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Pesticides and Non-Hodgkin's Lymphoma[1]

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Abstract

The incidence of non-Hodgkin's lymphoma (NHL) has increased over 50% in the last 15 years. This paper reviews the possible role of pesticides in this increase. While small increases in risk of NHL among farmers have been observed in general occupational surveys, recent studies focusing on specific pesticides have observed much larger risks. Frequent use of phenoxyacetic acid herbicides, in particular, 2,4-dichlorophenoxyacetic acid, has been associated with 2- to 8-fold increases of NHL in studies conducted in Sweden, Kansas, Nebraska, Canada, and elsewhere. Canine malignant lymphoma has also been associated with dog owner use of 2,4-dichlorophenoxyacetic acid and commercial lawn pesticide treatments. There are much fewer data linking NHL to other types of pesticides, but triazine herbicides, organophosphate insecticides, fungicides, and fumigants have also been associated with increased risk of NHL. Pesticide exposures are not limited to agricultural populations but are widespread in the general population through use on lawns, golf courses, rights-of-way, and elsewhere. Since the use of pesticides, particularly phenoxy herbicides, has increased dramatically preceding and during the time period in which the incidence of NHL has increased, they could have contributed to the rising incidence of NHL.

Introduction

The incidence of NHL[2] has increased over 50% in the last 15 years (1). The United States cancer mortality time trends map for NHL during 1950–1980 shows a significant increase in the central part of the United States, a predominantly agricultural area (2). This report focuses on one group of agricultural exposures, pesticides, that might be contributing to this increase. Pesticides include herbicides (weed killers), insecticides, fungicides, and other agents. Other exposures common to agriculture that may also play a role in NHL etiology are mentioned in other reports in this volume (3, 4).

Non-Hodgkin's Lymphoma and Farming

In a recent review of the descriptive and analytical studies concerning agriculture and cancer (5), we found 21 cohort studies of farmers or broad occupational surveys of cancer that presented descriptive data on NHL and farming (Table 1). In these 21 studies, the risk ratios for NHL ranged from 0.6 to 2.6. Eleven reported excesses among farmers, but only three were statistically significant. One survey had a significantly depressed risk ratio for NHL. The range of risk ratios was not large and the excess risks were generally small. The analytical studies reviewed included both case-control studies and cross-sectional studies of NHL that evaluated the farming occupation. Of 19 such studies, 12 reported excess NHL among farmers with 8 statistically significant associations. Six studies had less than expected NHL among farmers with one significant deficit observed. The range in the risk estimates was again small, 0.6–1.9.

Both the descriptive and analytical data tend to show excesses, but are not impressive overall. This may be because they are based on the broad occupational category "farmers." Farming is a highly variable occupation with exposures that differ considerably depending upon the commodity produced. Combining farmers with different exposures would tend to dilute the effects of relevant exposures and bias risk estimates toward the null value. For example, among the population-based controls from a National Cancer Institute study in Iowa/Minnesota, 16% of those who had lived on farms had never used insecticides and 49% had never used herbicides (6). Only 40% had used phenoxyacetic acid herbicides and 20% had used organophosphate insecticides, the two most frequently used pesticide classes. If the subgroup of farmers who had used phenoxy herbicides had twice the risk of NHL as nonusers, an analysis of all farmers combined would yield a relative risk of only 1.4. Thus, it is not surprising that risks among farmers as a group are small.

Non-Hodgkin's Lymphoma and Pesticides

There have been some, but not many, studies that have tried to go beyond the job title farmer and examine the associations between specific agricultural exposures and NHL. These studies have identified the following types of pesticides as possible risk factors for NHL: phenoxyacetic acid herbicides, triazine herbicides, organophosphate insecticides, and fungicides and fumigants.

Phenoxy Herbicides. Phenoxy herbicides include 2,4-D, 2,4,5-T (banned for all uses in the United States in 1978), 2-methyl-4-chlorophenoxyacetic acid, and other related compounds. 2,4-D is one of the most commonly used broadleaf herbicides in North America (7). It is widely used in agriculture on crops such as wheat, corn, oats, rye, barley, sugar cane, and sorghum. It is also used on range and pastureland, in forestry, on rights-of-way, and on lawns and other turf, such as golf courses. The Environmental Protection Agency estimates that 40–65 million pounds of 2,4-D and related compounds are applied yearly in the United States (8).

Some death certificate-based studies have shown an association between NHL mortality and county per capita use of herbicides (9, 10), but stronger evidence linking herbicides and, in particular, phenoxy herbicides to NHL comes from interview-based case-control studies. In 1981, Hardell *et al.* from Sweden [11] reported a 6-fold risk of malignant lymphoma among persons exposed to phenoxyacetic acids or chlorophenols. Although no site-specific relative risks were presented, the authors said that the association existed for both NHL and Hodgkin's disease. We conducted a population-based case-control study of NHL in Kansas that showed a 2-fold excess (odds ratio, 2.2) of NHL among farmers who used phenoxy herbicides (12). Risk rose with days per year of use of herbicides to over 7-fold among those reporting use for 21 or more days per year and who specifically reported use of 2,4-D, a trend that was highly significant (Table 2). The risk was higher among farmers who did not regularly use protective equipment when applying pesticides. The association could not be explained by exposure to other herbicides, insecticides, or other risk factors for NHL.

We obtained similar findings from a study in Nebraska (13). An overall risk of 1.5 for NHL was found among farmers who

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[2] The abbreviations used are: NHL, non-Hodgkin's lymphoma; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

Table 1 *Review of epidemiologic studies concerning farming and non-Hodgkin's lymphoma*[a]

Study type	No. of studies	RR[b] range	RR> 1.0	RR> 1.0[c]	RR< 1.0	RR< 1.0[c]
General occupational surveys or farmer cohorts	21	0.6–2.6	11	3	7	1
Case-control or cross-sectional	19	0.6–1.9	12	8	6	1

[a] Source: Blair and Zahm, 1991 (5).
[b] RR, risk ratio.
[c] Statistically significant.

mixed or applied 2,4-D. Risk rose to 3.3 for farmers who handled 2,4-D 21 or more days per year (Table 2). Risk also rose the longer farmers wore their application work clothes before changing to clean work garments. This finding is consistent with investigations that show the dermal route is the most important for 2,4-D and most other pesticide exposures (14). Although the risks were lower than in Kansas, the patterns were similar.

A New Zealand case-control study of NHL, using other cancers as controls, found no excess risk associated with potential exposure to phenoxy herbicides (15, 16). In a later report, Pearce (17) examined NHL risk by days per year of phenoxy herbicide use in these New Zealand data (Table 2). The trend was not significant, but risk did increase to a 2-fold level in the 10–19 days per year category and then decreased to 1.1. Considering all three studies, it is hard to dismiss these risks as due to chance. It should be noted that, in contrast to the United States where the phenoxy herbicide evaluated was 2,4-D, the predominant phenoxy herbicide in use in New Zealand was 2,4,5-T.

There have been three other case-control studies, conducted in Washington State, Sweden, and Italy, that examined the association between herbicides and NHL (18–20). None had information on days per year. In Italy, a significant trend with duration of exposure to herbicides was observed (20). In a Swedish study, Persson *et al.* (19) reported an odds ratio of 4.9 (95% confidence interval, 1.3–18) for NHL for occupations exposed to phenoxy acids. A study in Washington State reported significant odds ratios of 1.3 for farmers and 4.8 for persons who sprayed forests with herbicides. Most other exposed occupations had nonsignificantly elevated risks (16). In a second report, the Washington farmers who used 2,4-D had no elevation in NHL risk, but, again, no days per year data were available (21).

Another Swedish report, by Olsson and Brandt (22), is interesting and unusual in that the authors examined the risk for patients with cutaneous NHL. Phenoxy herbicides were associated with an odds ratio of 1.3 for NHL overall, but with an odds ratio of 10.0 for NHL localized to the skin.

In a cohort mortality study of male farmers in Saskatchewan, Canada, NHL was associated with use of herbicides, as recorded in the 1971 Census of Agriculture (23). Among farmers with operations of less than 1000 acres, risk ratios rose significantly with the number of acres sprayed with herbicides from 1.3 for less than 100 acres, 1.9 for 100–249 acres, to 2.2 for 250 or more acres (Table 3). No other cause of death showed this pattern. Although the association is with herbicides in general, the authors noted that 90% of the herbicides used by weight in Saskatchewan in the 1960s and 75% in the 1970s was 2,4-D. It seems unlikely, therefore, that the association could be due to some herbicide other than 2,4-D.

Three manufacturing cohorts exposed to phenoxy herbicides have demonstrated slight excesses of NHL, based on small numbers of cases (Table 4) (24–26). A cohort study of cancer incidence among Swedish licensed pesticide applicators did not show an excess of NHL, but the predominant phenoxy herbicide was 2-methyl-4-chlorophenoxyacetic acid, with much less 2,4-D and 2,4,5-T used (27). An international cohort study of both manufacturing production workers and applicators exposed to a variety of phenoxy herbicides in 10 countries showed a small, nonsignificant excess in mortality from NHL among production workers, but not applicators (28).

The most recent study, to our knowledge, to be published on herbicides and lymphoma was a hospital-based case-control study of lymphoma in dogs (29). Excess risk was associated with the dog owners' use of 2,4-D on their lawns and/or treatment of yards by commercial lawn care companies (Table 5). The risk of canine lymphoma rose significantly to a 2-fold excess with 4 or more yearly owner applications of 2,4-D.

Other Pesticides. There are much fewer data linking NHL to pesticides other than phenoxy herbicides. Triazine herbicides were associated in the Kansas case-control study (12). For atrazine, a member of the triazine family, an odds ratio of 2.7 (95% confidence interval, 1.2, 5.9) was observed. In Nebraska, farmers who used atrazine for more than 15 years had a 2-fold risk of NHL (13). The Nebraska study also demonstrated a more

Table 2 *Number of white male NHL cases and controls and odds ratios by days per year of exposure to herbicides in Kansas, Nebraska, and New Zealand*[a]

State	Type of herbicide	Days/yr	No. of NHL cases	No. of controls	Odds ratio[b]
Kansas	2,4-D users:	0	37	286	1.0
	Days/yr exposed to herbicides[c]	1–2	6	17	2.7
		3–5	4	16	1.6
		6–10	4	16	1.9
		11–20	4	9	3.0
		21+	5	6	7.6
Nebraska	Days/yr handled 2,4-D[d]	0	54	184	1.0
		1–5	16	44	1.2
		6–20	12	25	1.6
		21+	3	4	3.3
New Zealand	Use of phenoxy herbicides (primarily 2,4,5-T)[e]	0	139	266	1.0
		1–4	20	40	0.9
		5–9	8	11	1.2
		10–19	4	3	2.2
		20+	5	7	1.1

[a] Source: Hoar et al., 1986 (12), Zahm *et al.*, 1990 (13), Pearce, 1989 (17).
[b] Statistically significant.
[c] Kansas: *P*-value for trend, 0.0001.
[d] Nebraska: *P*-value for trend, 0.051.
[e] New Zealand: *P*-value for trend, 0.290.

Table 3 *Number of NHL deaths and relative risks (RR) for acres sprayed with herbicides in 1970, restricted to farms less than 1000 acres, in Saskatchewan farmers, 1971–1985*[a]

Acres sprayed	No. of NHL deaths	RR (95% CI)[b]
0	35	1.0
1–99	14	1.3 (0.7, 2.4)
100–249	28	1.9 (1.2, 3.3)
250+	10	2.2 (1.0, 4.6)

[a] Source: Wigle *et al.*, 1990 (23).
[b] RR (95% CI), relative risk (95 % confidence interval), multivariate Poisson regression analysis.

Table 4 *Number of observed and expected number of NHL deaths and standardized mortality ratios (SMR) for manufacturing and pesticide applicator cohorts exposed to phenoxyacetic acid herbicides*

Cohort type	Study	Ref. no.	No. of NHL deaths	No. of expected deaths	SMR
Manufacturing	Bond (1988)	24	2	0.5	391
	Coggon (1991)	25	2	0.7	272
	Fingerhut (1991)	26	10	7.3	137
	Saracci (1991)[a]	28	8	5.4	149
Applicators	Wiklund (1987)[b]	27	21	20.8	101
	Saracci (1991)	28	3	6.3	49

[a] Saracci *et al.* (28) is an international study with data from 10 countries and includes both manufacturing production workers and pesticide applicators.
[b] Wiklund *et al.* (27) studied cancer incidence, so the data represent numbers of cases and standardized morbidity (or incidence) ratios.

Table 5 *Number of canine malignant lymphoma cases and controls and odds ratios (OR) by dog owners' use of 2,4-D and/or commercial lawn treatment*[a]

Owner application of 2,4-D and/or commercial lawn treatment	No. of cases	No. of controls	OR
None or dog never allowed in yard	300	641	1.0
Yes	191	304	1.3[b]
Commercial treatment only	115	189	1.3
Owner applied 2,4-D only	60	99	1.3
Both	16	16	1.9
No. of dog owner applications of 2,4-D/yr[c]			
1	20	34	1.3
2	28	47	1.3
3	11	17	1.3
4+	17	17	2.0

[a] Source: Hayes *et al.*, 1991 (29).
[b] Statistically significant.
[c] *P*-value for trend < 0.02.

than 2-fold risk of NHL associated with use of organophosphate insecticides (odds ratio, 2.4), adjusted for 2,4-D use. Chlorophenols have been linked to NHL in case-control studies from New Zealand (16, 17) and Sweden (11), although the New Zealand findings were not statistically significant. Fungicides in general were associated with NHL in Kansas (12). Grain millers, exposed to fungicides and fumigant pesticides, have been reported to have excess NHL (30). A nested case-control study within a cohort mortality study of 22,938 grain millers reported a 4-fold excess of NHL among flour mill employees. Risk rose to 9-fold after 25 years of follow-up. Garry *et al.* (31) reported that fumigant applicators previously exposed, 6 weeks to 3 months earlier, to phosphine or to phosphine plus other pesticides, had significantly increased stable chromosome rearrangements, primarily translocations in G-banded lymphocytes.

Evaluation of the Role of Pesticides in the Increasing Incidence of Non-Hodgkin's Lymphoma

Studies from a number of countries and a variety of exposure situations suggest that pesticides may contribute to the development of NHL. To determine the proportion of the recent increases in NHL incidence that may be caused by pesticides, we need better information on the risks associated with specific pesticide exposures, information on the prevalence of pesticide exposures, and, in particular, information on the changes of exposure over time.

To refine risk estimates, future research on pesticides and NHL needs to incorporate improved exposure assessment techniques. Considering farmers or other pesticide applicators as a group, without detailed exposure data, introduces misclassification and dilutes risk estimates (32, 33). Two approaches should be used. First, etiologic studies may need to be preceded by methodological research to assess the reliability and validity of current techniques used to estimate agricultural exposures and to develop new approaches. This would provide a better basis for exposure assessment in retrospective studies. Another approach would be to conduct a prospective study of an agricultural population (men, women, and farm dependents), which would provide the opportunity for repeated exposure assessment. The need for better exposure data extends beyond occupational situations to general population contacts that may arise from lawn care treatments and other pesticide uses in urban areas. Research on biomarkers of exposure and intermediate outcomes are needed to shed light on the mechanisms of action of pesticides. Possible areas of research include the role of phenoxy herbicides in immunosuppression, peroxisome proliferation, and other epigenetic mechanisms.

The prevalence of use of phenoxy herbicides has changed over the last 45 years, going from essentially zero in 1945 to one of the most commonly used pesticide classes in the United States in 1989 (8). The phenoxy herbicides were discovered in 1942 and were first field tested during World War II by the United States government with the goal of destroying the Japanese rice crop (34). Since 1965, the amount of herbicides used per year in the United States has quadrupled while insecticide use has declined slightly (35).

It is important to remember that pesticide exposures are not limited to agricultural workers. Approximately 70 million pounds of pesticides are applied on lawns each year (36) and the use of lawn care pesticides is increasing 5 to 8% annually (37). The Environmental Protection Agency has estimated that in 1988 as many as 11% of single family households used a commercial lawn care service (36), with about twice as many householders applying pesticides to their lawns themselves (37). The amount of pesticides per treated acre of household lands is almost five times the application rate for treated agricultural lands (38).

Conclusion

In conclusion, NHL is associated with pesticide use, particularly phenoxy herbicides. Exposure to phenoxy herbicides is widespread in the agricultural and general populations. The use has increased dramatically preceding and during the time period in which the incidence of NHL has increased, which could explain at least part of the rising incidence of NHL.

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