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Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma

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A population-based case-control study of soft-tissue sarcoma (STS), Hodgkin's disease (HD), and non-Hodgkin's lymphoma (NHL) in Kansas found farm herbicide use to be associated with NHL (odds ratio [OR], 1.6; 95% confidence interval [CI], 0.9, 2.6). Relative risk of NHL increased significantly with number of days of herbicide exposure per year and latency. Men exposed to herbicides more than 20 days per year had a sixfold increased risk of NHL (OR, 6.0; 95% CI, 1.9, 19.5) relative to nonfarmers. Frequent users who mixed or applied the herbicides themselves had an OR of 8.0 (95% CI, 2.3, 27.9) for NHL. Excesses were associated with use of phenoxyacetic acid herbicides, specifically 2,4-dichlorophenoxyacetic acid. Neither STS nor HD was associated with pesticide exposure. This study confirms the reports from Sweden and several US states that NHL is associated with farm herbicide use, especially phenoxyacetic acids. It does not confirm the case-control studies or the cohort studies of pesticide manufacturers and Vietnam veterans linking herbicides to STS or HD.

(*JAMA* 1986;256:1141-1147)

EPIDEMIOLOGIC studies from Sweden have suggested that workers exposed to phenoxyacetic acid herbicides and chlorophenols are at excess risk of soft-tissue sarcoma (STS), Hodgkin's disease (HD), and non-Hodgkin's lymphoma (NHL).¹⁻³ For all three cancers, risks were increased fivefold to sixfold, regardless of whether exposures were contaminated by polychlorinated dibenzodioxins or di-

benzofurans. There have also been several reports of increased STS and NHL among workers producing phenoxyacetic acid herbicides^{4,7} and among farmers.⁸⁻¹⁰

See also p 1176.

Concern over possible carcinogenic risks from phenoxyacetic acids and chlorophenols is heightened by the potential for widespread exposure. In addition to herbicide formulations used in agriculture and in the Vietnam war, these chemicals occur in blue stain retardants used in sawmills, slime control preparations in paper and pulp manufacturing, cutting oils and fluids, wood preservatives, waterproofing

agents for leather and textiles, and medications.¹ For these reasons, a population-based case-control study was conducted to clarify whether agricultural use of herbicides and insecticides affects risk of STS, HD, and NHL in the United States.

METHODS

Kansas, a major wheat-producing state, was chosen as the location for the study, since herbicides have been used more frequently than other pesticides on wheat. 2,4-Dichlorophenoxyacetic acid (2,4-D) has been the most commonly used herbicide in Kansas; substantial amounts of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) have also been used, along with myriad other chemicals.¹¹

Cases

All newly diagnosed cases of STS, HD, and NHL among white male Kansas residents, aged 21 years or older, from 1976 through 1982, were identified through the University of Kansas (Kansas City) Cancer Data Service, a population-based registry covering the state of Kansas. Cancer reporting, mandated by Kansas law, is considered complete, as evidenced by a higher annual incidence rate for STS (4.1/100 000) than reported by the nearby Iowa National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results registry (3.4/100 000). There were 200 men diagnosed with

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Table 1.—Soft-Tissue Sarcoma, Hodgkin's Disease, and Non-Hodgkin's Lymphoma in Relation to Duration and Frequency of Herbicide Use

	Soft-Tissue Sarcoma			Hodgkin's Disease		Non-Hodgkin's Lymphoma	
	No. of Controls	No. of Cases	Odds Ratio (95% Confidence Interval)	No. of Cases	Odds Ratio (95% Confidence Interval)	No. of Cases	Odds Ratio (95% Confidence Interval)
Nonfarmers	286	38	1.0	50	1.0	37	1.0
Farmers	662	95	1.0 (0.7, 1.6)	71	0.8 (0.5, 1.2)	133	1.4 (0.9, 2.1)
Duration of herbicide use, y							
0	470	73	1.1 (0.7, 1.8)	43	0.7 (0.5, 1.2)	93	1.3 (0.8, 2.1)
1-5	53	5	0.7 (0.2, 2.0)	9	0.9 (0.4, 2.2)	9	1.3 (0.6, 3.1)
6-15	58	5	0.7 (0.2, 1.9)	8	0.8 (0.3, 1.9)	12	1.6 (0.7, 3.4)
≥16	57	11	1.4 (0.6, 3.1)	10	1.2 (0.5, 2.6)	16	2.0 (1.0, 4.0)
Unknown	24	1	...	1	...	3	...
χ for trend			0.13		0.11		2.06
P (one-tailed)			.45		.46		.02
Frequency of herbicide use, d/y							
0	497	74	1.1 (0.7, 1.7)	45	0.7 (0.4, 1.1)	94	1.3 (0.8, 2.0)
1-5	102	9	0.6 (0.3, 1.5)	16	1.0 (0.5, 1.9)	19	1.4 (0.7, 2.6)
6-10	29	2	0.5 (0.1, 2.3)	2	0.4 (0.1, 1.7)	6	1.6 (0.5, 4.3)
11-20	13	5	2.9 (0.8, 9.5)	2	1.3 (0.2, 6.8)	5	2.6 (0.8, 8.8)
≥21	12	1	0.8 (0.04, 6.5)	3	1.0 (0.2, 4.1)	7	6.0 (1.9, 19.5)
Unknown	9	4	...	3	...	2	...
χ for trend			0.002		-0.56		3.33
P (one-tailed)			.50		.29		.0004

STS and 173 men with HD. A random sample of 200 men was drawn from the 297 men diagnosed with NHL from 1979 through 1981.

Pathology specimens for 87% of the cases were reviewed by a panel of three pathologists to confirm the diagnoses and to standardize the subgroup terminology.^{12,13} Specimens for the remaining cases either could not be obtained (11%) or were of poor or insufficient quantity to allow review (2%). For STS, HD, and NHL cases, the confirmation rates were 81%, 85%, and 90%, respectively. Among the eligible histologically confirmed cases, 139 were STS, 132 HD, and 172 NHL.

Controls

The controls were white men from the general population of Kansas. Three controls (N=1005) were matched to each patient on age (± 2 years) and vital status. For living patients, controls aged 65 years or older were selected from the Health Care Financing Administration file (Medicare), whereas controls aged 64 years or younger were selected by telephone, using a two-staged random digit-dialing technique.¹⁴ Control selection was not biased by differences in telephone coverage for urban (91%) and rural (90%) white Kansan households.¹⁵ For

92.3% of the working residential telephone numbers called, a person answered who was willing to provide the names and ages of household members aged 21 to 64 years and, if someone in the household was selected as a control, the household address. For deceased patients, the controls were selected from Kansas state mortality files, with the additional matching factor of year of death. Persons with a cause of death of STS, HD, NHL, a malignancy of an ill-defined site (*International Classification of Diseases code 195*), homicide, or suicide were excluded. One half of the patients with STS and NHL died before the initiation of the study, while only one third of the patients with HD had died. The next of kin were interviewed for deceased subjects. The same controls were used for comparisons with the three different cancer series when of comparable age.

Interview

The patients and controls, or their next of kin, were interviewed by telephone between December 1982 and January 1984. The questions on farming practices covered the calendar years working or living on farmland during which any of four specific crops (wheat, corn, sorghum, or pasture) were grown or livestock was raised, the

farm locations and sizes, herbicides and insecticides used, years and acres treated, names and locations of companies where pesticides were purchased, method of application, days per year exposed, and use of protective equipment. Information on other crops was not obtained; however, in 1978, these four crops constituted 94% of Kansas farm acreage and 87% of acres treated with herbicides.^{11,16} All but four subjects who lived or worked on farmland as adults grew at least one of the four specified crops.

Interviews were obtained from 133 patients with STS, 121 with HD, 170 with NHL, and 948 controls, which represented 95% of the eligible subjects (patients, 96%; controls, 94%). The overall response rate, a weighted average accounting for the initial refusals in the random digit-dialing control selection process, was 93%.

Pesticide Suppliers' Survey

To evaluate potential observation bias, corroborative evidence of the self-reported pesticide exposures was sought for a sample of 130 subjects with farming experience. Suppliers for 110 subjects were located and provided information on the subject's crops and herbicide and insecticide purchases.

Table 2.—Non-Hodgkin's Lymphoma in Relation to Herbicide Group

Herbicide Group	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)
Never farmed	37	286	1.0
Ever use*			
Phenoxyacetic acids	24	78	2.2 (1.2, 4.1)
Triazines	14	43	2.5 (1.2, 5.4)
Amides	8	22	2.9 (1.1, 7.6)
Benzoics	1	2	4.0 (0.1, 62.6)
Carbamates	2	3	5.6 (0.6, 45.9)
Trifluralin	3	2	12.5 (1.6, 116.1)
Uracils	19	114	1.3 (0.7, 2.5)
Nonspecified	8	11	5.8 (1.9, 17.2)
Hierarchical use†			
Phenoxyacetic acids	24	78	2.2 (1.2, 4.1)
Uracils; no phenoxyacetic acids	13	101	1.0 (0.5, 2.1)
Triazines; no phenoxyacetic acids or uracils	3	11	2.2 (0.4, 9.1)
Amides; no phenoxyacetic acids, uracils, or triazines	0	1	...

*Farmers could report more than one group.

†Farmers were assigned to only one group.

Risk Measurements

The measure of association between pesticide exposures and risk of cancer was the odds ratio (OR). All estimates were adjusted for the effects of age by stratification. Maximum likelihood estimates of the overall risk and the 95% confidence interval (CI) were computed by Gart's method.¹⁷ Matched analyses yielded results similar to those provided by the unmatched approach. The unmatched analyses are presented since they allowed control of additional factors that were not matching factors and increased power by pooling controls for each case series. For duration-response relationships, significance was assessed by means of Mantel's one-tailed linear trend test.¹⁸ Logistic regression was also performed to evaluate simultaneously several components of pesticide exposure.¹⁹

RESULTS

Ninety-five patients with STS, 71 with HD, and 133 with NHL reported having worked or lived on farmland, compared with 662 controls, yielding ORs of 1.0 (95% CI, 0.7, 1.6), 0.8 (95% CI, 0.5, 1.2), and 1.4 (95% CI, 0.9, 2.1), respectively (Table 1). No trend with years spent working or living on a farm was observed. Risks did not vary by crop or farm acreage.

Herbicides

Farm herbicide use on any of the four specific crops (wheat, corn, sor-

ghum, or pasture) was reported by 22 patients with STS, 28 with HD, and 40 with NHL, compared with 192 controls, yielding ORs of 0.9 (95% CI, 0.5, 1.6), 0.9 (95% CI, 0.5, 1.5), and 1.6 (95% CI, 0.9, 2.6), respectively. There was a significant trend ($P=.02$) in risk of NHL with increasing years of herbicide use and with number of days of herbicide exposure per year ($P=.0004$) (Table 1). Persons exposed to herbicides more than 20 days per year had an OR of 6.0 (95% CI, 1.9, 19.5). There was no association with years of herbicide use after adjustment for annual days. On the other hand, adjustment for years of herbicide use changed the OR for the five patients and six controls exposed more than 20 days per year from 6.0 to 7.4 (95% CI, 1.6, 38.9), relative to the least exposed users. The risk of NHL associated with herbicide use did not change significantly when restricted to exposures incurred before 1976, the earliest possible date of death for the pooled control series. The NHL risk also rose with increasing time since first exposure. Farmers who started using herbicides after 1965, from 1956 through 1965, 1946 through 1955, and before 1946 had ORs of 1.3, 1.7, 1.7, and 3.3, respectively. This trend was diminished by controlling for frequency of herbicide use, but farmers who began use before 1946 still had an excess risk (OR, 2.2). No association was seen with number of acres treated with herbicides. No consistent patterns of excess

risk of STS or HD were seen with either duration or frequency of herbicide use. More detailed analyses showed no association between agricultural factors and the occurrence of STS or HD, so the remainder of this report will describe only the NHL results.

Subjects who reported usually mixing or applying the herbicides themselves (OR, 1.9; 95% CI, 1.1, 3.3) had higher risks for NHL than those who reported that someone else performed these functions (OR, 1.1). Indeed, the trends in the OR with increasing frequency and duration of use derived mainly from the workers who mixed or applied the herbicides themselves. For example, men who mixed or applied the herbicides and who were exposed for one to five, six to ten, 11 to 20, and more than 20 days per year had ORs of 1.4 (95% CI, 0.7, 3.0), 1.5 (95% CI, 0.5, 4.6), 1.8 (95% CI, 0.4, 7.4), and 8.0 (95% CI, 2.3, 27.9; seven patients, nine controls). Farmers who did not use protective equipment, such as rubber gloves or masks, had a higher OR associated with herbicide use (OR, 2.1; 95% CI, 1.0, 4.2) than those who protected themselves (OR, 1.5; 95% CI, 0.7, 3.1). Higher risks for herbicide use were also seen among farmers who used backpack or hand sprayers (OR, 2.3; 95% CI, 1.0, 5.2), an application method with greater potential for personal exposure than other methods.²⁰ After excluding persons who used backpack or hand sprayers, the ORs for tractor-mounted or mist-blower spraying and aerial application of herbicides were both 1.5. Too few subjects remained for evaluation of the group that applied herbicides only in the soil.

A logistic regression analysis was performed to examine risk accounting for all pesticide exposure variables simultaneously. The results showed that age and annual days of herbicide exposure were significantly related to NHL risk. Restricting the analysis to persons exposed to herbicides and using categorical variables yielded ORs of 1.1 (95% CI, 0.3, 4.0), 1.3 (95% CI, 0.3, 6.0), and 10.3 (95% CI, 2.1, 49.5) for persons exposed to herbicides six to ten, 11 to 20, and more than 20 days per year, respectively, relative to persons exposed one to five days per year. Increased risk was also associated with use of a backpack or hand sprayer (OR, 1.3; 95% CI, 0.5, 3.7) and failure to use protective equipment (OR, 2.0; 95% CI, 0.8, 5.1). Total period of herbicide use was not associated with NHL when the other pesticide exposure variables were controlled. The effect of personally mixing or applying herbicides could not be evaluated; the overwhelming major-

Table 3.—Non-Hodgkin's Lymphoma in Relation to Duration, Frequency, and Latency of 2,4-Dichlorophenoxyacetic Acid Use

	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)
Never farmed	37	298	1.0
Duration of use,* y			
1-5	3	16	1.3 (0.3, 5.1)
6-15	7	22	2.5 (0.9, 6.8)
16-25	8	15	3.9 (1.4, 10.9)
≥26	6	17	2.3 (0.7, 6.8)
χ for trend	3.580
P (one-tailed)	.0002
Frequency of use,† d/y			
1-2	6	17	2.7 (0.9, 8.1)
3-5	4	16	1.6 (0.4, 5.7)
6-10	4	16	1.9 (0.5, 6.7)
11-20	4	9	3.0 (0.7, 11.8)
≥21	5	6	7.6 (1.8, 32.3)
χ for trend	3.733
P (one-tailed)	.0001
First year of use‡			
1966 or later	5	21	1.9 (0.6, 6.0)
1956-1965	9	23	2.9 (1.1, 7.2)
1946-1955	6	24	2.1 (0.8, 5.6)
Before 1946	2	2	6.2 (0.6, 65.3)
χ for trend	3.561
P (one-tailed)	.0002

*Five controls had missing data.

†One patient and ten controls had unknown frequency of exposure.

‡First available for use in 1942.

ity of subjects involved in the logistic analysis either mixed or applied the herbicides themselves.

Significant excesses were associated with ever use of phenoxyacetic acids, triazines (eg, atrazine, cyanazine, metribuzin, prometon, propazine, terbutryn), amides (eg, alachlor, propachlor), trifluralin, and nonspecified herbicides, such as "liquids," "sprays," and "dusts" (Table 2). Most farmers reported use of chemicals in several of the herbicide subgroups. Since the a priori hypotheses dealt with phenoxyacetic acids, we assessed risks associated with herbicides ranked in a hierarchical manner (Table 2). In the absence of phenoxyacetic acid exposure, the NHL risk associated with triazine exposure was reduced to 1.9 (95% CI, 0.4, 8.0) and the risk with uracil herbicides (eg, bromacil, terbacil) was reduced to 1.0 (95% CI, 0.5, 2.1).

In this study, phenoxyacetic acid herbicide use was essentially synonymous with use of 2,4-D (OR, 2.3; 95% CI, 1.3, 4.3), since only three patients and 18 controls had used 2,4,5-T, and all but two of these controls had also used 2,4-D. Use of 2,4-D only, ie, eliminating 2,4,5-T users, was associated with an OR of 2.6 (95% CI, 1.4, 5.0). There were significant, although inconsistent, increases in NHL risk in relation to the duration, frequency, and latency of 2,4-D use (Table 3). The 2,4-D users exposed to herbicides more

Table 4.—Non-Hodgkin's Lymphoma in Farmers in Relation to Use of Herbicides and Insecticides

Annual Days of Use	Never Used Insecticides			Ever Used Insecticides			Adjusted for Insecticide Use		
	No. of Cases	No. of Controls	Odds Ratio* (95% Confidence Interval)	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)	No. of Cases	No. of Controls	Odds Ratio (95% Confidence Interval)
Herbicides									
0	90	474	1.0	4	21	1.1 (0.3, 3.5)	94	495	1.0
1-5	11	57	1.1 (0.5, 2.3)	8	43	1.2 (0.5, 2.9)	19	100	1.1 (0.6, 2.1)
≥6	6	18	2.1 (0.7, 5.9)	12	35	2.3 (1.0, 4.9)	18	53	2.1 (0.9, 4.9)
Insecticide use, adjusted for herbicide use						1.1 (0.6, 2.2)			
	Never Used Herbicides			Ever Used Herbicides			Adjusted for Herbicide Use		
	No. of Cases	No. of Controls	Odds Ratio* (95% Confidence Interval)	No. of Cases	No. of Controls	Odds Ratio* (95% Confidence Interval)	No. of Cases	No. of Controls	Odds Ratio* (95% Confidence Interval)
Insecticides									
0	90	474	1.0	17	75	1.3 (0.7, 2.4)	107	549	1.0
1-2	2	12	0.9 (0.1, 4.2)	8	30	1.7 (0.7, 4.1)	10	42	1.2 (0.5, 2.8)
≥3	2	9	1.5 (0.2, 8.1)	12	48	1.7 (0.8, 3.5)	14	57	1.4 (0.6, 3.1)
Herbicide use, adjusted for insecticide use						1.4 (0.8, 2.4)			

*Odds ratio relative to farmers, no herbicide or insecticide use.

than 20 days per year had an OR of 7.6 (95% CI, 1.8, 32.3). However, these variables cannot be determined with complete accuracy because the questionnaire elicited dates and frequency of use of any herbicide on each farm instead of dates and frequency for each specific herbicide. Therefore, the actual years or days of 2,4-D use may be less than that reported for all herbicides on a farm.

Risk associated with herbicide exposure was also examined by subgroups of NHL. There were no differences in the ORs associated with herbicide use when cases were categorized by histologic types (follicular, diffuse, and not specified) and by grade (prognostic groupings of low, intermediate, and high), as classified by the National Cancer Institute Working Formulation.¹³ In addition, no significant differences in risk for any tumor were associated with either age at diagnosis or vital status at interview. Deceased subjects had just slightly lower risks of NHL associated with overall herbicide exposure (OR, 1.5; 95% CI, 0.7, 3.3) or long-term exposure (OR, 5.5; 95% CI, 0.7, 41.3) than did living subjects (OR, 1.7; 95% CI, 0.8, 3.7; and OR, 5.6; 95% CI, 1.1, 28.9; respectively).

Insecticides

Insecticide use on crops or animals was reported by 54 patients with NHL and 275 controls, yielding an OR of 1.5 (95% CI, 0.9, 2.4). There was no association with increasing years of insecticide use. Risk increased significantly but inconsistently with days of exposure per year. Men exposed to insecticides more than six days per year had a 2.8-fold increased NHL risk (95% CI, 1.2, 6.5). Farmers who started using insecticides after 1965, from 1956 through 1965, 1946 through 1955, and before 1946 had ORs of 1.5, 0.7, 1.5, and 1.7, respectively. No association was seen with number of acres treated with insecticides. Other exposure variables, such as mixing and applying insecticides, application method, and insecticide type, showed little or no association with NHL risk.

Herbicides vs Insecticides

Table 4 shows that NHL risk increased with annual days of herbicide exposure, but was not further increased by simultaneous use of insecticides. Adjustment for insecticide exposure did not alter the ORs for herbicide use. On the other hand, risk increased only slightly with annual days of insecticide exposure within strata of herbicide use. Adjustment for herbicide use decreased the OR for

insecticide use from 1.5 to 1.1 (95% CI, 0.6, 2.2). Similar analyses based on years of exposure also suggested that risk was more strongly associated with exposure to herbicides than to insecticides. The number of subjects was too small for a more detailed stratified analysis of herbicide or insecticide use. In a logistic analysis of all pesticide variables, insecticide exposure was not found to be significantly related to risk. The important variables remained age and annual days of herbicide exposure.

The elevation in NHL risk (OR, 1.3) seen among farmers who did not report herbicide use may be due to other exposures encountered in farming activities or to biased misclassification of exposure status. However, it is not likely that more patients than controls underreported herbicide exposure. Slightly fewer "nonexposed" farming patients with NHL (52%) than controls (55%) were deceased, with interviews supplied by next of kin who might underreport exposures. Approximately the same percentage of "nonexposed" farming patients (4%) and controls (5%) were usually employed in agriculture.

Fungicides

Thirty-two patients with NHL and 105 controls treated seeds with fungicides (OR, 2.1; 95% CI, 1.2, 3.7). Risk was elevated among both herbicide users (22 patients, 68 controls; OR, 2.3; 95% CI, 1.2, 4.3) and farmers who had never used herbicides (ten patients, 37 controls; OR, 1.9; 95% CI, 0.8, 4.4). No other information on fungicide use was collected to allow further evaluation of this association.

Pesticide Suppliers' Data

Suppliers usually reported less pesticide use than subjects. Agreement on specific years of exposure was better for insecticide use than herbicide use. There were no consistent differences between agreement rates for patients and controls. Multiplying the number of patients and controls who reported any herbicide use by the percentage of verified herbicide use yielded a recalculated OR of 1.8 for NHL, which was slightly higher than the OR based on interview data only (1.6). Agreement between suppliers and subjects improved when pesticide use during the last ten years was considered.

Nonfarming Exposures

Nonfarming exposures did not confound the association between NHL and agricultural use of herbicides. Nonfarming pesticide use in home gardens

and yards was not associated with NHL. The OR associated with ever smoking at least 100 cigarettes was slightly below 1 (OR, 0.7; 95% CI, 0.5, 1.0), as it was for lifetime consumption of at least 100 cups of coffee (OR, 0.8; 95% CI, 0.5, 1.4). Consumption of raw, unpasteurized milk products had no effect on NHL risk (OR, 1.1; 95% CI, 0.8, 1.6). Eight patients with NHL had diabetes, half the expected number (OR, 0.5; 95% CI, 0.2, 1.2). No subjects had systemic lupus erythematosus, celiac disease, or immunodeficiency syndromes or had received immunosuppressive drugs. Seven patients with NHL reported previous radiation treatment (OR, 0.9; 95% CI, 0.4, 2.2). Subjects reporting a family history of cancer had a significant risk of NHL (OR, 2.3; 95% CI, 1.6, 3.2). Three patients and four controls reported a relative with lymphoma (OR, 4.0; 95% CI, 0.7, 22.2).

COMMENT

This investigation confirms the results of the case-control study by Hardell et al² that initially suggested an association between herbicide use and NHL. Our finding of a sixfold increase of NHL among farmers exposed to herbicides more than 20 days per year is consistent with the sixfold excess risk associated with exposure to either phenoxyacetic acids or chlorophenols in the Swedish study. In both Sweden and Kansas, risk was elevated among persons exposed to phenoxyacetic acids, eg, 2,4-D, not likely to be contaminated by dioxins.^{21,22} These findings are consistent also with a number of descriptive studies suggesting increased lymphoma risk among agricultural workers, particularly in regions where herbicide use is common.^{8-10,23,24}

Cohort studies of pesticide manufacturing workers and applicators have in general been too small to examine adequately the risk of NHL. Danish workers manufacturing 2-methyl-4-chlorophenoxyacetic acid had seven NHL deaths with 5.4 expected, a non-significant 30% excess.²⁵ No NHL cases have been observed in five other cohort studies of exposed workers, but the total number of workers involved was only 2705.²⁶⁻²⁸ Also, the Vietnam veteran experience offers little evidence to date for an association between NHL and herbicide exposure. The mortality study of 1247 men who applied herbicides in Project Ranch Hand reported no deaths due to lymphoma, as of December 1982,³⁰ but less than one such death was expected in this small cohort.

An unusual presentation of NHL of

the scalp was reported in two men of 158 who developed chloracne while employed in a British plant manufacturing pentachlorophenol.²¹ The expected number of cases of cutaneous NHL was far less. A similar association of cutaneous NHL with occupations involving spraying phenoxyacetic acid herbicides was found in Sweden.³² In our study, only one patient had cutaneous NHL, but he reported no herbicide exposure.

An association between phenoxyacetic acid herbicides and NHL may have biologic plausibility through the relationships between dioxin contaminants and the immune system, as postulated by Hardell et al.³ Dioxin suppresses cell-mediated immunity³³ and causes thymic involution in laboratory animals,³⁴ while NHL occurs excessively in various immunodeficiency states of humans.³⁵⁻³⁷ Dioxin is also a potent animal carcinogen, with the risk seen for squamous cell carcinomas of the lung, hard palate/nasal turbinates/tongue, hepatocellular carcinomas, follicular cell thyroid adenomas, and skin fibrosarcomas.³⁸⁻⁴³ However, it should be noted that 2,4-D, the herbicide most frequently used by subjects in this study, has not been shown to be carcinogenic in animals⁴⁴ or immunosuppressive^{21,45} (S. Wong, PhD, written communication, Dec 12, 1985). 2,4-Dichlorophenoxyacetic acid does not contain 2,3,7,8-tetrachlorodibenzo-p-dioxin, the most carcinogenic dioxin isomer, although other less toxic isomers may occur.^{21,22} The increased risk for farmers first using 2,4-D before 1946 may indicate the presence of carcinogenic impurities in the early formulations, with subsequent improvements in the manufacturing process. Alternatively, the high risk of NHL among persons exposed 40 years ago may reflect a long latency period. The technology necessary to identify the isom-

ers of the contaminants was not available in the early time period.²¹

The Swedish case-control studies and several of the industrial cohort studies have been criticized on a variety of grounds, including possible inaccurate diagnoses, observation and/or recall bias, and lack of control for confounding variables.^{5,46} The current study was designed to address a number of these concerns. The cases were drawn from all incident cases in a defined population. Included for analysis were only cases histologically confirmed as NHL by an expert review panel. The response rate for both cases and controls was high. The relationship between NHL and herbicide use was specific: there was no relationship between such use and the two other cancer sites studied, and the association was with herbicide and not insecticide use. Indeed, the association was limited to two subcategories of herbicides, phenoxyacetic acids and triazines. This degree of specificity argues against a significant role for either observation or recall bias in the association. In addition, independent assessments of herbicide exposure (as reported by self or next of kin, and by pesticide supplier) yielded similar estimates of risk. Finally, while the origins of NHL in the general population are largely unknown, some known risk factors (eg, immune-altering conditions and drugs, family history)^{35,37,47-54} as well as several speculative factors (eg, cigarette smoking, coffee consumption, ionizing radiation)^{5,52,56-57} were assessed and found not to confound the herbicide association.

Several circumstances offered opportunities for inaccuracies in the assessment of pesticide exposures. These include the memories of subjects, the knowledge of relevant practices by next of kin, the vagueness of some questions concerning exposure, and the opportu-

nities for more than one pesticide supplier per subject. The evidence suggests that the errors introduced by these factors are likely to be similar for cases and controls. This random misclassification of exposure would tend to dilute risk estimates, rather than produce spurious associations. While this may have led us to miss an association between pesticide use and STS or HD, it is unlikely to have created the association with NHL. If inaccurate exposure assessment occurred, we would have underestimated the magnitude of the risks involved. If the risks reported are accurate, and if they reflect a true causal relationship, then the amount of NHL in the current study attributable to herbicide exposure would be 11%.⁵⁸

Despite the limitations of the exposure information, the sixfold excess risk of NHL among high-intensity users of herbicides is cause for concern, particularly since the association was mainly for phenoxyacetic acids and was apparent using several different measures of exposure. Since over 42 million pounds of phenoxyacetic acid herbicides were applied to US farmlands in 1976,⁵⁹ the carcinogenic effects suggested by this study and others have important public health implications.

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