, detailed sets of questions (known as job-specific modules) were obtained from the US National Cancer Institute (9) and modified to suit this study. The resulting modules included 6–23 questions asking about specific tasks performed in that occupation. Respondents were asked how many weeks per year and how many hours per week they had spent in each task. Modules were allocated to subjects by an occupational hygienist according to whether or not the subjects had worked in one or more of the 44 jobs and industries. The questions in the relevant modules were asked in a customized computer-assisted telephone interview. The hygienist and the interviewers were blinded to the case or control status of subjects.

The same expert occupational hygienist (again blind to status) reviewed the occupational histories and the answers to the module questions and determined exposure to various substances, including organophosphates, organochlorines, phenoxy herbicides, other herbicides, and other pesticides. The hygienist allocated exposures occurring before 1985 and after 1985 separately, because use of organochlorines had been phased out around 1985 and use of other pesticides (mainly pyrethrins) had become widespread. A pesticide-crop matrix was developed for assistance with exposure assessment (10). The matrix included information on what kinds of pesticides were known to be used (or recommended by the Australian Department of Agriculture) for each combination of crop or animal raised and pest type (insect, weed, etc.). A table was also prepared for assistance with identification of chemical composition from trade names reported by the subjects. Former Department of Agriculture employees, environmental scientists, and pesticide manufacturers assisted with construction of the matrix.

The hygienist first allocated likelihood of exposure to each substance as probable, possible, or no exposure. He then allocated one of three levels of exposure using previous literature and his own professional knowledge, without

regard to the probability of exposure. The reference levels were internationally recognized occupational safety guidelines (time-weighted average threshold limit values set by the American Conference of Governmental Industrial Hygienists (11)). Levels of exposure higher than the time-weighted average threshold limit values were considered high; those less than or equal to one 10th of the time-weighted average threshold limit values were considered low; and other exposures were considered medium. For the few people who reported wearing gloves and overalls while mixing and applying pesticides, the exposure level was dropped one level lower. Frequency of exposure was allocated as number of 8-hour days per year and was calculated using responses to the task questions. If no data on frequency of exposure were available ($n = 4$), subjects were assumed to have been exposed for 2 days per year.

Amount of exposure was calculated by combining data from all jobs held over the person's entire working life. Amount was classified as substantial if the subject was probably exposed to the substance at a medium or high level for more than five 8-hour days per year for a combined total of more than 5 years, and nonsubstantial if the dose involved any other combination of exposures.

Statistical analysis

The data were first examined by use of contingency tables and comparisons of mean values. Logistic regression was used to calculate odds ratios (as estimates of relative risk) for non-Hodgkin's lymphoma associated with exposure to any pesticide and exposure to each pesticide subtype in each amount category (substantial or nonsubstantial), with adjustment for age, sex, ethnic origin, and state of residence. In addition, logistic regression analyses were carried out for exposure to any pesticide after restricting the sample to males only and after excluding cases that were not on the electoral roll. We also repeated the analyses for each pesticide for B-cell non-Hodgkin's lymphomas only, for follicular lymphomas only, and for diffuse large B-cell lymphomas only. We also examined the odds of non-Hodgkin's lymphoma using the following metrics of exposure to any pesticide: maximum exposure level (low, medium, high); ever being exposed before 1985 (yes, no); maximum frequency of exposure (0, $\leq$4, or $>$4 days/year); and total number of years exposed (0, $\leq$5, or $>$5 years). For the latter two metrics, 4 days per year and 5 years were the median frequency and duration, respectively, in control subjects. All p values were two-sided.

Approval for this study was given by the human research ethics committee at each participating institution. Participants were sent detailed information sheets and were subsequently telephoned to obtain their consent.

RESULTS

Cases and controls were well-matched by sex and age, but controls were more likely to be of British or Irish ethnic origin (table 1), possibly because of a relative deficit of people of other origins on the electoral roll (12). There was no appreciable difference in socioeconomic status (based on the subjects' residential postcodes) between cases and controls. The subtypes of lymphoma evaluated comprised the following: diffuse large B-cell lymphoma ($n = 231$); follicular lymphoma ($n = 227$); extranodal marginal zone B-cell lymphoma ($n = 37$); chronic lymphocytic leukemia or small lymphocytic lymphoma ($n = 27$); lymphoplasmacytic lymphoma or Waldenstrom's macroglobulinemia ($n = 26$); mantle cell lymphoma ($n = 22$); other B-cell lymphoma subtypes ($n = 39$); combined B-cell lymphoma subtypes ($n = 31$); B-cell lymphoma, not otherwise classified ($n = 25$); T-cell lymphoma ($n = 25$); and non-Hodgkin's lymphoma, not otherwise classified ($n = 4$).

TABLE 1. Characteristics (%) of cases and controls in an Australian study of non-Hodgkin's lymphoma, 2000–2001

Characteristic	Controls ($n = 694$)	Cases ($n = 694$)
Sex		
Male	57.2	58.2
Female	42.8	41.8
Age group (years)		
20–29	3.0	2.9
30–39	6.6	6.2
40–49	16.4	17.1
50–59	28.1	29.4
60–69	30.1	30.4
70–74	15.7	14.0
Ethnic origin		
British/Irish	78.5	73.2
Asian	2.0	3.3
Mixed	9.4	9.5
Southern European	3.2	5.8
Other European	3.5	4.6
Other	3.5	3.6
State of residence		
New South Wales	95.2	96.0
Australian Capital Territory	4.8	4.0

Approximately 10 percent of cases and controls had been exposed to any pesticide at any level. Approximately 1 percent of controls ($n = 9$) and 4 percent of cases ($n = 26$) had incurred a substantial amount of exposure (table 2). Of those substantially exposed to any pesticide, the average total time of exposure was 675 8-hour days for cases and 494 days for controls. All but seven subjects substantially exposed to any pesticide (three controls and four cases) had been exposed for the total equivalent of 6 months or more.

Exposure to a substantial amount of any pesticide was associated with a trebling of the risk of non-Hodgkin's lymphoma (odds ratio (OR) = 3.09, 95 percent confidence interval (CI): 1.42, 6.70). Subjects with substantial exposure to each pesticide subgroup had increased risks of non-Hodgkin's lymphoma, although the lower bound of the 95 percent confidence interval was greater than 1.0 only for those with substantial exposure to ''other pesticides.''

TABLE 2. Degree of exposure to pesticides and non-Hodgkin's lymphoma in an Australian case-control study, 2000–2001

Degree of exposure	Controls		Cases		All subjects	
	No.	%	No.	%	Odds ratio*	95% confidence interval
Any pesticide						
None	621	89.5	621	89.6	1.0	
Nonsubstantial	64	9.2	47	6.7	0.73	0.49, 1.09
Substantial	9	1.3	26	3.7	3.09	1.42, 6.70
Organophosphates						
None	660	95.1	662	95.4	1.0	
Nonsubstantial	28	4	20	2.8	0.71	0.39, 1.28
Substantial	6	0.9	12	1.7	2.11	0.78, 5.68
Organochlorines						
None	679	97.8	674	97.1	1.0	
Nonsubstantial	13	1.9	14	2	1.07	0.50, 2.32
Substantial	2	0.3	6	0.9	3.27	0.66, 16.4
Phenoxy herbicides						
None	677	97.6	679	97.9	1.0	
Nonsubstantial	14	2	10	1.4	0.73	0.32, 1.66
Substantial	3	0.4	5	0.7	1.75	0.42, 7.38
Other herbicides						
None	671	96.7	659	95	1.0	
Nonsubstantial	20	2.9	26	3.7	1.37	0.75, 2.49
Substantial	3	0.4	9	1.3	3.29	0.88, 12.3
Other pesticides						
None	640	92.2	639	92.2	1.0	
Nonsubstantial	51	7.3	43	6.1	0.86	0.56, 1.32
Substantial	3	0.4	12	1.7	4.24	1.18, 15.2

* Adjusted for sex, age, ethnicity, and region of residence.

Restricting the subjects to subgroups produced similar patterns, with statistically significant increases in risk for substantial exposure to any pesticide (table 3). The odds ratio for substantial exposure to any pesticide for males only was 3.7, and for persons on the electoral roll only, it was 2.9. The odds ratio for the 584 cases and 694 controls who were on the electoral roll was only 7 percent below the odds ratio for the entire group; this suggests that any bias which might have been due to the use of electoral rolls as a sampling frame for controls was largely controlled by adjustment for ethnic origin.

When we examined the individual exposure metrics separately (probability, level, frequency, duration, and years exposed), none of the individual effect estimates were statistically significant (table 3). When we used a continuous measure, number of years exposed to any pesticide, we found that risk of non-Hodgkin's lymphoma increased slightly with every year of exposure (OR = 1.01, 95 percent CI: 0.994, 1.027). Among those probably or definitely exposed to any pesticide, the mean number of years of exposure to any pesticide was 12.7 for controls and 16.6 for cases.

Restricting the case group to persons with B-cell lymphoma ($n = 665$) produced results similar to those for the entire sample (table 4). Restricting the cases to persons with diffuse large B-cell lymphoma ($n = 231$) resulted in generally lower effect measures, except that for ''other pesticides'' (OR = 4.96, 95 percent CI: 1.17, 21.1). When we used only cases with follicular lymphoma ($n = 227$), we found stronger associations, especially for exposures to any pesticide, organophosphates, and ''other herbicides.''

Of the 26 cases that entailed substantial exposure to pesticides, three (11.5 percent) involved T-cell subtypes as compared with 3.3 percent of the remaining 668 cases (Fisher's exact test: $p = 0.07$). Two were nasal natural killer T-cell lymphomas and one was an angioimmunoblastic T-cell lymphoma; all three contained Epstein-Barr virus early RNA upon in-situ hybridization.

DISCUSSION

We found that substantial exposure to any pesticide trebled the risk of non-Hodgkin's lymphoma. Although

TABLE 3. Relations between exposure to any pesticides and risk of non-Hodgkin's lymphoma using different metrics and sample subgroups in an Australian case-control study, 2000–2001

Metric or subgroup and degree of exposure	Controls		Cases		All subjects	
	No.	%	No.	%	Odds ratio*	95% confidence interval
Males only						
None	335	84.4	343	84.9	1.0	
Nonsubstantial	55	13.9	36	8.9	0.64	0.41, 1.00
Substantial	7	1.8	25	6.2	3.67	1.56, 8.65
Persons on electoral roll only						
None	621	89.5	525	89.9	1.0	
Nonsubstantial	64	9.2	38	6.5	0.70	0.46, 1.07
Substantial	9	1.3	21	3.6	2.89	1.30, 6.41
Probability of exposure						
None	621	89.5	621	89.5	1.0	
Possible	5	0.7	5	0.7	0.96	0.27, 3.36
Probable	68	9.8	68	9.8	1.02	0.71, 1.47
Level of exposure						
None	621	89.2	621	89.5	1.0	
Low	35	5.3	30	4.3	0.81	0.49, 1.33
Medium	21	3.0	29	4.2	1.39	0.78, 2.49
High	17	2.4	14	2.0	0.86	0.42, 1.77
Frequency of exposure						
Never	621	89.5	621	89.9	1.0	
≤4 days/year	36	5.2	32	4.6	0.89	0.54, 1.46
>4 days/year	37	5.3	41	5.9	1.14	0.71, 1.81
Years of exposure						
None or <1	626	90.2	627	90.3	1.0	
1–5	34	4.9	19	2.7	0.57	0.32, 1.02
>5	34	4.9	48	6.9	1.42	0.89, 2.25
Exposed before 1985						
No	651	93.8	644	92.9	1.0	
Yes	43	6.2	49	7.1	1.18	0.77, 1.81

* Adjusted for sex, age, ethnicity, and region of residence.

many, but not all, previous studies have found increases in non-Hodgkin's lymphoma risk with exposure to pesticides (13–19), our finding is at the high end of the range of reported results. Our definition of substantial exposure was exposure that was at or above one 10th of the time-weighted average threshold limit values for more than five 8-hour days per year for a combined total of more than 5 years. Most people exposed had the equivalent of more than 6 months of use for 8 hours per day every day.

Exposure to pesticides is often seasonal, and spraying seasons may be only a few days to a few weeks in duration each year. Many previous studies have used any exposure (14, 16) or any exposure for more than 1 year (17–19). Case-control studies that have tried to isolate persons with higher levels of exposure have found results similar to ours. For example, in a US study, exposure to pesticides for more than 10 years increased the risk nearly threefold (OR = 2.72, 95 percent CI: 1.4, 5.4) (15), and in an Italian study, exposure to herbicides for more than 10 years increased the risk 5.2-fold (16). These definitions of high exposure take into account the length of exposure, which may be the important factor in determining risk. In our data, there was a weak relation between the number of years exposed to any pesticide and non-Hodgkin's lymphoma which was of borderline significance. There was little or no increase in risk with higher levels or frequencies of exposure; thus, from our data, it seems as though any risk of non-Hodgkin's lymphoma may be related to relatively high exposure to pesticides over a long period of time.

Substantial exposure to organophosphate pesticides approximately doubled the risk of non-Hodgkin's lymphoma in our study, although this finding was not statistically

TABLE 4. Results from logistic regression analysis of the association between pesticide exposure and different subtypes of non-Hodgkin's lymphoma in an Australian case-control study, 2000–2001

Degree of exposure	B-cell lymphoma ($n = 665$)		Diffuse large B-cell lymphoma ($n = 231$)		Follicular lymphoma ($n = 227$)	
	OR*,†	95% CI*	OR†	95% CI	OR†	95% CI
Any pesticide						
None	1.0		1.0		1.0	
Nonsubstantial	0.75	0.50, 1.12	1.04	0.61, 1.76	0.56	0.29, 1.09
Substantial	2.88	1.31, 6.32	2.21	0.77, 6.35	4.3	1.73, 10.7
Organophosphates						
None	1.0		1.0		1.0	
Nonsubstantial	0.63	0.34, 1.17	0.63	0.26, 1.57	1.07	0.49, 2.33
Substantial	2.22	0.83, 5.97	2.14	0.60, 7.72	4.28	1.41, 13.0
Organochlorines						
None	1.0		1.0		1.0	
Nonsubstantial	1.13	0.52, 2.45	1.2	0.42, 3.44	1.84	0.72, 4.75
Substantial	3.46	0.69, 17.3	1.62	0.15, 18.1	3.46	0.48, 25.2
Phenoxy herbicides						
None	1.0		1.0		1.0	
Nonsubstantial	0.61	0.25, 1.47	0.45	0.10, 2.00	0.45	0.10, 2.01
Substantial	1.47	0.33, 6.64	2.16	0.36, 13.1	1.15	0.12, 11.2
Other herbicides						
None	1.0		1.0		1.0	
Nonsubstantial	1.38	0.75, 2.53	1.82	0.85, 3.91	0.64	0.21, 1.90
Substantial	3.1	0.81, 11.8	1.12	0.12, 10.9	4.83	1.06, 22.0
Other pesticides						
None	1.0		1.0		1.0	
Nonsubstantial	0.9	0.59, 1.38	1	0.55, 1.81	1.1	0.62, 1.96
Substantial	3.35	0.90, 12.5	3.18	0.63, 16.0	1.19	0.12, 11.6

* OR, odds ratio; CI, confidence interval.
† Adjusted for sex, age, ethnicity, and region of residence.

significant. A Canadian case-control study (20) found that exposure to any organophosphate insecticide was associated with a non-Hodgkin's lymphoma risk of 1.69 (95 percent CI: 1.28, 2.46), with statistically significant associations being found for malathion and diazinon. A US case-control study (21) that examined exposure to a large number of specific pesticides (adjusted for exposure to other pesticides) found significant associations with coumaphos (OR = 2.4, 95 percent CI: 1.0, 5.8) and diazinon (OR = 1.9, 95 percent CI: 1.1, 3.6) but not with malathion. However, another large US study of pesticide exposure did not find any association between organophosphate use and non-Hodgkin's lymphoma (19). It may be that different organophosphate pesticides have different effects, but we had insufficient numbers of subjects to analyze specific types of organophosphates.

Few people had substantial exposure to organochlorine pesticides in our study, so although the point estimate was quite high, the confidence intervals were wide. Previous studies have attempted to examine individual organochlorine pesticides, such as DDT, and have also found suggestive increases but wide confidence intervals (19, 21–24). Prediagnostic serum levels of various organochlorines were not associated with non-Hodgkin's lymphoma in a nested case-control study (25).

Phenoxy herbicides were not strongly associated with non-Hodgkin's lymphoma in our study. The literature on phenoxy herbicides is inconsistent. Several case-control studies have found increased risks of non-Hodgkin's lymphoma (20, 22, 23, 26, 27), while others have found no association (19, 28, 29). Cohort studies of pesticide users and manufacturers have found risks ranging from 1.0 to 2.4, not all of which were statistically significant (30–32). In general, the literature seems to show that case-control studies with more sophisticated exposure assessment (such as ours) tend to find smaller risks than those based on self-reports, which are liable to recall bias (Neil Pearce, Centre for Public Health Research, Massey University (Palmerston North, New Zealand), personal communication, 2004). In addition, studies carried out in Sweden tend to find higher risks than studies conducted elsewhere, and it is possible that conditions of use in Australia are more similar to those in New Zealand (where no increase in risk was found by

Pearce (29)) than to those in Sweden. A German study of pesticide manufacturing workers found higher risks of non-Hodgkin's lymphoma in plants where dioxin contamination of the phenoxy herbicides had occurred (33) and suggested that the risk arises from dioxin, not the herbicide itself. However, Pearce argues that this explanation does not fit the available data and that there is more likely to be a small but real increase in risk due to exposure to phenoxy herbicides (Neil Pearce, Centre for Public Health Research, Massey University, personal communication, 2004).

We found increases in the risk of non-Hodgkin's lymphoma for persons exposed to ''other herbicides'' (mainly glyphosate and carbamates) and ''other pesticides'' (mainly phosphine, arsenicals, and pyrethrins). Past and present use of phosphine as a fumigant for grain crop storage was commonly reported by subjects in our study. Arsenicals were used in Australia until the 1970s, and their use was reported by subjects only in jobs held prior to 1985. The pyrethrins were introduced in the 1980s, and reported exposures occurred mainly in the 1990s. The herbicide glyphosate has been found to be associated with non-Hodgkin's lymphoma in three case-control studies (20–22), although in the last of these studies (22) the confidence intervals included unity. Several other studies have examined exposure to carbamates and have found risks ranging from 0.9 to 1.5, mostly not statistically significant (19–22, 28, 34).

Overall, our study was limited by the relatively small numbers of subjects exposed at a substantial level. This resulted in quite wide confidence intervals, especially in the analysis of subgroups. Still, the findings were reasonably consistent in showing a statistically significant trebling of risk with high exposure to pesticides.

There was some suggestion of a stronger link between organophosphates and ''other pesticides'' with follicular non-Hodgkin's lymphomas as compared with diffuse large B-cell subtypes. Findings from studies that used earlier classifications of lymphoma (such as the Working Formulation (35)) are difficult to extrapolate to the new classifications of non-Hodgkin's lymphoma. In addition, these studies had conflicting results. One found the effect estimates for pesticides to be slightly higher for follicular lymphomas than for large-cell diffuse lymphomas (19), while another found the effect estimates to be higher for small lymphocytic non-Hodgkin's lymphoma (36). One possible mechanism is a translocation involving the immunoglobulin heavy chain t(14;18). This translocation is found in farmers with heavy exposure to pesticides (37, 38), and it is most common in follicular and diffuse large (B)-cell lymphomas in the Revised European-American Lymphoma classification of histologic subtypes (37).

Of the cases that involved substantial exposure to pesticides, more than expected were T-cell subtypes, and all of them were positive for Epstein-Barr virus early RNA. An association of nasal natural killer T-cell lymphoma with pesticide use has been reported in a father and son (39), and elevated Epstein-Barr virus antibodies have been reported in several studies of non-Hodgkin's lymphoma that included measures of pesticide exposure (24, 40), suggesting a possible interaction. One subtype of T-cell non-Hodgkin's lymphoma that has been examined is mycosis fungoides, a very rare form of T-cell non-Hodgkin's lymphoma; it does not appear to be linked with pesticide exposure (41, 42).

Small numbers of subjects in each subgroup limit the conclusions that can be made regarding associations between pesticides and histologic subtypes of non-Hodgkin's lymphoma in a single study. Collaborative studies with pooling of rare subtypes and multifactorial analyses are needed. One factor moderating the effect of pesticides is the use of personal protective equipment, such as masks and respirators, when preparing and spraying chemicals (43). We found that use of personal protective equipment was low overall and only appeared at all common in jobs held from the mid-1980s onwards. In assessing the level of exposure, the hygienist considered the use of personal protective equipment where it was used.

Exposure assessment in this study was very detailed and used the best methods available for assessing exposure to pesticides (9). A complete job history was taken from each subject, and then additional questions were asked about specific jobs, including farming, pest control, gardening, crop dusting, and janitorial work (44). The job-specific module for farmers and pesticide users was highly detailed and elicited information from subjects regarding the types of crops and animals which the hygienist found appropriate. The pesticide exposure matrix developed for the study (10) was found to be very useful for identifying the likely pesticides used. We did not rely on the subjects' recall of exactly which pesticide(s) they had used, unlike previous studies that have used self-reports for assessment of pesticide exposure. A recent study found that self-reports of pesticide exposure 20 years prior to the study were reasonable when compared with self-reports recorded 20 years earlier (45). Another study compared self-reports from licensed pesticide applicators with known dates of introduction and use of specific pesticides and found that most responses were ''plausible'' (46). In our study, approximately 10 percent of farmers answered ''unable to recall'' when asked for specific product details. A study that compared matrix-derived exposures and self-reports of pesticide use found different odds ratios for non-Hodgkin's lymphoma with use of the two measures—1.16 for matrix-derived data and 0.76 for self-reports—but offered no evidence on which of the measures better classified exposure (13).

Other studies, even recent ones, have simply used job titles as a surrogate for exposure (47–50). Problems with this method include the facts that not all people with a particular job title will be exposed to the same pesticides and that people exposed to pesticides often have a number of different job titles, resulting in small numbers for any given title.

The major limitation of the exposure assessment method we used was its cost. Review of job histories, administration of telephone interviews, and review of responses to the assigned occupational modules are highly labor-intensive. In addition, lengthy consultation with experts in agriculture, farming, and pesticide exposure monitoring was required to construct the pesticide exposure matrix. Use of an existing job exposure matrix would have been less intensive but possibly subject to significant nondifferential misclassification.

In this study, we had a reasonably large sample size and used an intensive exposure assessment process. We found increases in risk of non-Hodgkin's lymphoma with high levels of pesticide exposure and no evidence of risk with lower levels of exposure. This study strengthens the existing evidence that occupational exposure to pesticides increases risk of non-Hodgkin's lymphoma.

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