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Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States)

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Abstract

Objective: Data from three population-based case–control studies conducted in Kansas, Nebraska, Iowa, and Minnesota were pooled to evaluate the relationship between the use of organophosphate pesticides and non-Hodgkin's lymphoma (NHL) among white male farmers.
Methods: The data set included 748 cases of non-Hodgkin's lymphoma and 2236 population-based controls. Telephone or in-person interviews were utilized to obtain information on the use of pesticides. Odds ratios (OR) adjusted for age, state of residence, and respondent status, as well as other pesticide use where appropriate, were estimated by logistic regression.
Results: Use of organophosphate pesticides was associated with a statistically significant 50% increased risk of NHL, but direct interviews showed a significantly lower risk (OR = 1.2) than proxy interviews (OR = 3.0). Among direct interviews the risk of small lymphocytic lymphoma increased with diazinon use (OR = 2.8), after adjustment for other pesticide exposures.
Conclusions: Although we found associations between the risk of NHL and several groupings and specific organophosphate pesticides, larger risks from proxy respondents complicate interpretation. Associations, however, between reported use of diazinon and NHL, particularly diffuse and small lymphocytic lymphoma, among subjects providing direct interviews are not easily discounted.

Introduction

Organophosphate pesticides (OPPs) are a class of pesticides developed in the late 1930s whose mechanism of action is the inhibition of acetylcholinesterase in the nervous system. Their use has grown so that today they represent the major class of insecticides in use. In agriculture they are widely used on crops and livestock. Human exposure to OPPs can lead to acute cholinergic poisoning and to other subacute and chronic neurological, neurobehavioral, and psychiatric syndromes [1]. In addition to cholinergic effects there is evidence that some OPPs can cause cancer in laboratory animals [2]. Three epidemiologic studies conducted at the National Cancer Institute and collaborating institutions evaluated associations between pesticide use and the development of non-Hodgkin's lymphoma (NHL) among farmers [3–8]. These individual studies, however, were too small to evaluate risks from individual OPPs in detail. Data from the three case–control studies were pooled to provide larger numbers to further evaluate the relationship between NHL and OPPs.

Methods

We conducted three population-based case–control studies of NHL during the 1980s in Nebraska [3],

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Iowa/Minnesota [4], and Kansas [8]. Data from these studies were pooled for the current analysis. Methods have previously been described in detail [3, 4, 8]. The studies in Iowa/Minnesota and Kansas included only white men, while the Nebraska study included both white men and white women. This report evaluates NHL among white men only because there were too few women for analysis.

Cases

In the Iowa/Minnesota study we ascertained newly diagnosed cases of NHL among white men, aged 30 or older, from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records (n = 780). The diagnosis period of eligibility was March 1981 through October 1983 in Iowa, and October 1980 through September 1982 in Minnesota. In Minnesota we excluded cases who resided in the cities of Minneapolis, St Paul, Duluth, or Rochester at the time of diagnosis because agricultural exposures were the primary focus of the original investigation [4]. In Kansas we randomly drew 200 white men, aged 21 years or older, who were diagnosed with NHL from 1979 through 1981 from a statewide cancer registry, the University of Kansas Cancer Data Service [8]. In Nebraska we identified all cases of NHL diagnosed between 1 July 1983 and 30 June 1986 among white subjects, aged 21 years or older, and residing in the 66 counties of eastern Nebraska through the Nebraska Lymphoma Study Group and area hospitals (n = 227) [3].

Tumor tissue from the eligible cases was reviewed by expert pathologists and classified by the Working Formulation [9–11]. Analyses of four NHL types, small lymphocytic (Working Formulation category A), follicular (Working Formulation categories B–D), diffuse (Working Formulation categories E–G), and other (Working Formulation categories H–J) are presented.

Controls

Controls were frequency-matched to the cases by state, race, gender, 5-year age group, and vital status at the time of interview. We selected controls for living cases under the age of 65 by two-stage random-digit dialing (RDD) [12]. We selected controls for living cases 65 years of age or older from the Health Care Financing Administration records. Controls for deceased cases were selected from state mortality records with additional matching for year of death. A total of 3379 controls (Nebraska 831, Kansas 1005, Iowa and Minnesota 1543) were identified.

Interviews

We conducted interviews by telephone in Kansas and Nebraska and in-person in Iowa and Minnesota. In all we interviewed 993 cases and 2918 controls, or their respective proxies, and obtained information on demographic factors, medical conditions, family history of cancer, tobacco and alcohol use, occupation, agricultural practices, hobbies, and an abbreviated dietary history. Detailed questions on agricultural practices included personal use of specific pesticides used, years of use, days per year of use (in Kansas and Nebraska), protective practices, livestock and crops grown, and other farm-related activities. Only individuals reporting personal use of pesticides were classified as potentially exposed. Although the questionnaires regarding pesticide use and exposure for the three studies were similar, some differences occurred which required coding modifications to allow pooling. In Kansas, days per year of pesticide use and years of use were asked about herbicides and insecticides overall, not by specific pesticide. In Nebraska, days per year of use and years of use were asked for each pesticide used. In Iowa and Minnesota, no information was collected about days per year of pesticide use at the initial interview. An attempt to collect such information in Iowa at a later date was judged to be unsuccessful because of the differential survival of cases and controls; consequently these data are not used in these analyses [13]. In Kansas the subjects were asked to volunteer the pesticides they had used, while in Iowa, Minnesota, and Nebraska subjects were asked about a predetermined list of approximately 90 pesticides.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression analysis using a SAS program [14]. Non-farmers, *i.e.* individuals who had not lived or worked on a farm as an adult, served as the reference population. Although farmers who did not use organophosphate pesticides had a relative risk of 1.0 when compared to non-farmers, we did not include them in the reference population because of a possibility of the impact of misclassification, *i.e.* false-negatives, in analyses of specific chemicals where numbers were often small. We excluded subjects missing critical data, or those who did not know if they had used organophosphate pesticides, from the pooled data set, leaving 748 cases and 2236 controls eligible for analysis. ORs were adjusted for age, state, and respondent type. Adjustment for other potential risk factors for NHL had no effect on the ORs.

Results

Characteristics of the subjects are described in Table 1. Among farmers, 158 cases and 279 controls reported use of OPPs. These included 117 direct and 41 proxy respondents among cases and 224 direct and 55 proxy respondents among controls. The majority of proxy respondents were spouses.

Table 2 presents the ORs for NHL among farmers with regard to OPP use compared to non-farmers. Farmers without OPP use had no increased risk, while farmers with OPP use had a statistically significant 50% increase. The risk of NHL among farmers excluded from the analysis because of missing data was similar to that among non-farmers. Further adjustment for the use of 2,4-D and lindane, two pesticides previously associated with increased NHL risk [3, 6, 8], had little effect on the risk of NHL from OPP use. Farmers from Kansas, Nebraska, and Minnesota using OPPs had an elevated risk of NHL, but those from Iowa did not. Risks by histological category showed some variation with diffuse NHL, the only type with a statistically significant excess. Risks increased with time since first use and with years of use of OPPs.

ORs differ by type of respondent (Table 3) with OR = 1.2 for direct respondents and OR = 3.0 for proxies. Among proxies, wife proxies yielded an OR of 3.7 *versus* 2.5 for other next-of-kin. Higher risks from data provided by proxies than subjects were observed in every state, for short- and long-duration users, and for all histological types, except for risk of small lymphocytic lymphoma, where there was only one case among the proxies. Among direct respondents, risk increased slightly with time since first use and years of use, but among proxies the greatest risk was among farmers who first used OPPs less than 20 years in the past (OR = 4.3) and used OPPs less than 10 years (OR = 4.3).

Table 4 displays ORs for NHL by individual chemical and for four groupings of OPPs by chemical structure. Analyses of groupings of pesticides in Table 4 included farmers who reported use of only a single OPP. In these analyses by chemical class, all except halogenated aliphatic OPPs showed elevated ORs for NHL, but only non-halogenated aliphatics were statistically significant. Analyses of individual pesticides in Table 4 included all farmers, not just those who reported use of a single OPP. Farmers who used multiple OPPs are included in the analysis of each of the pesticides they reported using. Twelve of the 18 OPPs studied had OR $\geq$1.5 and the CI for four did not include 1.0 (chlorpyrifos (OR = 3.2), diazinon (OR = 1.7), fonofos (OR = 1.7), and malathion (OR = 1.6)). Dichlorvos, ethoprop, famphur, phorate, and terbufos had ORs of 1.1 or less.

Table 1. Numbers and (proportions) of various characteristics of cases and controls

	Non-farmers		Farmers (no OPP use)		Farmers (used OPP)	
	Cases	Controls	Cases	Controls	Cases	Controls
All subjects	243	775	347	1182	158	279
State of residence						
Iowa	69 (15)	144 (19)	94 (27)	208 (18)	58 (37)	101 (36)
Kansas	37 (34)	281 (36)	104 (30)	506 (43)	9 (1)	36 (13)
Minnesota	83 (22)	166 (21)	113 (33)	248 (21)	45 (28)	60 (22)
Nebraska	54 (11)	184 (24)	36 (10)	220 (19)	46 (29)	82 (29)
Respondent status						
Direct	164 (67)	442 (57)	219 (63)	650 (55)	117 (74)	224 (80)
Proxy	79 (33)	333 (43)	128 (37)	532 (45)	41 (26)	55 (20)
Wife	48 (20)	202 (26)	70 (20)	268 (23)	28 (18)	33 (12)
Other	27 (11)	128 (17)	51 (15)	257 (22)	11 (7)	20 (7)
Unknown[a]	4 (2)	3 (<1)	7 (2)	7 (<1)	2 (<1)	2 (<1)
Histological type						
Follicular	76 (31)	NA	91 (26)	NA	50 (32)	NA
Diffuse	90 (37)		127 (37)		63 (40)	
Small lymphocytic	22 (9)		48 (14)		18 (11)	
Other	55 (23)		81 (23)		27 (17)	

[a] Unknown proxies are proxy respondents whose relationship to the subject was not reported.
NA = not applicable.

Table 2. Odds ratios and 95% confidence intervals for NHL risk from OPP use

	Cases/controls	OR[a]	95% CI
Non-farmer	243/775	1.0	(Reference)
Farmers no OPP use	347/1182	1.0	0.8–1.3
Farmers used OPP	158/279	1.5	1.2–1.9
Adjusted for 2,4-D use		1.5	1.0–2.3
Adjusted for lindane use		1.5	1.1–2.0
By state of residence			
Iowa only	58/101	1.1	0.7–1.7
Kansas only	9/36	2.5	1.0–5.8
Minnesota only	45/60	1.5	1.0–2.4
Nebraska only	46/82	1.9	1.2–3.0
By histological type			
Follicular	50/279	1.3	0.9–2.0
Diffuse	63/279	1.8	1.2–2.6
Small lymphocytic	18/279	1.6	0.8–3.2
Other types	27/279	1.2	0.7–2.0
First OPP use[b]			
<20 years ago	44/94	1.0	0.7–1.5
20+ years ago	79/188	1.6	1.1–2.2
Years of OPP use[b]			
<10 years	34/69	1.1	0.7–1.7
10–19 years	44/71	1.4	0.9–2.1
20+ years	39/59	1.5	1.0–2.4

[a] Relative to non-farmers and adjusted for age, state of residence, and respondent status (proxy/direct). ORs for individual states are not adjusted for state of residence.
[b] Cases/controls from Iowa, Minnesota, and Nebraska only. Subjects missing data for year of first use and duration of use were excluded from this analysis.

Table 3. Odds ratios[a] and confidence intervals for NHL among farmers who used OPPs by interview respondent type

	Direct		Proxy	
	Cases/controls	OR[a] (95% CI)	Cases/controls	OR[a] (95% CI)
All respondents	117/224	1.2 (0.9–1.6)	41/55	3.0 (1.8–5.0)
Wife proxy			28/33	3.7 (2.0–7.1)
Other proxy			11/20	2.5 (0.9–6.4)
State of residence				
Iowa	54/92	1.0 (0.6–1.6)	4/9	1.5 (0.4–5.8)
Kansas	6/31	1.8 (0.6–5.2)	3/5	3.7 (0.8–16.8)
Minnesota	30/48	1.3 (0.7–2.2)	15/12	2.7 (1.1–6.7)
Nebraska	27/53	1.2 (0.6–2.2)	19/29	4.0 (1.8–5.0)
Histological type				
Follicular	44/224	1.2 (0.8–1.8)	6/55	3.4 (1.1–10.1)
Diffuse	39/224	1.2 (0.7–1.9)	24/55	4.0 (2.1–7.7)
Small lymphocytic	17/224	1.8 (0.9–3.9)	1/55	0.7 (0.1–6.1)
Other types	17/224	0.9 (0.5–1.7)	10/55	2.3 (1.0–5.3)
First used OPP				
<20 years ago	34/86	0.8 (0.5–1.2)	10/8	4.3 (1.6–11.9)
20+ years ago	64/90	1.4 (1.0–2.1)	15/28	2.0 (0.9–4.0)
Years used OPP[b]				
<10 years	27/63	0.8 (0.5–1.3)	7/6	4.3 (1.3–14.4)
10–19 years	35/55	1.2 (0.8–2.0)	9/16	1.9 (0.8–4.6)
20+ years	32/49	1.3 (0.8–2.1)	7/10	2.4 (0.8–6.7)

[a] Relative to non-farmers and adjusted for age and state of residence. ORs for individual states are not adjusted for state of residence.
[b] Cases/controls from Iowa, Minnesota, and Nebraska only. Subjects missing data for year of first use and duration of use were excluded from this analysis.

Table 4. Odds ratios and 95% confidence intervals for NHL among farmers by type and class of OPP used

Chemicals and classes	Number of cases/controls	OR[b]	95% CI
Chemical class groups[a]			
Halogenated aliphatic	7/15	1.1	0.4–2.7
Non-halogenated aliphatic	41/72	1.5	1.0–2.3
Halogenated aromatic	7/10	2.4	0.8–6.5
Non-halogenated aromatic	11/17	1.9	0.9–4.3
Individual chemicals[c]			
Halogenated aliphatics			
Dichlorovos	23/51	1.0	0.6–1.7
Trichlorfon	7/11	1.8	0.7–4.7
Non-halogenated aliphatics			
Dimethoate	12/22	1.8	0.9–3.8
Diazinon	60/93	1.7	1.2–2.5
Disulfoton	7/13	2.0	0.8–5.3
Ethoprop	7/17	0.9	0.4–2.3
Malathion	91/147	1.6	1.2–2.2
Phorate	44/97	1.1	0.8–1.7
Terbufos	32/70	1.1	0.7–1.8
Halogenated aromatics			
Chloropyrifos	7/8	3.2	1.1–9.2
Coumaphos	23/37	1.7	1.0–2.9
Crufomate	5/8	1.6	0.5–4.9
Ronnel	6/11	1.3	0.5–3.6
Tetrachlorvinphos	9/17	1.8	0.7–4.7
Non-halogenated aromatics			
Fensulfothion	4/4	2.0	0.5–8.2
Famphur	18/47	1.0	0.5–1.8
Fonofos	43/67	1.7	1.1–2.6
Parathion	5/8	2.9	0.9–9.7

[a] For chemical class groups only farmers who used pesticides in one group are included in the analysis.
[b] Relative to non-farmers and adjusted for age, state of residence, and respondent type (proxy or direct).
[c] For individual OPPs farmers could occur in multiple categories, *i.e.* in each pesticide they reported using.

Five OPPs – diazinon, malathion, fonofos, phorate, and terbufos – were chosen for further analysis because they were the most widely used in the study. For each pesticide, separate analyses were conducted by type of respondent (proxy or direct). Only ORs from direct respondents are presented in Table 5. ORs for proxy respondents were consistently larger than for direct respondents. Among direct respondents the risk of NHL was not significantly increased for any of the five OPPs. There was considerable variability by state, with Nebraska showing slight excesses for all five pesticides, Iowa no excesses, and Kansas and Minnesota inconsistent patterns. Excess risk of small lymphocytic lymphoma was seen for all five pesticides with a range of OR = 1.9 for malathion to OR = 2.8 (which was statistically significant) for diazinon. For each of the OPPs except terbufos the ORs were elevated among farmers who first used OPP more than 20 years in the past and among farmers who did not use protective equipment. Only farmers who used diazinon and fonofos had consistently increased risks by years of use. For each pesticide except malathion, farmers who used an OPP on 5 or more days per year had larger ORs than farmers who used an OPP less than 5 days per year.

Table 6 presents ORs for NHL overall and for histological types among direct respondents reporting use of fonofos, malathion, and diazinon, with and without adjustment for use of each other. The elevated ORs for small lymphocytic lymphoma from fonofos (OR = 2.6) and malathion use (OR = 1.9) were largely eliminated (OR = 1.0) when adjusted for diazinon use. Conversely, the risk of small lymphocytic lymphoma from diazinon use (OR = 2.8) was little affected by adjustments for use of the other chemicals.

Discussion

Some OPPs, including dichlorvos, methyl parathion, and tetrachlorvinphos, are carcinogenic in laboratory

Table 5. Odds ratios and 95% confidence intervals for NHL risk among direct respondent farmers who used specific OPPs

	Malathion		Diazinon		Fonofos		Phorate		Terbufos	
	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)
Farmers used OPP	68/121	1.2 (0.9–1.8)	44/69	1.3 (0.8–2.0)	31/53	1.2 (0.7–2.0)	35/77	0.9 (0.6–1.4)	26/56	0.9 (0.5–1.5)
State of residence										
Iowa	30/52	1.0 (0.6–1.7)	22/33	1.1 (0.6–2.1)	15/24	1.0 (0.5–2.1)	20/41	0.8 (0.4–1.5)	14/35	0.6 (0.3–1.3)
Kansas	3/11	2.7 (0.7–11.2)	1/1	13.0 (0.7–230)	1/2	4.9 (0.4–57.6)	0/4		0/0	
Minnesota	19/26	1.5 (0.8–2.9)	5/8	1.3 (0.4–4.0)	1/7	0.3 (0.0–2.4)	2/7	0.6 (0.1–2.9)	2/4	1.0 (0.2–5.7)
Nebraska	16/32	1.2 (0.6–2.4)	16/27	1.4 (0.7–2.9)	14/20	1.6 (0.7–3.5)	13/25	1.2 (0.5–2.6)	10/17	1.3 (0.6–3.2)
Histologic type										
Follicular	29/121	1.3 (0.8–2.2)	17/69	1.3 (0.7–2.3)	14/53	1.2 (0.6–2.4)	10/77	0.7 (0.3–1.4)	9/56	0.7 (0.3–1.6)
Diffuse	19/121	1.1 (0.6–1.9)	13/69	1.2 (0.6–2.4)	10/53	1.3 (0.6–2.7)	10/77	0.8 (0.4–1.8)	7/56	0.8 (0.4–2.0)
Small lymphocytic	10/121	1.9 (0.8–4.7)	9/69	2.8 (1.1–7.3)	5/53	2.6 (0.8–8.5)	8/77	2.3 (0.9–6.0)	5/56	2.2 (0.7–7.4)
Other types	10/121	0.9 (0.4–2.0)	5/69	0.7 (0.3–2.0)	2/53	0.4 (0.1–1.7)	7/77	0.9 (0.4–2.3)	5/56	0.8 (0.3–2.3)
First used OPP[b]										
<20 years ago	22/46	0.9 (0.5–1.6)	20/34	1.1 (0.6–2.0)	20/36	1.0 (0.6–1.9)	19/43	0.8 (0.4–1.5)	23/51	0.9 (0.5–1.5)
20+ years ago	35/39	1.7 (1.1–2.9)	16/24	1.4 (0.7–2.7)	5/6	1.6 (0.5–5.5)	14/23	1.3 (0.6–2.6)	0/1	
Years used OPP[b]										
<10 years	22/39	1.1 (0.6–1.9)	20/40	0.9 (0.5–1.7)	16/25	1.2 (0.6–2.4)	20/33	1.2 (0.6–2.1)	13/38	0.6 (0.3–1.3)
10–19 years	23/23	1.9 (1.0–3.5)	10/11	1.8 (0.7–4.4)	7/9	1.5 (0.5–4.1)	9/19	0.9 (0.4–2.1)	6/8	1.5 (0.5–4.4)
20+ years	10/18	1.1 (0.5–2.4)	1/1	1.9 (0.1–31.6)	2/1	4.2 (0.4–47.2)	4/5	1.5 (0.4–5.9)	0/1	
Day per year of use[c]										
< 5 days	7/8	2.1 (0.7–6.1)	6/11	1.3 (0.5–3.9)	2/6	0.7 (0.1–3.8)	5/9	1.3 (0.4–4.0)	3/8	0.8 (0.2–3.3)
5+ days	5/7	1.5 (0.5–5.2)	6/6	2.4 (0.7–8.0)	9/6	3.4 (1.1–10.3)	7/8	2.0 (0.7–5.9)	7/4	4.0 (1.1–14.5)
Protective year[d]										
Used	22/46	1.1 (0.6–1.9)	12/29	0.9 (0.4–1.9)	8/23	0.7 (0.3–1.7)	8/30	0.5 (0.2–1.2)	7/18	0.8 (0.3–2.0)
Not used	43/67	1.4 (0.9–2.1)	17/23	1.4 (0.7–2.8)	15/14	2.1 (1.0–4.4)	18/22	1.6 (0.8–3.0)	11/21	1.0 (0.5–2.1)

[a] Relative to non-farmers and adjusted for age and state of residence. ORs for individual states are not adjusted for state of residence.
[b] Cases/controls from Iowa, Minnesota, and Nebraska only. Subjects missing data for year of first use and duration of use were excluded from this analysis.
[c] Cases/controls from Nebraska only. Some subjects did not report days per year use and thus were excluded from this analysis.
[d] Cases/controls from all four states. Subjects missing data for protective year were excluded from this analysis.

Table 6. Risk of NHL among direct respondent farmers from use of three OPPs adjusting for use of each other

	Any NHL		Follicular		Diffuse		Small lymphocytic		Other	
	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)	Cases/ controls	OR[a] (95% CI)
Fonofos use	31/53	1.2 (0.7–2.0)	14/53	1.2 (0.6–2.4)	10/53	1.3 (0.6–2.7)	5/53	2.6 (0.8–8.5)	2/53	0.4 (0.1–1.7)
Adjusted for diazinon		0.8 (0.4–1.7)		0.9 (0.3–2.4)		1.2 (0.4–3.3)		1.0 (0.1–8.5)		0
Adjusted for malathion		0.9 (0.4–1.9)		0.5 (0.1–2.0)		1.2 (0.4–3.7)		2.7 (0.5–13.4)		0.5 (0.1–3.9)
Malathion use	68/121	1.2 (0.9–1.8)	29/121	1.3 (0.8–2.2)	19/121	1.1 (0.6–1.9)	10/121	1.9 (0.8–4.7)	10/121	0.9 (0.4–2.0)
Adjusted for diazinon		1.1 (0.7–1.8)		1.2 (0.6–2.3)		1.1 (0.5–2.2)		1.0 (0.3–3.6)		1.1 (0.5–2.7)
Adjusted for fonofos		1.1 (0.7–1.6)		1.1 (0.6–2.0)		0.9 (0.4–1.8)		1.6 (0.6–4.5)		1.2 (0.5–2.6)
Diazinon use	44/69	1.3 (0.8–2.0)	17/169	1.3 (0.7–2.3)	13/69	1.2 (0.6–2.4)	9/69	2.8 (1.1–7.3)	5/69	0.7 (0.3–2.0)
Adjusted for fonofos		1.2 (0.7–2.1)		1.1 (0.5–2.4)		1.5 (0.7–3.2)		2.5 (0.8–7.6)		0.7 (0.2–2.6)
Adjusted for malathion		1.8 (0.9–3.5)		1.1 (0.3–3.3)		3.0 (1.3–7.0)		2.7 (0.7–10.7)		1.0 (0.2–4.4)

[a] Relative to non-farmers and adjusted for age and state of residence.

assays [15, 16]. Concern over possible risk to humans is also raised by previous epidemiological studies, which have suggested an association between use of OPPs and increased risk of NHL among farmers [3–7]. The epidemiological studies, however, lacked the power to fully evaluate risks from a specific OPP while adjusting for use of others. By combining data from three previous NCI case–control studies, pooled analyses provided an opportunity to evaluate the potential risk of NHL from OPP use, both as a group and at the level of individual pesticides while adjusting for potential confounders. In all, 748 cases of NHL and 2236 population-based controls were used in this analysis. Farmers who reported use of OPPs had a 50% greater risk of NHL than non-farmers (OR = 1.5, 95% CI 1.2–1.9), while farmers not using OPPs had no excess. Diffuse (OR = 1.8) and small lymphocytic (OR = 1.6) lymphomas were the histological types with the most notable associations. Risks were greater among farmers who first used OPPs earlier (*i.e.* 20 or more years ago) and longer (*i.e.* 10 or more years); however, disparity in risk between direct (OR = 1.2) and proxy (OR = 3.0) respondents casts doubt on the validity of the overall association between any OPP use and NHL. Given the strong evidence that proxies cannot provide as accurate or as detailed information on an individual's use of pesticides as the farmers themselves [17–21], it seems unlikely that proxy reporting would uncover an association where the direct interviews would not. It is possible, however, that the more aggressive tumors (which are more likely to require proxy respondents) have a different etiology than the less aggressive types.

Among direct respondents risk of small lymphocytic lymphoma was associated with OPP use, but other histological types were not. Elevated risks of small lymphocytic lymphoma associated with use of malathion and fonofos, however, were eliminated when adjusted for diazinon use. On the other hand, ORs from diazinon use were not appreciably changed by adjustment for use of other OPPs. Numbers of exposed cases and controls were not large, which poses a problem when adjusting for other pesticide use. Our finding for diazinon could thus represent a chance finding from subgroup analysis and requires confirmation elsewhere.

Little is known about the etiology and molecular pathogenesis of small lymphocytic lymphoma. It has been hypothesized that exposure to organophosphorus compounds may lead to lymphomagenesis through the inhibition of serine esterases [22], which are necessary for cytotoxic activity in cytotoxic T cells, natural killer cells, and monocytes. Few epidemiological studies have evaluated the relationship between OPPs and histological types of lymphoma. Pathologists have suggested that small lymphocytic lymphoma and chronic lymphocytic leukemia are closely related diseases and could be grouped in epidemiologic studies [23]. Farming has been linked to risk of chronic lymphocytic leukemia in several case–control studies [24–27]. One study noted a link between use of organophosphate pesticides and risk of chronic lymphocytic leukemia [27].

The finding of a higher OPP-related risk for NHL among proxy than direct respondents might be due to chance, differential misclassification, or larger risk among deceased farmers who may have had a more aggressive disease. Chance is a possible explanation, but the larger risk among proxy respondents in each state argues against this explanation. Differential misclassification of exposure because of better recall by the cases (or their proxies) than by the controls is always a concern in case–control studies [28]. A previous study using this data set to evaluate the risk of NHL from lindane use found similar differences in results between direct and proxy respondents [6]. Risk estimates could also be biased because dead controls are not representative of the population [29]. The use of proxies in case–control studies is a potential source of nondifferential misclassification because proxies cannot provide information on pesticide use as accurately as farmers themselves [17–21]. Proxies are also more likely to give "don't-know" answers [19] and less likely to report the use of specific pesticides than direct respondents [21]. One would expect such misclassification to lower the observed risk among proxies as compared to direct respondents.

A major strength of our study was the large number of cases (n = 748) and controls (n = 2236) available for analysis. Detailed information on the use of pesticides and on common agricultural practices was available, allowing us to adjust for possible confounding from other pesticides, and to evaluate risk by such factors as use of protective gear, duration of pesticide use, and days per year of pesticide use. The size of the study also allowed us to analyze risk for specific types of NHL, and to measure exposure from the use of individual OPPs. Even here, however, the number of exposed cases and controls was quite small for some histological type and specific exposure subgroups.

In summary, we found a 50% increased risk of NHL among farmers who used OPPs with the elevated risk primarily among the proxy respondents. Although we have no clear explanation for this finding, we are concerned that it could be a spurious lead caused by differential misclassification of exposure. Among direct respondents, although overall risk of NHL was elevated very little, we did observe associations between small lymphocytic lymphoma and use of OPPs, particularly diazinon. The findings of other studies linking farming practice and organophosphate use with chronic lymphocytic leukemia risk may support our small lymphocytic lymphoma findings, but we hesitate to draw strong conclusions from our data because there were only 17 direct respondent cases of this histological type. Overall, our analysis does not indicate that the use of OPPs is a major risk factor for NHL, although investigations which can focus on individual chemicals are needed.

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