1990

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[CANCER RESEARCH 50, 6585-6591, October 15, 1990]

Pesticide Exposures and Other Agricultural Risk Factors for Leukemia among Men in Iowa and Minnesota

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ABSTRACT

Mortality surveys and death certificate studies have suggested an association between leukemia and farming. To investigate whether exposure to carcinogens in an agricultural setting is related to risk of leukemia, the authors conducted a population-based case-control interview study of 578 white men with leukemia and 1245 controls living in Iowa and Minnesota. Consistent with recent mortality studies, there were slight, but significant, elevations in risk for all leukemia [odds ratio (OR) 1.2] and chronic lymphocytic leukemia (OR 1.4) for farmers compared to nonfarmers. There were no significant associations with leukemia for exposure to specific fungicides, herbicides (including 2,4-D and 2,4,5-T), or crop insecticides. However, significantly elevated risks for leukemia of ≥2.0 were seen for exposure to specific animal insecticides including the organophosphates crotoxyphos (OR 11.1), dichlorvos (OR 2.0), and famphur (OR 2.2) and the natural product pyrethrins (OR 3.7) and the chlorinated hydrocarbon methoxychlor (OR 2.2). There were also smaller, but significant, risks associated with exposure to nicotine (OR 1.6) and DDT (OR 1.3). This finding of elevated risks for insecticides used on animals deserves further evaluation.

INTRODUCTION

A number of mortality surveys and death certificate studies have suggested that farmers may experience elevated rates of leukemia (1-9). However, specific agents that account for this association have not been identified. Farmers routinely perform many tasks and may come in contact with a variety of potentially hazardous substances including pesticides, paints, fuels and solvents, engine exhausts, grain dusts, and zoonotic viruses and microbes. A number of these substances, including the pesticides DDT,[1] chlordane, and dichlorvos have demonstrated carcinogenic effects in animal studies (10, 11). To investigate whether exposure to agricultural pesticides or other agricultural exposures are related to the risk of leukemia, we conducted a case-control study of leukemia in Iowa and Minnesota, states with large agricultural populations where mortality rates for leukemia exceed the national average (12, 13).

MATERIALS AND METHODS

Initial Interview. Parallel population-based case-control interview studies of leukemia (including myelodysplasias, a condition thought to be related to acute non-lymphocytic leukemia) and non-Hodgkin's lymphoma were conducted in Iowa and Minnesota during 1981-1984. The present paper presents results for the leukemia cases and the pooled controls.

All newly diagnosed cases of leukemia among white men aged 30 years or older were ascertained from tumor registry or hospital records both retrospectively (1 year before the start of the study) and prospectively (2 years after the start of the study). Because survival for adult leukemia is generally poor, approximately 26% of the ascertained cases were deceased or too ill to be interviewed when identified for inclusion in the study and an additional 15% were found to be deceased or too ill at the time of interview.

In Iowa, cases were ascertained from March 1981 to October 1983 through the Iowa Tumor Registry. In Minnesota, a special surveillance network including hospitals and pathology laboratories was created to identify all cases occurring between October 1980 and September 1982. Participating hospitals in Minnesota provided 97% of the beds available in the state during the study period. Since the design of the study was to investigate potential agricultural hazards, cases residing in cities with little farming activity (*i.e.*, Minneapolis, St. Paul, Duluth, and Rochester) at the time of diagnosis were excluded from the study.

Pathology slides for all cases were reviewed by regional pathologists. Because myelodysplasias presented some diagnostic problems, they received a special review by one of us (F. D.). A total of 669 cases of leukemia (including both living and deceased cases) were eligible for inclusion in the study.

Controls were a population-based stratified sample of white men without lymphatic or hematopoietic cancer frequency matched to the leukemia and non-Hodgkin's lymphoma cases by 5-year age group, vital status at time of interview, and state of residence. Controls were selected from three sources: 474 living controls younger than 65 years from random digit dialing (14), 519 living controls ≥65 years from Medicare records provided by the Health Care Financing Administration, and 550 deceased controls from state death certificate files. Residents of Minneapolis, St. Paul, Duluth, and Rochester, MN, were not eligible to be selected as controls.

During 1981-1984, in-person interviews lasting approximately 50 min were conducted with the subjects or with close relatives if the subjects were deceased or unable to be interviewed. A standardized questionnaire was used to obtain detailed information concerning residential history, drinking water sources, non-farm occupational history, smoking and alcohol use, use of unpasteurized dairy products, medical conditions, family history of cancer, and farm activities. The questions regarding farming covered farm locations and the number and types of animals and crops raised. Information concerning the use of 24 animal insecticides, 34 crop insecticides, 38 herbicides, and 16 fungicides used on the farm was also obtained. This included the first and last year used and whether the subject personally mixed or applied the pesticide. The usual number of days per year that each pesticide was used was not collected in the initial interview.

Interviews were completed for 86% of the cases. The response rates were 77% [telephone screener response rate (87.5%) × interview response rate (88%)] for the random digit dialing controls, 79% for the Health Care Financing Administration controls, and 77% for the deceased controls. The final study population consisted of 578 (340 living, 238 deceased) cases and 1245 (820 living, 425 deceased) controls. The number of cases from Iowa (n = 293) and Minnesota (n = 285) were approximately equal. The most common cell type was CLL (n = 244, 42.2%), followed by ANL (n = 143, 24.7%), myelodysplasias (n = 63, 10.9%), CML (n = 51, 8.8%), acute lymphocytic leukemia (n = 16, 2.8%), and other (n = 61, 10.9%). The median age was 67 years for cases and 66 years for controls.

Supplemental Interview. In 1987, a supplemental interview of the Iowa subjects who participated in the initial interview was conducted

Received 4/9/90; accepted 7/13/90.

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[1] The abbreviations used are: DDT, dichlorodiphenyltrichloroethane; CLL, chronic lymphocytic leukemia; ANL, acute non-lymphocytic leukemia; CML, chronic myelogenous leukemia; OR, odds ratio; CI, confidence intervals; 2, 4-D, 2,4-dichlorophenoxyacetic acid; 2, 4, 5-T, 2, 4, 5-trichlorophenoxyacetic acid.

to obtain information regarding the usual number of days per year that each previously reported pesticide had been handled. We restricted the supplemental interview to the 92 cases and 211 controls or their next of kin from Iowa who had reported agricultural use of pesticides in their initial interview. The 10-min supplemental questionnaire was administered by trained interviewers over the telephone. It sought information concerning the number of days per year that each pesticide reported in the initial interview was personally handled by the study subject during two time periods (before and after 1960).

A total of 90 cases and 203 controls (97% of those eligible) were located for reinterview. Of those located, interviews were completed for 86 (23 living, 63 deceased) cases and 203 (146 living, 57 deceased) controls.

Statistical Analysis. The OR comparing farmers with the exposure of interest to nonfarmers provided the measure of association between agricultural exposures and the risk of leukemia with 95% CI calculated by the method of Gart (15). ORs among farmers exposed to individual pesticides and families of pesticides were calculated for all leukemia and for the leukemia cell types, when there were sufficient numbers of exposed subjects. Presented are ORs for those pesticides that were personally handled by at least five cases or five controls. ORs for pesticides handled by farmers in the supplemental interview were calculated using the 243 case and 547 control nonfarmers from the initial interview as the nonexposed group. Risks were also calculated using only Iowa nonfarmers as the unexposed group, but the ORs were similar. ORs computed separately for the number of days a pesticide was handled before and after 1960 were similar to ORs for the larger of these two measures (maximum frequency of pesticide use), so only the combined results are presented. Unconditional binary logistic models (16, 17) were used to calculate risks for all leukemia for the farm and pesticide variables of interest. Risks for the specific histological types of leukemia were calculated using a computer program for polychotomous logistic models developed by the Epidemiology and Biostatistics Program of the National Cancer Institute. Vital status (alive, dead), age (<45, 45–64, ≥65 years), state (Iowa, Minnesota), ever used tobacco daily (yes, no), parent, sibling, or child with a lymphopoietic cancer (yes, no), nonfarming job related to risk of leukemia in this study (yes, no), and exposure to substances (benzene, naphtha, hair dyes) related to risk of leukemia in this study (yes, no) were included in all models to adjust for potential confounding.

RESULTS

Farming. There was a small, but significant, risk for all leukemia (OR 1.2) among persons who lived or worked on a farm as an adult (Table 1). More than half of the cases (58%) and the controls (56%) reported some farm activity. Significantly elevated risks were also seen for CLL among farmers (OR 1.4) (Table 1). ORs were not positively associated with duration of farming for all leukemia or for any individual cell type. Risks were the lowest for those employed as farmers for ≥45 years.

Crops and Animals. Neither the risk for all leukemia nor for any specific cell type was significantly elevated among farmers by type of crop grown or by type of livestock raised. There were also no significant patterns by acres of crops grown or by number of livestock handled (data not presented).

Ever Use of Pesticides. Most of the farmers [258 cases (77%), 603 controls (86%)] reported use of at least one pesticide (OR for leukemia, 1.1; 95% CI 0.9–1.4). Although farmers who reported no exposure to pesticides were at increased risk for leukemia (OR 1.9, 95% CI 1.3–2.9), this finding was seen in Iowa (OR 2.9, 95% CI 1.7–5.0; 42 cases, 37 controls) but not in Minnesota (OR 0.8, 95% CI 0.4–1.8; 10 cases, 28 controls). The pesticide exposure for the remainder of the farmers was unknown.

The risks of leukemia according to ever use of types of

Table 1 *Risk of leukemia according to number of years farmed and ever use of types of pesticides*[a]

		Leukemia subtype																			
		All leukemia			Acute non-lymphocytic			Chronic myelogenous			Chronic lymphocytic			Acute lymphocytic			Myelodysplasias			Other		
	Co[b]	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI	Ca	OR	95% CI
Never farmed	547	243	1.0		62	1.0		24	1.0		88	1.0		9	1.0		31	1.0		29	1.0	
Ever farmed	698	335	1.2	1.0–1.5	81	1.2	0.8–1.8	27	1.1	0.6–2.0	156	1.4	1.1–1.9	7	0.9	0.3–2.5	32	0.8	0.5–1.4	32	1.0	0.6–1.6
Farmed (yr)																						
1–9	158	85	1.3	0.9–1.7	20	1.3	0.7–2.2	9	1.5	0.7–3.3	40	1.6	1.0–2.4	2	1.1	0.2–5.2	12	1.3	0.7–2.7	2	0.2	0.1–1.0
10–29	183	93	1.2	0.9–1.7	26	1.4	0.8–2.3	6	0.9	0.4–2.3	33	1.2	0.8–1.9	4	1.2	0.3–3.9	9	0.9	0.4–1.9	15	1.7	0.9–3.2
30–44	178	95	1.4	1.0–1.8	22	1.4	0.8–2.4	7	1.2	0.5–3.0	55	2.0	1.3–3.0	0			5	0.5	0.2–1.4	6	0.8	0.3–2.1
45+	165	59	0.9	0.6–1.3	12	0.8	0.4–1.7	5	0.1	0.4–3.1	28	1.1	0.7–1.8	0			5	0.5	0.2–1.4	9	1.4	0.6–3.3
Unknown	14	3			1			0			0			1			0			0		
Used any fungicide	62	33	1.3	0.8–2.1	13	2.3	1.2–4.7	2	0.9	0.2–4.0	14	1.4	0.7–2.7	0			2	0.7	0.2–3.2	2	0.7	0.2–3.3
Used any herbicide	344	157	1.2	0.9–1.6	39	1.3	0.8–2.0	16	1.3	0.7–2.6	74	1.4	1.0–2.0	2	0.5	0.1–2.2	10	0.7	0.3–1.5	16	1.0	0.5–2.0
Used any insecticide	588	250	1.1	0.9–1.3	58	1.0	0.7–1.6	20	1.0	0.5–1.8	122	1.3	1.0–1.8	5	0.8	0.2–2.5	16	0.6	0.3–1.1	29	1.1	0.6–1.8
Animal	563	238	1.1	0.8–1.3	53	1.0	0.7–1.5	20	1.0	0.5–1.9	118	1.3	1.0–1.8	5	0.8	0.2–2.6	15	0.6	0.3–1.1	27	1.1	0.6–1.9
Crop	319	134	1.1	0.8–1.4	32	1.1	0.6–2.1	14	1.2	0.6–2.5	59	1.2	0.8–1.8	3	0.8	0.2–3.0	10	0.7	0.3–1.6	16	1.1	0.6–2.1
Animal and crop	294	122	1.1	0.8–1.4	27	1.0	0.6–1.6	14	1.3	0.7–2.7	55	1.2	0.8–1.8	3	0.8	0.2–3.2	9	0.7	0.3–1.6	14	1.1	0.5–2.1

[a] All OR relative to risk for subjects who were never farmers. All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposure in a logistic analysis.
[b] *Co*, controls; *Ca*, cases.

pesticides are presented in Table 1. For all leukemia, the ORs were not significantly elevated among farmers reporting the use of any fungicide (OR 1.3), any herbicide (OR 1.2), or any insecticide (OR 1.1). When risks were calculated for each histological type, ORs were significantly elevated for ANL for use of any fungicide (OR 2.3) and for CLL for use of any herbicide (OR 1.4), any insecticide (OR 1.3), and any animal insecticide (OR 1.3).

Pesticide Families. ORs for leukemia by families of pesticides are presented for herbicides in Table 2 and insecticides in Table 3. Risk of all leukemia was not associated with use of any herbicide family. None of the ORs which ranged from 0.9 to 1.5 were statistically significant, nor were significantly elevated risks seen for any of the specific histological types.

Although none of the ORs for all leukemia were significantly elevated for use of any insecticide family on crops (Table 3), ORs for use of insecticide families on animals were significantly elevated for the natural products (OR 1.5) and organophosphate (OR 1.5) families. Within the organophosphate family, significantly elevated ORs for leukemia of ≥2.0 were seen for use of halogenated aliphatic, halogenated aromatic, and nonhalogenated aromatic organophosphate animal insecticides. For nonhalogenated aromatic organophosphate crop insecticides, the OR was nonsignificantly elevated (OR 2.5). For the leukemia subtypes, significantly elevated risks were seen for CLL for carbamates used on crops (OR 2.0, 95% CI 1.1–3.5; 21 cases), carbamates used on animals (OR 3.1, 95% CI 1.0–9.3; 5 cases), and organophosphate insecticides used on animals (OR 1.7, 95% CI 1.0–2.8; 25 cases). The organophosphate excess occurred with halogenated aliphatics (OR 2.9, 95% CI 1.5–5.6; 16 cases), halogenated aromatics (OR 2.7, 95% CI 1.2–6.3; 9 cases), and nonhalogenated aromatics (OR 2.5, 95% CI 1.0–6.4; 10 cases).

Selected Pesticides. The OR for all leukemia for subjects who handled captan, the only fungicide used by enough farmers for analysis, was 1.5 (95% CI 0.7–3.3; 10 cases, 17 controls). ORs for the two most common cell types were 2.5 (95% CI 0.8–7.2; 5 cases) for CLL and 1.5 (95% CI 0.4–5.4; 3 cases) for ANL.

Risks for all leukemia also were not significantly increased among subjects who personally mixed, handled, or applied specific herbicides (Table 4). Nonsignificantly elevated ORs (>1.5) were seen for MCPA and profuralin. When the analyses were restricted to persons first exposed to specific herbicides ≥20 years before interview, risks increased for MCPA (OR 2.4, 95% CI 0.7–8.2; 5 cases, 6 controls) and 2,4,5-T (OR 1.8, 95% CI 0.8–4.0; 11 cases, 18 controls).

Among specific cell types, ORs for those who ever handled 2,4-D were 1.5 (95% CI 0.9–2.5; 28 cases) for ANL, 1.9 (95% CI 0.9–3.9; 13 cases) for CML, and 1.3 (95% CI 0.8–2.0; 45 cases) for CLL. The OR for those who handled 2,4,5-T was 2.1 (95% CI 0.9–4.9; 8 cases) for ANL and 1.6 (95% CI 0.7–3.4; 10 cases) for CLL. The risk for those who first handled 2,4,5-T at least 20 years prior to interview was significantly elevated for CLL (OR 3.3, 95% CI 1.2–8.9; 7 cases, 18 controls).

Table 5 presents ORs for subjects who ever personally mixed, handled, or applied selected crop insecticides. Nonsignificantly elevated risks >1.5 were seen for ethoprop and lindane. When the analysis was restricted to subjects who had first handled crop insecticides at least 20 years prior to interview, risks increased for carbaryl (OR 4.1, 95% CI 1.1–1.4; 6 cases, 4 controls) and malathion (OR 1.7, 95% CI 0.5–5.3; 5 cases, 8 controls) but decreased for lindane (OR 1.2, 95% CI 0.5–3.2; 7 cases, 5 controls). For the leukemia histological types, nonsignificantly elevated risks (≥1.5) were seen for CLL (OR 1.6, 95% CI 0.9–3.0; 16 cases) and CML (OR 2.4, 95% CI 0.9–6.5; 6 cases) among those farmers who reported handling DDT.

ORs for all leukemia for subjects who ever personally mixed, handled, or applied selected animal insecticides and for subjects who first mixed, handled, or applied these insecticide at least 20 years before interview are shown in Table 6. Without latency considerations, significantly elevated risks were seen for crotoxyphos (OR 11.1), DDT (OR 1.3), dichlorvos (OR 2.0), famphur (OR 2.2), methoxychlor (OR 2.2), nicotine (OR 1.6), and pyrethrins (OR 3.7). Nonsignificantly elevated risks >1.5 were seen for ronnel and tetrachlorvinphos. Risks for those subjects who had first handled these insecticides at least 20 years prior to interview were generally greater than for all users combined. Risks more than doubled for carbaryl and famphur.

Significantly elevated risks by histological type (without latency considerations) were seen for CLL among persons who ever handled the animal insecticide dichlorvos (OR 2.2, 95% CI 1.0–4.6; 11 cases) and nicotine (OR 1.8, 95% CI 1.0–3.5; 15 cases) and for CML among farmers who ever handled dichlorvos (OR 3.3, 95% CI 1.0–10.6; 4 cases). The OR for

Table 2 *Risks of leukemia according to ever use of herbicide families*

Herbicide families	No. of cases	No. of controls	OR[a]	95% CI
Amides	58	145	1.1	0.7–1.6
Arsenicals	19	55	1.0	0.6–1.7
Benzoics	39	122	0.9	0.6–1.3
Carbamates	23	62	1.0	0.6–1.6
Dinitroanalines	42	122	1.0	0.6–1.4
Heterocyclics	25	62	1.1	0.7–1.9
Phenoxy acids	120	263	1.2	0.9–1.6
Triazines	67	172	1.1	0.8–1.5
Ureas	14	23	1.5	0.7–3.0

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 3 *Risks of leukemia according to ever use of insecticide families*

Insecticide families	Ever used on crops				Ever used on animals			
	No. of cases	No. of controls	OR[a]	95% CI	No. of cases	No. of controls	OR[a]	95% CI
Carbamates	44	87	1.4	0.9–2.2	8	15	1.5	0.6–3.6
Chlorinated hydrocarbons	70	176	1.0	0.7–1.4	105	213	1.2	0.9–1.7
Inorganics	33	80	1.1	0.7–1.7				
Natural products					43	76	1.5	1.0–2.2
Organophosphates	51	118	1.2	0.8–1.8	55	106	1.5	1.0–2.1
Halogenated aliphatics	0	1			32	42	2.2	1.3–3.7
Nonhalogenated aliphatics	47	112	1.2	0.8–1.7	34	70	1.3	0.8–2.1
Halogenated aromatics					19	26	2.0	1.0–3.7
Nonhalogenated aromatics	4	5	2.5	0.6–9.5	17	22	2.2	1.1–4.2

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 4 *Risks of leukemia for mixing, handling, or applying specific herbicides*

Herbicides	No. of cases	No. of controls	Adjusted OR[a]	Adjusted 95% CI
Alachlor	41	109	1.0	0.7–1.5
Atrazine	38	108	1.0	0.6–1.5
Bentazon	14	45	0.9	0.5–1.7
Butylate	16	44	1.0	0.5–1.8
Chloramben	29	70	1.1	0.7–1.8
Cyanazine	21	64	0.9	0.5–1.6
2,4-D	98	227	1.2	0.9–1.6
Dicamba	15	57	0.7	0.4–1.4
Glyphosate	15	49	0.9	0.5–1.6
Linuron	9	18	1.2	0.5–2.8
MCPA	11	16	1.9	0.8–4.3
Metribuzen	13	38	1.0	0.5–1.9
Popachlor	12	25	1.3	0.6–2.6
Profluralin	5	5	2.9	0.8–10.3
2,4,5-T	22	48	1.3	0.7–2.2
Trifluralin	32	87	1.0	0.7–1.6

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 5 *Risk of leukemia for mixing, handling, or applying specific crop insecticides*

Insecticides	No. of cases	No. of controls	Adjusted OR[a]	Adjusted 95% CI
Aldrin	33	97	0.9	0.6–1.4
Bufencarb	8	16	1.4	0.6–3.5
Carbaryl	9	26	0.9	0.4–2.1
Carbofuran	24	65	1.0	0.6–1.7
Chlordane	7	26	0.7	0.3–1.6
Copper acetoarsenite	26	63	1.1	0.6–1.8
DDT	35	75	1.2	0.7–1.8
Diazinon	17	39	1.2	0.6–2.1
Dieldrin	8	26	0.8	0.4–2.0
Ethoprop	7	10	1.9	0.7–5.3
Fonofos	12	30	1.1	0.5–2.2
Heptachlor	14	43	0.9	0.5–1.7
Lead arsenate	5	26	0.6	0.2–1.6
Lindane	14	23	1.6	0.8–3.2
Malathion	10	30	0.9	0.4–1.9
Phorate	18	48	1.1	0.6–2.0
Terbufos	16	36	1.3	0.7–2.4

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 6 *Risk of leukemia for mixing, handling, or applying specific animal insecticides ever and at least 20 years prior to interview*

Insecticides	Ever handled: No. of cases	Ever handled: No. of controls	Ever handled: Adjusted OR[a]	Ever handled: Adjusted 95% CI	Handled at least 20 yr ago: No. of cases	Handled at least 20 yr ago: No. of controls	Handled at least 20 yr ago: Adjusted OR[a]	Handled at least 20 yr ago: Adjusted 95% CI
Carbaryl	7	15	1.3	0.5–3.2	4	4	3.0	0.7–12.4
Chlordane	19	38	1.3	0.7–2.3	13	22	1.5	0.7–3.1
Coumaphos	10	18	1.5	0.7–3.4	4	5	2.3	0.6–8.8
Crotoxyphos	7	2	11.1	2.2–55.0	4	0		
DDT	80	149	1.3	1.0–1.8	69	123	1.4	1.0–2.0
Dichlorvos	26	38	2.0	1.2–3.5	12	15	2.4	1.1–5.4
Famphur	11	14	2.2	1.0–5.0	4	1	11.6	1.2–107.0
Lindane	38	90	1.1	0.7–1.7	28	55	1.4	0.8–2.3
Malathion	30	67	1.2	0.8–2.0	15	29	1.5	0.8–2.9
Methoxychlor	11	16	2.2	1.0–5.0	5	8	2.1	0.7–6.6
Nicotine	30	47	1.6	1.0–2.6	28	36	2.0	1.2–3.4
Pyrethrins	8	7	3.7	1.3–10.6	5	4	3.8	1.0–14.8
Ronnel	5	5	2.6	0.7–9.3	2	0		
Rotenone	7	23	0.9	0.4–2.1	6	14	1.3	0.5–3.4
Tetrachlorvinphos	5	5	2.9	0.8–10.6	2	0		
Toxaphene	10	19	1.4	0.6–3.1	5	6	2.6	0.8–8.8

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

CLL increased to 2.4 (95% CI 1.2–4.6; 15 cases, 36 controls) when the analysis was restricted to farmers who had handled nicotine at least 20 years prior to interview. The risks for DDT use on animals was similar to risks for DDT use on crops for CLL (OR 1.5, 95% CI 0.9–2.3; 36 cases) and CML (OR 1.9, 95% CI 0.9–4.2; 10 cases). For those farmers who had first handled DDT at least 20 years prior to interview, the OR for ANL was significantly elevated (OR 1.8, 95% CI 1.0–3.2; 19 cases, 123 controls).

Maximum Frequency of Pesticide Use. No consistent dose-response patterns by days per year handled were seen for any of the herbicides, including 2,4-D (OR 1.1 for the highest dose category of ≥10 days/year) (data not presented). ORs for all leukemia by the number of days per year selected insecticides were reportedly handled are presented in Table 7. There were no consistent patterns of dose-response for any of the insecticides used, whether on animals or on crops. However, for most of the animal insecticides, risks were greatest for subjects who handled the insecticide for ≥10 days/year. The ORs for the most frequent users were significantly elevated for DDT (OR 2.1), dichlorvos (OR 3.8), and malathion (OR 3.2).

DISCUSSION

This case-control study of leukemia was conducted among white men in Iowa and Minnesota, two states with large agricultural populations, to investigate agricultural risk factors including exposure to specific pesticides. We found slightly, but significantly, elevated risks among farmers for all leukemia (OR 1.2) and for CLL (OR 1.4). Although several studies (1–9, 18, 19) have found farmers to be at excess risk of leukemia, other studies, including those based on incident cases, have not (20–25). In the studies in which associations have been noted, the risk of all leukemias combined has generally been in the range of 1.1–1.3 and the risk for CLL in the range of 1.4–1.7. In these studies, leukemia has not been consistently associated with any one agricultural practice or factor (2–5, 18, 19). Excess mortality from leukemia has been reported among farmers residing in counties where dairy (5, 18), poultry (2, 5), corn (3, 5, 19), or soybean (5) production were important agricultural activities. The excess risks that have been reported for incident cases have been for specific farming operations (26) or specific histological types of leukemia (hairy cell) (27).

In our study there were no clear patterns of dose-response with the number of years farmed and no excess risks for farmers by type of crops or animals raised; however, risks for many of the animal insecticides were greatest for the most frequent users. While none of the ORs for the three general groups of pesticides (any fungicide, herbicide, or insecticide) were significantly elevated for all leukemia, risks for the animal insecticides became more strongly associated with leukemia when the exposed group was restricted to farmers who personally handled specific insecticides. The significant 2-fold elevation in risk for use of any fungicide for ANL was not accounted for by the use of captan, the only specific fungicide used by a sufficient number of the study subjects to estimate risk. Although fungicides have not been associated with having leukemia, they have been associated with non-Hodgkin's lymphoma (28). Risks were also significantly elevated for use of any herbicide (OR 1.4) and any insecticide (OR 1.3) for CLL.

The relationship between herbicides, primarily the phenoxyacetic acid herbicides 2,4-D and 2,4,5-T, and cancer of the lymphatic and hematopoietic system and soft-tissue sarcoma

Table 7 *Risks of leukemia according to the number of days per year selected insecticides were handled*

		Used on crops				Used on animals			
				Adjusted				Adjusted	
Insecticides	days/yr	No. of cases	No. of controls	OR[a]	95% CI	No. of cases	No. of controls	OR[a]	95% CI
Aldrin	1–4	11	29	1.0	0.5–2.0				
	5–9	7	25	0.8	0.3–2.0				
	10+	4	20	0.5	0.2–1.4				
	Unknown	1	7						
Carbofuran	1–4	8	19	1.2	0.5–2.8				
	5–9	2	11	0.5	0.1–2.5				
	10+	2	9	0.5	0.1–2.4				
	Unknown	1	7						
Chlordane	1–4	1	8	0.3	0.0–2.5	7	16	1.1	0.4–2.8
	5–9	2	1	1.5	0.1–17.5	0	5	0	
	10+	1	7	0.3	0.0–2.5	6	5	3.2	0.9–11.0
	Unknown	0	3			0	1		
DDT	1–4	7	24	0.7	0.3–1.8	7	30	0.6	0.3–1.4
	5–9	8	9	2.4	0.9–6.4	7	16	1.1	0.4–2.7
	10+	5	12	1.0	0.3–2.8	21	26	2.1	1.1–3.9
	Unknown	3	5			7	7		
Diazinon	1–4	8	11	2.1	0.8–5.6				
	5–9	2	10	0.5	0.1–2.4				
	10+	0	7	0					
	Unknown	0	1						
Dichlorvos	1–4					5	10	1.3	0.4–4.0
	5–9					0	3	0	
	10+					5	4	3.8	1.0–14.8
	Unknown					1	3		
Heptachlor	1–4	6	13	1.2	0.4–3.3				
	5–9	4	11	1.0	0.3–3.2				
	10+	1	11	0.2	0.0–1.8				
	Unknown	1	1						
Lindane	1–4	6	4	3.5	0.9–12.6	15	37	1.1	0.5–2.0
	5–9	2	4	1.2	0.2–6.9	3	8	1.1	0.3–4.1
	10+	3	6	1.3	0.3–5.3	10	16	1.6	0.7–3.7
	Unknown	0	2			1	6		
Malathion	1–4	4	9	1.2	0.3–3.9	5	25	0.5	0.1–1.3
	5–9	2	6	0.8	0.2–4.4	0	6	0	
	10+	0	6	0		7	6	3.2	1.0–10.0
	Unknown	0	1			1	2		
Nicotine	1–4					9	9	2.6	1.0–7.0
	5–9					1	4	0.7	0.1–6.0
	10+					0	4	0	
	Unknown					3	5		

[a] All OR relative to risk for subjects who were never farmers (243 cases, 547 controls). All OR adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

has been studied in a number of investigations (5, 6, 28–38). Although significantly elevated risks have been reported for soft-tissue sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma, there have been no reports of an increased risk for all leukemia or leukemia cell types with use of specific herbicides. Correlations with herbicide use were noted for leukemia deaths in Iowa (5) and an increased risk for ANL (OR 2.2, 95% CI 0.7–6.9) was reported among forestry workers in New Zealand possibly exposed to phenoxyherbicides or chlorophenols (39).

This study found no striking excesses with any measure of herbicide use overall; however, nonsignificant excesses for specific leukemia cell types, including ANL, were associated with use of the phenoxyacetic acids 2,4,5-T and 2,4-D. Although these excesses should not be disregarded, the failure of these risks to increase with increasing frequency of use of herbicides [in contrast to findings for non-Hodgkin's lymphoma (28, 37)] suggests that a strong relationship does not exist between leukemia and use of herbicides in these data.

We found significantly elevated risks (OR 1.5) for selected families of animal insecticides, *i.e.*, organophospates and natural products (nicotine, pyrethrins, rotenone), particularly for CLL. When the organophosphate category was further divided into whether the insecticide was an aliphatic or an aromatic and whether it was halogenated, significantly elevated risks of approximately 2-fold were seen for halogenated aliphatics (dichlorvos, trichlorfon), halogenated aromatics (chlorophyrifor, coumaphos, crufomate, ronnel, tetrachlorvinphos), and nonhalogenated aromatics (azinphos-menthyl, crotoxyphos, dioxathion, famphur, fensulfothion, methyl parathion, parathion, phosmet). In addition to risks being significantly elevated for specific animal insecticides in the organophosphate (crotoxyphos, dichlorvos, famphur) and natural products families (nicotine, pyrethrins), risks were also significantly elevated for DDT (OR 1.3) and methoxychlor (OR 2.2), two insecticides in the chlorinated hydrocarbon family. The increase in risks associated with 20 years since first exposure and the larger ORs among farmers reporting ≥10 or more days of use for several of the animal insecticides (chlordane, DDT, dichlorvos, lindane, and malathion) suggest that they may be involved in the etiology of leukemia.

The epidemiological literature contains other reports that link leukemia with animal insecticides. Elevated risks of leukemia have been reported among livestock farmers in New Zealand (26) and Sweden (40, 41). Although it is not clear which insecticides might be involved, both DDT (10) and dichlorvos (11) are carcinogenic in animals and a significantly elevated risk (OR 6.1, 95% CI 1.9–19.0; 6 cases, 4 controls) of CLL associated with DDT exposure was reported in Sweden (40).

In contrast with the findings for animal insecticides, except for an association between CLL and use of carbamates, there

were no significantly elevated risks for leukemia from use of crop insecticides. ORs for the use of specific insecticides on crops were consistently smaller than the ORs for use of these same insecticides on animals. Even though this may be a chance finding, the potential for exposure while treating animals may be greater than when treating crops because application on animals often occurs inside barns or in other confined quarters. A similar finding was reported from a case-control study of soft-tissue sarcoma among farmers in Kansas (42).

As in any investigation using case-control methods, the associations found or the failure to find associations could be due to bias. There are many opportunities for inaccuracies in the evaluation of pesticide exposures that could lead to exposure misclassification. These include difficulty in recalling information by self-respondents and lack of knowledge by their next of kin. This type of misclassification is usually random and could have resulted in an underestimation of risk and a dilution of dose-response gradients which may have caused us to miss some associations between pesticide use and leukemia. Differences in reporting between self- and surrogate respondents would have the most impact in the supplemental interview, where only 25% of the cases were interviewed themselves compared with 75% of the controls.

Regarding accuracy of reporting, however, farmers and their next of kin are likely to recall details of their use of pesticides because it is a critical part of their commercial operation. The farmer typically purchases and applies the pesticide, activities likely to enhance recall. Accurate recall of pesticide use, however, probably declines with the passage of time. Thus, the accuracy of reported exposures in earlier years may be poorer than that of recent years. Because the associations noted in these data involve specific histological types of leukemia and specific pesticides, it seems unlikely that case-response bias, which might result in false-positive associations, is a plausible explanation for our findings. A critical concern regarding false-positive associations, however, results from multiple statistical comparisons which makes it difficult to separate real associations from chance findings. A full exploration of the data, however, dictated the need for detailed subgroup analyses.

Nevertheless, the study has several strengths for evaluating agricultural associated risks for leukemia. It is a relatively large population-based case-control study (578 cases and 1245 controls) located in two agricultural states. Pathology slides were reviewed to verify diagnoses. In-person interviews were conducted to obtain detailed information concerning farm activities which included probes for use of specific pesticides.

The findings from this study support recent cohort, death certificate, and ecological comparisons which have suggested an association between leukemia and farming (9). Although a few associations between leukemia and pesticides used on crops (either herbicides or insecticides) were noted, stronger associations were observed with insecticides used on animals. This may reflect the greater opportunity for pesticide exposure around animals and deserves further evaluation in other studies.

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