# 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 dibenzofurans. 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, sorghum, 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 | 286 | 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 | 3.560 | ... | ... |
| *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 | 8 | 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, prometone, 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: No. of Cases | No. of Controls | Odds Ratio* (95% Confidence Interval) | Ever Used Insecticides: No. of Cases | No. of Controls | Odds Ratio (95% Confidence Interval) | Adjusted for Insecticide Use: 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) | | | |

| Annual Days of Use | Never Used Herbicides: No. of Cases | No. of Controls | Odds Ratio* (95% Confidence Interval) | Ever Used Herbicides: No. of Cases | No. of Controls | Odds Ratio* (95% Confidence Interval) | Adjusted for Herbicide Use: 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 al[3] 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 nonsignificant 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.[26-29] 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.[31] 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 immunity[33] 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 animals[44] 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 isomers 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)[5,52,55-57] 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 opportunities 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.

The study was supported in part by contract N01-CP-ES-11027 from National Cancer Institute.

We thank Ariel B. Baker and Naomi E. Washburn for assisting the study manager; Rita Kingma, Lois I. Murphy, and Jeanine M. Peterson for interviewing; Vesta Gee and Claudia J. Oblak for coding; Shelley Hobbs and Melanie Wall for secretarial assistance; Joan L. Van Nice, Pros Bunag, and Dolores Wiesmann for identifying and locating study subjects; Fritz Lin, MD, and H. Clarke Anderson, MD, for reviewing pathology samples; Edward Brown, Ila Dave, and Ko Jam Liu for computer programming; and Richard H. Adamson, PhD, Susan M. Sieber, PhD, and Elizabeth K. Weisburger, PhD, for reviewing the manuscript.

## References

1. Hardell L, Sandstrom A: Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer* 1979; 39:711-717.
2. Eriksson M, Hardell L, Berg NO, et al: Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. *Br J Ind Med* 1981;38:27-33.
3. Hardell L, Eriksson M, Lenner P, et al: Malignant lymphoma and exposure to chemicals especially organic solvents, chlorophenols and phenoxy acids: A case-control study. *Br J Cancer* 1981; 43:169-176.
4. Honchar PA, Halperin WA: 2,4,5-T,trichlorophenol, and soft-tissue sarcoma. *Lancet* 1981; 1:268-269.
5. Cook RR: Dioxin, chloracne, and soft-tissue sarcoma. *Lancet* 1981;1:618-619.
6. Moses M, Selikoff IJ: Soft-tissue sarcomas, phenoxy herbicides, and chlorinated phenols. *Lancet* 1981;1:1370.
7. Johnson FE, Kugler MA, Brown SM: Soft-tissue sarcomas and chlorinated phenols. *Lancet* 1981; 2:40.
8. Cantor KP: Farming and mortality from non-Hodgkin's lymphoma: A case-control study. *Int J Cancer* 1982;29:239-247.
9. Burmeister LF, Everett GD, Van Lier SF, et al: Selected cancer mortality and farm practices in Iowa. *Am J Epidemiol* 1983;118:72-77.
10. Buesching DP, Wollstadt L: Cancer mortality among farmers. *JNCI* 1984;72:503.
11. Waldron AC, Park EL: *Pesticide Use on Major Crops in the North Central Region . . . 1978*, research bulletin 1132, Wooster, Ohio, Ohio Agricultural Research and Development Center, 1981.
12. *International Classification of Disease for Oncology*. Geneva, World Health Organization, 1976.
13. Non-Hodgkin's Lymphoma Pathologic Classification Project: NCI sponsored study of classification of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112-2135.
14. Waksberg J: Sampling methods for random digit dialing. *J Am Stat Assoc* 1978;73:40-46.
15. *Census of the Population: 1970*, vol 1, *General Housing Characteristics*, pt 18, *Kansas*. US Bureau of the Census, 1973.
16. Kansas Crop and Livestock Reporting Service: *Pesticides: 1978 Pesticide Usage*. Topeka, Kan, US Dept of Agriculture, Economics, Statistics, and Cooperatives Service.
17. Gart JJ: Point and interval estimation of the common odds ratio in the combination of 2×2 tables with fixed marginals. *Biometrika* 1970; 57:471-475.
18. Mantel N: $\chi^2$ test with 1 degree of freedom, extension of the Mantel-Haenzel procedure. *Am Stat Assoc J* 1963;58:690-700.

19. Engelman L: *Stepwise Logistic Regression in BMDP STATISTICAL SOFTWARE*, Dixon WJ (ed). Berkeley, University of California Press, 1983, pp 330-344.
20. Libich S, To JC, Frank R, et al: Occupational exposure of herbicide applicators to herbicides used along electric power transmission line right-of-way. *Am Ind Hyg Assoc J* 1984;45:56-62.
21. International Programme on Chemical Safety: *Environmental Health Criteria 29: 2,4-Dichlorophenoxyacetic Acid (2,4-D)*. Geneva, World Health Organization, 1984.
22. Cochrane WP, Singh J, Miles W, et al: Determination of chlorinated dibenzo-*p*-dioxin contaminants in 2,4-D products by gas chromatography-mass spectrometric techniques. *J Chromatogr* 1981;217:289-299.
23. Stubbs HA, Harris J, Spear RC: A proportionate mortality analysis of California agricultural workers, 1978-1979. *Am J Ind Med* 1984;6:305-320.
24. Pearce NE, Smith AH, Fisher DO: Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. *Am J Epidemiol* 1985;121:225-237.
25. Lynge E: A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer* 1985;52:259-270.
26. Zack JA, Suskind RR: The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *J Occup Med* 1980;22:11-14.
27. Ott MG, Holder BB, Olson RD: A mortality analysis of employees engaged in the manufacture of 2,4,5-trichlorophenoxyacetic acid. *J Occup Med* 1980;22:47-50.
28. Cook RR, Townsend JC, Ott MG, et al: Mortality experience of employees exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *J Occup Med* 1980;22:530-532.
29. Riihimaki V, Asp S, Hernberg S: Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: First report of an ongoing prospective cohort study. *Scand J Work Environ Health* 1982;8:37-42.
30. *Project Ranch Hand II: An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides, Baseline Mortality Study Results.* Brooks Air Force Base, Tex, Epidemiology Division, Data Sciences Division, US Air Force School of Aerospace Medicine, 1983.
31. Bishop CM, Jones AH: Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. *Lancet* 1981;2:369.
32. Olsson H, Brandt L: Non-Hodgkin's lymphoma of the skin and occupational exposure to herbicides. *Lancet* 1981;2:579.
33. Vos JG, Moore JA, Zinkl JG: Effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the immune system of laboratory animals. *Environ Health Perspect* 1973;5:149-162.
34. Harris MW, Moore JA, Vos JG, et al: General biological effects of TCDD in laboratory animals. *Environ Health Perspect* 1973;5:101-109.
35. Hoover R, Fraumeni JF Jr: Risk of cancer in renal transplant recipients. *Lancet* 1973;2:55-57.
36. Kinlen LJ, Sheil AGR, Peto J, et al: Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 1979;1461-1466.
37. Filipovich AH, Spector BD, Kersey J: Immunodeficiency in humans as a risk factor in the development of malignancy. *Prev Med* 1980;9:252-259.
38. Crow KD: Soft tissue sarcomas and chlorinated phenols. *Lancet* 1981;2:369.
39. Kociba RJ, Keyes DG, Beyes JE, et al: Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in rats. *Toxicol Appl Pharmacol* 1978;46:279-303.
40. Kociba RJ, Keyes DG, Beyer JE, et al: Long-term toxicologic studies of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in laboratory animals. *Ann NY Acad Sci* 1979;320:397-404.
41. Van Miller JP, Lalich JJ, Allen JR: Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Chemosphere* 1977;10:625-632.
42. *National Toxicology Program (Report 80-31): Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (Gavage Study)*, technical report series 209, National Institutes of Health publication 82-1765. Research Triangle Park, NC, Dept of Health and Human Services, 1982.
43. *National Toxicology Program (Report 80-32): Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study)*, technical report series 209, National Institutes of Health publication 82-1757. Research Triangle Park, NC, Dept of Health and Human Services, 1982.
44. Young AL, Calcagni JA, Thalken CE, et al: *The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin*, US Air Force technical report 78-92. Brooks AFB, Tex, US Air Force Occupational and Environmental Health Laboratory, 1978.
45. Blakely BR, Schiefer BH: The effect of topically applied n-butylester of 2,4-dichlorophenoxyacetic acid on the immune response in mice. *J Appl Toxicol*, in press.
46. Cole P: Direct testimony before the Administrator of the Environmental Protection Agency of the United States of America in re. The Dow Chemical Company, et al. FIFRA Docket No. 415, et al, Washington, DC, Oct 23, 1980.
47. Li FP, Fraumeni JF Jr, Mantel N, et al: Cancer mortality among chemists. *JNCI* 1969;43:1159-1164.
48. Olin GR: The hazards of a chemical laboratory environment: A study of the mortality in two cohorts of Swedish chemists. *Am Ind Hyg Assoc J* 1978;39:557-562.
49. Searle CE: Epidemiologic study of the mortality of British chemists. *Br J Cancer* 1978;38:192-193.
50. Monson RR, Fine LJ: Cancer mortality and morbidity among rubber workers. *JNCI* 1978;61:1047-1053.
51. Cantor KP, Fraumeni JF Jr: Distribution of non-Hodgkin's lymphoma in the United States between 1950 and 1975. *Cancer Res* 1980;40:2645-2652.
52. Kalant N, Seemayer T: Malignant lymphoma in spontaneously diabetic rats. *N Engl J Med* 1979;300:737.
53. Green JA, Dawson AA, Walker W: Systemic lupus erythematosus and lymphoma. *Lancet* 1978;2:753-756.
54. Douglas AP: Celiac disease and lymphoma of intestines and brain. *N Engl J Med* 1977;296:821.
55. Vianna NJ, Polan A: Lymphomas and occupational benzene exposure. *Lancet* 1979;2:1394-1395.
56. Paffenbarger RS, Wing AL, Hyde RT: Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias. *JNCI* 1978;60:89-92.
57. Krikorian JG, Burke JS, Rosenberg SA, et al: Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. *N Engl J Med* 1979;300:452-458.
58. Cole P, MacMahon B: Attributable risk percent in case-control studies. *Br J Prev Soc Med* 1971;25:242-244.
59. Eichers TR, Andrilenas PA, Anderson TW: *Farmers' Use of Pesticides in 1976*, agricultural economic report 418. National Economic Analysis Division, Economics, Statistics, and Cooperatives Service, US Dept of Agriculture, 1978.

Frequency of Elevated* Serum Pesticide Metabolite Levels in Exposed Dairy-Farm Families Compared With National Background Data

| Population | Prevalence of Elevated Serum Analytes (%) | | |
|---|---|---|---|
| | Heptachlor Epoxide | Oxychlordane | Transnonachlor |
| Exposed farm-family members | 9/39† (23.1) | 9/39† (23.1) | 12/39† (30.8) |
| Participants in NHANES II‡ | 118/3172 (3.7) | 126/3174 (4.0) | 205/3174 (6.5) |

*Greater than or equal to 1 ppb.

†$P < .01$ by Fisher's exact test (two tailed).

‡NHANES II indicates Second National Health and Nutrition Examination Survey.

ranging up to 89.2 ppm (fat basis). Subsequently, thousands of gallons of milk and other dairy products were taken off of local groceries' shelves after laboratory analyses showed heptachlor epoxide contamination levels in the milk as high as 12.6 ppm (fat basis). These levels were over ten times greater than the Food and Drug Administration action level of 0.1 ppm (fat basis).[3]

*Study.*—To assess the potential extent of human exposures and health effects, we studied a group of people at highest risk of exposure, namely, dairy-farm families who consumed undiluted raw milk products known to be contaminated. Using a standardized questionnaire, we elicited from study participants basic demographic data and information about their consumption of dairy products. We also collected serum samples for pesticide analyses and for both routine liver function tests (LFTs) and specific assays for hepatic microsomal enzyme induction.

We compared results of analyses for the 45 study participants (representing 13 families) with national background population data collected in the Second National Health and Nutrition Examination Survey[4] and with unexposed reference populations from neighboring states. As shown in the Table, there was a statistically significant increased prevalence of serum pesticide levels elevated above 1 ppb among the farm-family members. Both before and after adjustment for age and sex differences, using analysis of covariance, the farm-family members had statistically significant higher mean levels of serum heptachlor epoxide (0.81±0.94 ppb), serum oxychlordane (0.70±0.75 ppb), and serum transnonachlor (0.79±0.60 ppb) compared with an unexposed urban population from this same region of the United States (Diane Rowley, MD, written communication, April 1, 1986). In logistic regression analyses and analysis of covariance in which we adjusted for age and sex, the high-risk farm-family members did not show increased prevalence of abnormally elevated LFT results or any consistent pattern of subclinical differences in mean LFT results, compared with a reference population of healthy, unexposed persons.[5]

*Comment.*—The purpose of this study was to evaluate the magnitude of exposures and the presence of acute and subacute health effects in a group of high-risk persons; it was not intended to address long-term, chronic disease risks (such as carcinogenesis). On the basis of these data, we concluded that, although there was evidence of somewhat elevated serum concentrations of heptachlor metabolites, these high-risk persons did not exhibit related metabolic effects. Thus, we were able to offer reassurance to persons in the general community that they are likely to be in no danger, since they were at even lower risk of exposure than were the members of the dairy-farm families whom we tested.

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1. Casarett LJ, Doull J: *Toxicology: The Basic Science of Poisons.* New York, Macmillan Publishing Co Inc, 1976.
2. Consolidated heptachlor/chlordane hearings. *Federal Register* 1976;41(Feb 19):7552-7585.
3. Heptachlor and heptachlor epoxide in milk: Revision of regulatory level. *Federal Register* 1982;47(Oct 26):47466.
4. Murphy R, Harvey C: Residues and metabolites of selected persistent halogenated hydrocarbons in blood specimens from a general population survey. *Environ Health Perspect* 1985;60:115-120.
5. Hoffman RE, Stehr-Green PA, Webb KB, et al: Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *JAMA* 1986;255:2031-2038.

## Attractive Method for Battery Removal

*To the Editor.*—We appreciated the article by Kavanagh and Litovitz[1] entitled "Miniature Battery Foreign Bodies in Auditory and Nasal Cavities." We would like to add the use of a magnet to the list of possible battery retrieval methods. Use of a magnet to remove batteries from the stomach has been described,[2] but, to our knowledge, a magnet has not been used for removal of batteries from other orifices. A magnetized screwdriver worked very well in the following case.

*Report of a Case.*—A 9-year-old girl awoke with acute otalgia in the left ear immediately after her 5-year-old playmate inserted a miniature toy watch battery in her ear canal. Her intense pain continued and she was examined in our clinic about 90 minutes after the incident. The battery was lodged midway in the canal and efforts to retrieve the battery with alligator forceps were unsuccessful and painful. After an intense hunt for a magnet, a hospital maintenance person brought several magnetized tools to the clinic. The first attempt with a magnetized screwdriver successfully and painlessly removed the battery. Examination of the ear canal showed moderate erythema of the canal without swelling or erosion. No further treatment was necessary.

*Comment.*—Since physicians are increasingly likely to be faced with a miniature battery as a foreign body in a body orifice, we propose that a magnet should be tried first to retrieve the battery. (The presence of a metal tympanotomy tube or similar metal appliance would probably be the only contraindication.) Perhaps medical offices and emergency rooms should be equipped with a permanently magnetized probe or a magnetized screwdriver!

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1. Kavanagh KT, Litovitz T: Miniature battery foreign bodies in auditory and nasal cavities. *JAMA* 1986;255:1470-1472.
2. Yasuo I, Noriyuki I, Satoru S: Magnetic removal of alkaline batteries from the stomach. *J Pediatr Surg* 1985;20:250-251.

## CORRECTION

**Incorrect Table Title.**—An error occurred in the article entitled "Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma," published in the Sept 5 issue of THE JOURNAL (1986;256:1141-1147). On page 1144, the title of Table 3 should have read as follows: "Table 3.—Non-Hodgkin's Lymphoma in Relation to Duration, Frequency, and Latency of Herbicide Use Among 2,4-Dichlorophenoxyacetic Acid Users" (not ". . . Duration, Frequency, and Latency of 2,4-Dichlorophenoxyacetic Acid Use").