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Agricultural Exposure to Carbamate Pesticides and Risk of Non-Hodgkin Lymphoma

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Recent epidemiological studies have suggested an increased risk of non-Hodgkin lymphoma (NHL) from carbamate insecticide use among farmers. To further explore the possible relationships, we conducted a pooled analysis of three population-based case-control studies conducted in four midwestern states in the United States. A total of 985 white male subjects and 2895 control subjects were included in this analysis. Unconditional logistic regression was used to estimate the association and control for confounding. Compared with nonfarmers, farmers who had ever used carbamate pesticides had a 30% to 50% increased risk of NHL, whereas farmers without carbamate pesticide use showed no increased risk. Analyses for individual carbamate pesticides found a more consistent association with Sevin but not carbofuran, butylate, or *S*-ethyl dipropylthiocarbamate plus protectant. Among farmers using Sevin, the risk of NHL was limited to those who personally handled the product, those who first used the product for ≥20 years before their disease diagnosis, and those who used the product for a longer period. These associations persisted after adjusting for other major classes of pesticides. These results suggest an increased risk of NHL associated with carbamate pesticide use, particularly Sevin. Further investigation of the association is warranted.

Introduction

In the early 1970s, many developed countries banned or restricted the use of various chlorinated hydrocarbon pesticides, such as *p*-dichloro-diphenyl-trichloroethene (DDT) and lindane. Since then, carbamate pesticides [such as Sevin® (Aventis CropScience, Research Triangle Park, NC), carbofuran, and butylate] have gained prominence and are now used extensively in the United States and throughout the world for control of agricultural pests, household and home garden pests, and for other industrial and commercial purposes. [1]

It is biologically plausible that exposure to carbamate pesticides may increase the risk of non-Hodgkin lymphoma (NHL). First, malignant lymphomas have occurred in mice after treatment with carbamate pesticides. [2][3] In addition, some of the carbamate pesticides, including Sevin, carbofuran, and aldicarb, alter immune status and cause immunosuppression both in experimental settings and in exposed human subjects. [4][5][6][7][8][9][10][11][12][13][14][15] Various immunosuppressive conditions are well-established risk factors for NHL. [16]

Recent epidemiological studies have also raised concerns about the potential adverse effects on human health from carbamate pesticide use. In a population-based case-control study conducted in Nebraska, [17] carbamate insecticide use was found to be associated with a twofold increased risk of NHL among farmers, and the risk rose with increasing duration of use of Sevin. An approximate twofold risk of NHL from Sevin use was also observed in a population-based case-control study of NHL in Iowa and Minnesota conducted in the early 1980s. [18] The risk was increased almost fourfold among farmers who handled the insecticide before 1965.

These studies did not examine the risk of NHL associated with carbamate pesticide use in great detail because the number of subjects who personally handled the compounds in any individual study was relatively small, making it difficult to examine the data by various exposure characteristics and to control for confounders. To investigate the relationship between agricultural use of carbamate pesticides and risk of NHL while controlling for other exposures, we pooled the two population-based case-control studies mentioned above with a third population-based case-control study of NHL conducted in Kansas. [18][19][20] These three studies had similar study designs and collected detailed information on lifetime pesticide use.

Materials and Methods

Study Population

The study populations and methods for the three population-based case-control studies are reported in detail elsewhere. [18][19][20][21][22][23] Briefly, the studies in Iowa-Minnesota and Kansas included white men, whereas the Nebraska study included both white men and white women. This pooled analysis evaluates NHL among white men because few women (five case subjects and eight control subjects) in the Nebraska study reported agricultural use of carbamate pesticides.

In the Nebraska study, patients with NHL aged 21 and over were identified (n = 227) through the Nebraska Lymphoma Study Group and area hospitals from 1983 to 1986. In the Iowa and Minnesota study, patients with NHL 30 years and older were ascertained (n = 780) from the records of the Iowa

State Health Registry and from a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1983. In the Kansas study, patients with NHL aged 21 and over were identified from the statewide cancer registry covering 1979 to 1981. A random sample of 200 men was drawn from the 297 patients diagnosed with NHL in Kansas during the eligible time period. In all areas, study pathologists reviewed tumor or slide samples for all patients and classified patients with NHL according to the working formulation. [24] The case subjects were further grouped into four histological types (follicular, diffuse, small lymphocytic, and other).

A total of 3379 population-based control subjects were identified from the same geographical areas as the patients with NHL. Efforts were made to frequency-match the case subjects and control subjects by gender, age, race, vital status, and state of residence using a matching ratio of 2:1 in Iowa and Minnesota and a matching ratio of approximately 4:1 in Kansas and Nebraska. For living patients with NHL aged <65, control subjects were selected by two-stage, random-digit dialing, as described previously by Waksberg. [25] For living patients with NHL aged 65 and over, control subjects were selected from the records of the Health Care Financing Administration. For deceased case subjects, control subjects were selected from death records in each state and matched to the case subjects by age and year of death.

Interview

Standardized and structured questionnaires were used to collect information on agricultural pesticide use and other major suspected or established risk factors for NHL. Interviews were conducted with the subjects or their next-of-kin if the subjects were dead or incapacitated. Interviews were conducted in person in Iowa and Minnesota and by telephone in Kansas and Nebraska. The participation rate among patients with histologically confirmed NHL or proxies was 89% in Iowa and Minnesota, 91% in Nebraska, and 96% in Kansas, as shown in Table 1. For control subjects, the overall response rate was 78% in Iowa and Minnesota, 85% in Nebraska, and 90% in Kansas.

Table 1. Characteristics of NHL Case and Control Subjects

	Iowa and Minnesota				Kansas				Nebraska			
	Case		Control		Case		Control		Case		Control	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Interviewed	622		1,245		170		948		201		725	
Response rate (%)		89		78		96		90		91		85
Respondent status												
Self	428	69.5	824	66.6	79	47.0	452	48.4	112	55.7	359	49.6
Proxy	188	30.5	414	33.4	89	53.0	482	51.6	89	44.3	364	50.4
Age												
20–44	65	10.5	104	8.4	19	11.3	240	25.7	18	9.0	73	10.1
45–64	211	34.3	396	32.0	54	32.1	241	25.8	57	28.4	213	29.5
65–74	161	26.1	345	27.9	51	30.4	206	22.1	62	30.8	190	26.3
≥75	179	29.1	393	31.7	44	26.2	247	26.4	64	31.8	247	34.1
Family cancer history												

No	274	44.5	649	52.4	59	35.1	532	57.0	104	51.7	460	63.6
Yes	333	54.0	564	45.6	107	63.7	395	42.3	96	47.8	253	35.0
Unknown	9	1.5	25	2.0	2	1.2	7	0.7	1	0.5	10	1.4
Tobacco smoking												
Never	116	18.8	286	23.1	50	29.8	216	23.1	74	36.8	183	25.3
Ever	499	81.0	952	76.9	118	70.2	716	76.7	127	63.2	539	74.6
Unknown	1	0.2	0		0		2	0.2	0		1	0.1
Histological type												
Follicular	194	31.5			34	20.3			56	27.8		
Diffuse	194	31.5			80	47.6			90	44.8		
Small lymphocytic	85	13.8			13	7.7			14	7.0		
Other	143	23.2			41	24.4			39	19.4		
Unknown	0				0				2	1.0		

* NHL, non-Hodgkin lymphoma.

Regarding pesticide use, subjects in Iowa, Minnesota, and Nebraska were asked whether they had used or personally handled specific pesticides; whether the pesticides were used on crops, animals, or both; year of first use and year of last use; and years of use for specific pesticides. In Kansas, duration and intensity measures were obtained for insecticides as a group and herbicides as a group, not individual pesticides. After this, specific chemicals used were reported in an open-ended question at the end of each section. Thus, the years and frequency of use refer to the broad categories, not specific chemicals. Information on days per year of use of pesticides was not collected from Minnesota subjects but was collected in Iowa about 4 years after completion of the original interviews. [26] The data collected from Iowa had a higher proportion of proxy respondents among case subjects (55%) than among control subjects (28%), which could bias relative risks. Thus, the information on days of use per year for Iowa subjects was not included in the pooled analysis.

Data Analysis

Subjects who had never lived or worked on a farm ("nonfarmers") were used as the nonexposed reference population. Those who were missing information regarding living or working on a farm (six case subjects and nine control subjects) were excluded from the study. Subjects whose information on date of birth was missing (two case subjects and 14 control subjects) were also excluded, leaving a total of 985 case subjects and 2895 control subjects for the pooled analysis. Unconditional logistic regression models were used to estimate the association between carbamate pesticide use and risk of NHL, and to control for confounding. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using SASsoftware. [27] ORs were adjusted for age at diagnosis as a continuous variable, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer (yes/no), use of hair dye (yes/no), use of private wells (ever/never), and tobacco smoking (yes/no). Although adjustment of

these variables individually did not bring material change to the risk estimates, adjustment of these variables as a group brought changes in ORs at the usual 10% levels. Thus, these variables were included in the final model. Use of various other pesticides or chemical classes were also adjusted when assessing the risk of NHL associated with carbamate pesticide uses.

Results

Descriptive information on the general characteristics of case and control subjects is shown in Table 1. The age distributions of the case and control subjects were similar, except in Kansas, where a higher proportion of control subjects for the youngest group was noted. The proportion of proxy interviews was also quite comparable between the case and control subjects at each study site. A significant difference, however, was noted between the case and control subjects for first-degree relatives having any type of cancer in the pooled analysis, as shown in Table 1 ($P < 0.01$).

Relative to men who never farmed, farmers who ever used carbamate pesticides had a 50% (OR, 1.5; 95% CI, 1.0 to 2.0) increased risk of NHL (Table 2). Farmers who did not use carbamate pesticides, however, showed no increased risk. The increased risk of NHL associated with carbamate pesticides was seen in each study site except for Iowa (data not shown). Both carbamate insecticides and herbicides were significantly associated with NHL risk.

Table 2. Risk of NHL Associated With Carbamate Pesticide Use*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR†**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmers	243	273	1.0		164	442	1.0	
Carbamate pesticide use								
Farmers (no use)	488	1,392	1.1	0.9–1.4	316	807	1.0	0.8–1.4
Farmers (used)	107	216	1.5	1.1–2.0	82	169	1.3	0.9–1.8
Carbamate herbicide use								
Farmers (no use)	612	1,771	1.1	0.9–1.4	388	1,015	1.1	0.8–1.4
Farmers (used)	60	108	1.5	1.1–2.3	45	86	1.3	0.8–2.0
Carbamate insecticide use								
Farmers (no use)	518	1,503	1.1	0.9–1.4	337	873	1.0	0.8–1.3
Farmers	89	172	1.6	1.2–2.2	67	135	1.4	0.9–2.0

(used)								

* NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval.

† Adjusted for age, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, and tobacco smoking.

‡ Without adjusting for type of respondent.

Of the 11 carbamate pesticides (Sevin, bufencarb, carbofuran, lannate, aldicarb, butylate, diallate, *S*-ethyl dipropylthiocarbamate [EPTC] + protectant, triallate, barban, and asulam) reported to have been used by farmers in this study, four (Sevin, carbofuran, butylate, and EPTC + protectant) were used by a sufficient number of subjects to evaluate individually. Each of the four carbamates showed an increased risk of NHL after adjusting for potential confounders among farmers who used these products (table 3, table 4, table 5, table 6).

Table 3. Risk of NHL Associated With Sevin (Carbaryl) Use*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR†**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmers	243	775	1.0		164	442		
Farmers (no use)	551	1,539	1.1	0.9–1.4	371	949	1.0	0.8–1.4
Farmers (used)	45	85	1.6	1.0–2.4	34	65	1.4	0.8–2.2
Personally handled								
No	4	11	0.8	0.3–2.7	3	10	0.6	0.2–2.3
Yes	36	58	1.8	1.1–2.8	28	43	1.6	0.9–2.8
Years since first use								
<20 years ago	19	44	1.1	0.6–2.0	15	37	0.9	0.5–1.8
≥20 years ago	14	21	1.8	0.9–3.7	12	14	2.0	0.9–4.6
Years of use								
<7	16	36	1.1	0.6–2.1	12	32	0.9	0.4–1.8
≥7	15	26	1.5	0.8–3.0	13	18	1.7	0.8–3.6
Days per year of use§								
<5	9	15	2.4	1.0–5.9	5	10	1.9	0.6–5.8
≥5	2	4	1.8	0.3–10.0	2	2	3.7	0.5–28
By histologic type								

Follicular	14	85	1.3	0.6–2.4	12	65	1.2	0.6–2.4
Diffuse	15	85	1.5	0.8–2.8	10	65	1.2	0.5–2.5
Small lymphocytic	9	85	2.9	1.2–7.0	9	65	4.0	1.5–10.5
Other types	7	85	1.2	0.5–2.9	3	65	0.6	0.2–2.2

* For definition of abbreviations, see Table 2.

† Adjusted for age, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, and tobacco smoking.

‡ Without adjusting for type of respondent.

§ Based on data from Nebraska only.

Further stratification by various exposure characteristics (whether personally handled products, latency, duration, and intensity of exposure), however, suggested that only the insecticide Sevin showed a consistent risk pattern (table 3, table 4, table 5, table 6). As shown in Table 3, the risk of NHL associated with Sevin use was limited to those who personally handled the product, to those who first used the product for more than 20 years before diagnosis, and to those who had used the product for ≥7 years. Among the direct interviews (Table 3), a higher risk was also observed among those who had ≥5 days per year of use. Analysis by histological type suggested a significantly increased risk for small-cell lymphoma for all subjects and among direct interviews. For proxy interviews (data not shown), only 11 case subjects and 20 control subjects were reported to have used Sevin (OR, 2.4; 95% CI, 1.0 to 5.4).

Unlike what was observed for Sevin, we found no increased risk of NHL among those who personally handled carbofuran, butylate, and EPTC + protectant (table 4, table 5, table 6). Rather, the excess risk occurred primarily in farmers who had not personally handled these chemicals, and the risk also did not increase with increased duration of use of these products.

Table 4. Risk of NHL Associated With Carbofuran Use*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR‡**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmers	243	775	1.0		164	442		
Farmers (no use)	543	1,512	1.1	0.9–1.4	361	916	1.0	0.8–1.4
Farmers (used)	66	131	1.6	1.1–2.3	50	102	1.4	0.9–2.1
Personally handled								
No	4	4	2.2	0.5–9.1	4	2	3.7	0.7–20.7
Yes	51	102	1.4	1.0–2.2	41	79	1.3	0.8–2.1
Years since first use								
<20 years	32	63	1.3	0.8–2.1	28	57	1.2	0.7–2.0

ago								
≥20 years ago	15	30	1.6	0.8–3.1	11	18	1.6	0.7–3.7
Years of use								
<7	30	48	1.7	1.0–2.9	28	43	1.7	1.0–2.9
≥7	24	47	1.4	0.8–2.4	16	34	1.1	0.6–2.2
Days per year of use§								
<5	9	15	2.7	1.1–6.4	6	9	2.7	0.9–8.1
≥5	12	16	3.1	1.4–6.8	9	10	3.4	1.3–9.0
By histologic type								
Follicular	22	131	1.4	0.8–2.4	18	102	1.2	0.7–2.2
Diffuse	24	131	1.6	1.0–2.7	17	102	1.3	0.7–2.4
Small lymphocytic	7	131	1.5	0.6–3.8	7	102	2.0	0.7–5.6
Other types	13	131	1.6	0.8–3.1	8	102	1.2	0.5–3.0

* For definition of abbreviations, see Table 2.

† Adjusted for age, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, and tobacco smoking.

‡ Without adjusting for type of respondent.

§ Based on data from Nebraska only.

Table 5. Risk of NHL Associated With Butylate Use*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR†**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmers	243	Tc775	1.0		164	442		
Farmers (no use)	615	1,720	1.2	0.9–1.4	400	1,027	1.1	0.8–1.4
Farmers (used)	45	76	1.6	1.0–2.4	34	61	1.3	0.8–2.1
Personally handled								
No	12	13	2.2	1.0–5.0	11	12	2.0	0.8–4.8
Yes	29	60	1.3	0.8–2.1	21	49	1.0	0.6–1.8

Years since first use								
<20 years ago	34	56	1.5	0.9–2.4	27	52	1.2	0.7–2.0
≥20 years ago	4	10	1.1	0.3–3.7	3	6	1.3	0.3–5.3
Years of use								
<7	21	35	1.5	0.9–2.8	16	31	1.2	0.6–2.3
≥7	20	37	1.5	0.8–2.7	15	28	1.3	0.6–2.5
Days per year of use§								
<5	3	5	2.6	0.6–11.1	1	5	0.7	0.1–6.6
≥5	2	2	4.7	0.6–34.5	2	2	4.6	0.6–35.2
By histologic type								
Follicular	17	76	1.5	0.8–2.8	16	61	1.5	0.8–3.0
Diffuse	15	76	1.6	0.9–3.1	11	61	1.3	0.6–2.7
Small lymphocytic	4	76	1.1	0.3–3.4	4	61	1.4	0.4–4.7
Other types	9	76	1.5	0.7–3.4	3	61	0.6	0.2–2.1

* For definition of abbreviations, see Table 2.

† Adjusted for age, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, and tobacco smoking.

‡ Without adjusting for type of respondent.

§ Based on data from Nebraska only.

Table 6. Risk of NHL Associated With EPTC + Protectant Use*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR†**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmers	243	775	1.0		164	442		
Farmers (no use)	634	1,745	1.2	0.9–1.4	415	1,051	1.1	0.8–1.4
Farmers (used)	23	49	1.6	0.9–2.7	17	36	1.4	0.7–2.7
Personally handled								

No	5	4	3.7	0.9–14.3	4	2	4.9	0.9–27.8
Yes	17	42	1.3	0.7–2.4	12	32	1.1	0.5–2.3
Years since first use								
<20 years ago	19	34	1.7	0.9–3.1	15	30	1.4	0.7–2.8
≥20 years ago	0	1			0	0		
Years of use								
<7	15	20	2.2	1.1–4.4	12	17	1.9	0.8–4.1
≥7	7	26	1.0	0.4–2.4	4	17	0.8	0.2–2.3
Days per year of use§								
<5	7	12	2.2	0.8–5.8	5	9	2.0	0.6–6.4
≥5	1	5	0.9	0.1–7.7	1	4	1.2	0.1–10.8
By histologic type								
Follicular	10	49	1.7	0.8–3.8	9	36	1.8	0.8–4.2
Diffuse	10	49	1.8	0.8–3.7	5	36	1.1	0.4–3.0
Small lymphocytic	2	49	1.5	0.3–7.1	2	36	2.1	0.4–10.4
Other types	1	49	0.4	0.04–2.7	1	36	0.5	0.1–3.9

* EPTC, *S*-ethyl dipropylthiocarbamate. For definition of other abbreviations, see Table 2.

† Adjusted for age, type of respondent (proxy or direct interview), state of residence, first-degree family history of cancer, use of hair dye, use of private wells, and tobacco smoking.

‡ Without adjusting for type of respondent.

§ Based on data from Nebraska only.

While assessing the association between Sevin use and NHL risk, we also evaluated the potential confounding effects of other pesticides (Table 7). Adjustment for organophosphates, natural products, inorganics, amides, and dinitroanilines had no significant impact on the relationship between Sevin use and NHL risk. Four classes of pesticides (trazines, benzoics, heterocyclics, and phenoxyacetic acids), however, showed individual impacts on the relationship between Sevin use and NHL risk. Simultaneous control for the four classes of pesticides and other potential confounders reached the same conclusion as reported in Table 3; that is, the risk of NHL associated with Sevin was limited to those who personally handled the product, to those who used the product for ≥20 years before their disease diagnosis, and to those who used the product for a longer period.

Table 7. Risk of NHL Associated With Sevin Use Adjusting for Other Pesticide Exposures*

	All Subjects				Direct Interview			
Factor	**Case**	**Control**	**OR†**	**95% CI**	**Case**	**Control**	**OR‡**	**95% CI**
Nonfarmer	243	775	1.0		164	442		
Farmers (no use)	551	1,539	1.1	0.9–1.3	371	949	1.0	0.8–1.3
Farmers (used)	45	85	1.4	0.9–2.2	34	65	1.2	0.7–2.1
Personally handled								
No	4	11	0.7	0.2–2.5	3	10	0.6	0.1–2.2
Yes	36	58	1.5	0.9–2.6	28	43	1.5	0.8–2.7
Years since first use								
<20 years ago	19	44	0.9	0.5–1.8	15	37	0.8	0.4–1.7
≥20 years ago	14	21	1.6	0.8–3.4	12	14	1.9	0.8–4.4
Years of use								
<7	16	36	1.0	0.5–1.9	12	32	0.8	0.4–1.7
≥7	15	26	1.3	0.7–2.7	13	18	1.5	0.7–3.4
Days per year of use§								
<5	9	15	2.0	0.8–5.0	5	10	1.6	0.5–5.0
≥5	2	4	1.5	0.3–8.8	2	2	3.3	0.4–26.1
By histologic type								
Follicular	14	85	1.1	0.5–2.3	12	65	1.1	0.5–2.5
Diffuse	15	85	1.2	0.6–2.3	10	65	0.8	0.3–1.9
Small lymphocytic	9	85	3.0	1.1–8.1	9	65	3.8	1.3–11.3
Other types	7	85	1.2	0.5–3.0	3	65	0.8	0.2–3.2

* For definition of abbreviations, see Table 2.

† Adjusted for confounders in Table 3 plus four groups of pesticide, including phenoxyacetic acids, triazines, benzoics, and heterocyclics.

‡ Without adjusting for type of respondent.

§ Based on data from Nebraska only.

We also analyzed the data based on whether Sevin was used on crops or on animals. The majority of the farmers reported using Sevin on crops only (38 case subjects and 71 control subjects); a few (eight case subjects and 18 control subjects) reported having used Sevin only on animals. Five case subjects and seven control subjects reported using Sevin on both crops and animals. A more detailed analysis for farmers who used Sevin on crops showed an increased risk only among those who personally handled the product (OR, 1.8; 95% CI, 1.1 to 3.0), those who first used Sevin for more than 20 years before diagnosis (OR, 1.9; 95% CI, 0.8 to 2.5), and those who used the product for ≥7 years (OR, 1.8; 95% CI, 0.9 to 3.8).

Discussion

In this pooled analysis, we found a 30% to 50% overall increased risk of NHL associated with carbamate pesticide use by farmers. This risk seems largely attributable to use of the carbamate insecticide Sevin, particularly among farmers who personally handled the product and farmers who used the product for more than 20 years before their disease diagnoses. The observed association persisted after adjusting for other major classes of pesticides and other potential confounders. This pooled analysis confirmed earlier reports suggesting that the use of carbamate pesticides (particularly Sevin) may increase the risk of NHL, [17] [18] whereas it was not possible to adjust for use of other pesticides.

A potential increased risk of NHL associated with carbamate pesticide exposure is supported by results of experimental studies showing that carbamate pesticide exposure may cause lymphomas and immunosuppression. Borzsonyi et al [2] reported that malignant lymphomas developed in Swiss mice after intragastric treatment with carbamate pesticides (including benomyl and thiabendazole) combined with sodium nitrite in their drinking water. They speculated that the risk may be related to the carcinogenic effect of *N*-nitroso compounds formed from carbamate pesticides in vivo. Borzsonyi et al [3] also reported lymphomas in 33.3% of young mice whose mothers were treated with methyl-2-benzididazole carbamate (carbendazim) together with sodium nitrite in the first week of pregnancy, 53.3% of those whose mothers were treated during the second week, and 38.8% of those born of mothers treated during the third week.

Some carbamates seem to affect the functions of the immune system, which might affect cancer development. Sevin has been reported to cause suppression of typhoid vaccine-induced immunity, and this suppression was shown to be correlated with the reduced phagocytic activity of leukocytes. [4] Street and Sharma [5] reported reductions in serum γ-globulin levels in Sevin- and carbofuran-treated rabbits. Wiltrout et al [6] reported significant suppression of specific antibody plaque forming cells in Balb/c mice orally exposed to Sevin. Sevin was also reported to increase quail susceptibility to a protozoan parasite [7] and to enhance the in vitro infectivity of viruses in human lung cells and green kidney cells. [8]

Carbofuran, a carbamate insecticide, was shown to decrease mitogen activity, reduce immunoglobulin levels, increase mortality after *Salmonella typhimurium* challenge in mice, [9] decrease lymphocyte and bone marrow populations, [10] and affect immunoglobulin subclass levels in mice. [11] Nevertheless, carbofuran did not show a risk pattern as clear as that observed for Sevin in this pooled analysis.

Aldicarb, another carbamate insecticide, was also shown to cause immunosuppression after exposure of mice to levels as low as 1 part per billion for 34 days in drinking water. [12] Fiore et al [13] reported that women chronically ingesting low levels of aldicarb-contaminated groundwater had altered numbers of T cells, including a decreased CD4/CD8 cell ratio. A study [14] from Bhopal, India, reported that exposure

to methyl isocyanate, an intermediate in the production of carbamate pesticides, caused a variety of effects on immune responses in exposed persons, including a decrease in lymphocyte mitogenesis. There were insufficient numbers of case and control subjects to evaluate aldicarb use and NHL risk here.

Strengths and weaknesses of the studies included in this pooled analysis should be considered in interpreting our results. The population-based nature and the high response rates from both the case and control subjects in the original studies lend confidence to the validity of the combined study analyses. The relatively large sample size in this pooled analysis also facilitates evaluation by exposure characteristics and control of confounding, which was limited in the original individual studies

A major concern is whether misclassification of exposure in the original studies may have affected the study results, as discussed elsewhere. [18] [19] [20] [21] [22] [23] Misclassification of exposure is possible because data related to past exposure to pesticides was obtained by interviews with study subjects or their proxy respondents. Differential misclassification is a concern in case-control studies. However, as reported by Hoar et al, [19] comparison of responses of case and control subjects regarding pesticide use with information obtained from pesticide suppliers in the Kansas study provided no indication of differential response bias. Case and control subjects also did not differ generally regarding the proportion of respondents who required a probe by the interviewer to elicit a positive response for the use of individual pesticides in the Nebraska study. [28] A similar proportion of case and control subjects volunteered the use of individual pesticides, whereas a greater proportion among case subjects would have been expected if case-response bias was operating.

Based on the results from studies of quality of information on pesticide use provided by farmers or their proxy respondents, [29] [30] it is also unlikely that differential misclassification of exposure could be entirely responsible for the observed increase in the risk of NHL among farmers who reported having used carbamate pesticides, particularly the carbamate insecticide Sevin. On the other hand, nondifferential misclassification of exposure could have occurred in the original studies, because study subjects, particularly proxy respondents, were unlikely to recall past lifetime pesticide exposure accurately. It is clear from methodological investigations comparing direct and proxy responses that proxies cannot provide as much information on pesticide use as the subjects themselves. [29] [30] [31] Nevertheless, the results based on direct interviews reached only the same conclusion as shown in table 2, table 3, table 4, table 5, table 6, table 7.

Another potential source of misclassification of exposure is that subjects might have been exposed to carbamate pesticides from sources other than agricultural. For example, farmers may also be exposed to carbamate pesticide through garden and lawn uses. Aldicarb, a carbamate insecticide, has been detected as a groundwater contaminant in many states, including Maine, Florida, California, Arizona, North Carolina, Virginia, New York, and Wisconsin. [32] [33] This type of misclassification of exposure, however, is likely to be nondifferential, which would tend to cause an underestimation of the association between carbamate pesticide use and NHL risk.

Conclusion

In summary, an increased risk of NHL was found among farmers who reported having used carbamate pesticides. Risk of NHL increased with the duration of Sevin use, and it was limited to those who personally handled the product and those who had used the product for more than 20 years before disease diagnosis. This association could not be explained by confounding from exposure to other

pesticides. Associations between NHL and carbofuran, butylate, and EPTC + protectant seemed unlikely because the excess occurred primarily in farmers who had not personally handled these chemicals. Considering the widespread use of carbamate pesticides, further investigation of the association in different populations is warranted.

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