

Agricultural pesticides and lymphoproliferative childhood cancer in California

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Objectives This study evaluated whether the rates of lymphoproliferative malignancies among children are elevated in areas of intensive agricultural pesticide use in the state of California in the United States.

Methods The study included all newly diagnosed, statewide cases of childhood lymphoma and acute lymphoblastic leukemia in 1988–1994 among children aged <15 years. Of the 2642 cases (over 6.6 million children in California and 46 million child-years of observation) during this period, 2570 (97.3%) could be successfully geocoded for the analyses. An a priori classification of the >850 chemical agents reported in use during the study was developed by assigning the agents to eight chemical groupings of interest and identifying seven individual high-use agents with high potential toxicity. Rate ratios for neighborhood (block group) levels of pesticide use were estimated with a Poisson regression and adjustment for age, race and ethnicity, and gender.

Results The rates of childhood lymphoma and leukemia were not generally higher in high pesticide-use areas. Those of Hodgkin's disease, although based on small numbers (N=258), were slightly elevated in the areas with the highest use of several pesticide groupings.

Conclusions The generally null results in this study systematically examining the risk relationships for residential proximity to agricultural pesticide use stand in contrast to existing epidemiologic literature suggesting elevated childhood cancer risks from reported household pesticide use. These differences may be due to different chemical agents or to differences in indoor versus outdoor exposure potential or both. Future studies should use refined methods that better characterize the exposure potential for children to these agents.

Key terms environmental pollutant; lymphoproliferative disorder; neoplasm.

Some childhood cancer case-control studies have suggested that household pesticide use may be a risk factor for many malignancies, particularly childhood leukemias (1, 2). This possibility, coupled with an observed higher risk of non-Hodgkin lymphomas for adults with occupational agricultural pesticide exposure (3–5), has raised concerns that exposure to agricultural pesticides may be a risk factor for lymphoproliferative malignancies among children. To date, the scientific literature has provided little evidence bearing on this hypothesis.

Childhood cancers differ from those of adulthood. Unlike adult cancers, lymphoproliferative cancers comprise the most common tumor types among children, with lymphoblastic leukemias and lymphomas contributing nearly half (over 40%) of all cancers in children

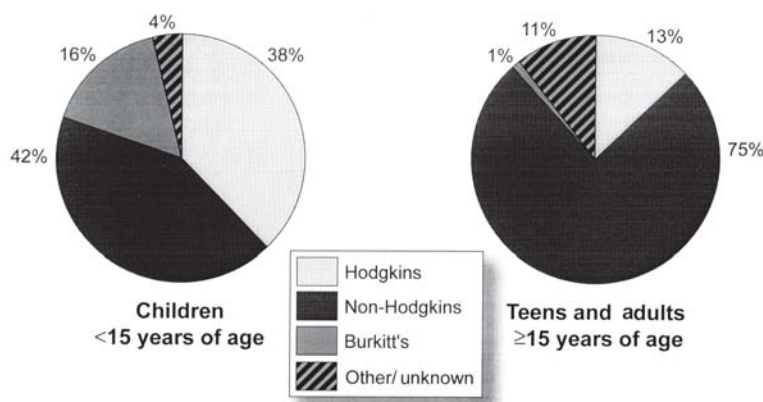
under the age of 15 years (6–8). In addition, these malignancies appear as different subtypes in children than they do in adults. The most common leukemias in children are the acute lymphoblastic leukemias (ALL), which comprise 80% of childhood leukemias and are very rare in adults. Hodgkin's and non-Hodgkin lymphomas are present in nearly equal proportions in childhood (39% and 41% of all lymphomas, respectively), while the non-Hodgkin lymphomas comprise the vast majority (76%) of adult lymphomas (figure 1). Certain specific lymphoma types, such as Burkitt's lymphoma (which comprises roughly 15% of childhood lymphomas), are also rare in adults. These differences, along with the molecular heterogeneity of malignancies in these broad groups, have made it challenging to study

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Based on California Cancer Registry data, for 1994–1999 diagnosis years, for all areas of California, (United States).

Figure 1. Types of lymphoma diagnosed in children versus adults for all areas of California, 1994–1999.

environmental risk relationships in such a rare group of health outcomes. Nonetheless, the issue has been one of great public health concern.

California is the largest agricultural state in the United States [9 & unpublished data of the US Department of Agriculture. Pesticide Properties Database (homepage on the Internet). US Department of Agriculture. Accessed 31 May 1999. Available at <http://www.arsusda.gov/acsi/services/ppdb>] and ranks highest for pesticide use, accounting for roughly 25% of the pesticide usage in the nation (10, 11). Nearly 170 million pounds (about 77 million kilograms) of pesticides are applied annually to agricultural areas in California, including over 22 million pounds (about 10 million kilograms) of agents classified as probable or possible carcinogens (12). Community concerns exist for pesticide-associated health risks among children in areas of high pesticide use (13–15). The California Department of Health Services (CDHS) has a history of responding to community concerns about perceived “clusters” of childhood cancer, particularly in intensively agricultural communities where exposure potential exists for resident children (16, 17). These “cluster” investigations, lacking sufficient power to detect moderate increases in cancer rates, have prompted efforts toward a broader scale approach. As part of a statewide study of childhood cancer patterns in California, a team of CDHS researchers undertook a systematic evaluation of the relationship between these cancers and residence in agricultural areas of the state. The team’s earlier reports provide detailed information on the prevalence of agricultural pesticide exposures among California children (11) and general patterns of childhood cancer incidence in high-use areas (18).

Methods

For their study, the CDHS researchers utilized information from the California population-based cancer

surveillance system [unpublished data of the California Cancer Registry (homepage on the Internet)]. Accessed 6 March 2003. Available at <http://www.ccrca.org/> and from the state’s mandatory Pesticide Use Reporting (PUR) system (19). California has maintained a statewide population-based cancer reporting system since 1988, with a much longer history of contributing to the Surveillance, Epidemiology and End-Results (SEER) program of the National Cancer Institute and the Cancer Incidence in Five Continents program of the International Agency for Research on Cancer (IARC) for the most populous areas of the state (20, 21). Since 1990, all agricultural pesticide use in California has been reportable to the Department of Pesticide Regulation and is available in detail from the California PUR system. Data from these two sources were integrated in the CDHS study using a geographic information system.

Population data

Denominator data was estimated for the ecologic study at the 1990 block group level of the United States (US) census. Block groups are the geographic units below a census tract and the smallest geographic unit for which detailed population characteristics are available. Age-, race-, and gender-specific person-year estimates for the study period were developed for each of the 21 443 Californian block groups. Because population growth in California varied by race or ethnicity and age group over this period, computed person-years of observation were adjusted by these factors on the basis of annual statewide data generated by the California Department of Finance (22).

Case information

The CDHS analysis included all newly diagnosed cases of ALL, Hodgkin’s disease, non-Hodgkin’s lymphoma, and Burkitt’s lymphoma [based on the International

Classification of Childhood Cancer (ICCC), groups Ia, IIa, IIb and IIc, respectively] (23) diagnosed among California residents under the age of 15 years between 1988 and 1994. A small number (N=36) of miscellaneous and unspecified lymphomas (ICCC classifications IId and IIe) were excluded from the analyses. During this time, 2642 cases occurred, of which 2570 (97.3%) could be geocoded to a block group of residence and included in the study.

Census data

So that potential confounding by socioeconomic status and urbanization could be examined, US census information (24) for each subject's neighborhood (block group) of residence was used to construct quartiles of median family income as a proxy for neighborhood socioeconomic status. The degree of each block group's urbanization was based on the census definition of an urbanized area and on census-defined metropolitan statistical areas.

Pesticide-use information

California maintains a unique resource in its PUR system. All agricultural pesticide use in California is reportable by law. Details on each pesticide's active ingredient, the number of pounds applied, the number of acres

covered, the date applied, and the location applied must to be reported for each pesticide application. These data are geographically reported for areas of approximately one square mile, based on the township, range, and section designation from the Public Land Survey System (25).

In the CDHS study individual reportable pesticides were selected for analysis according to various hazard measures (volume of use, risk score, toxicologic evidence, and exposure potential); the methods used have been explained in detail elsewhere (12). Pesticides were also grouped for analysis by toxicologic end point and chemical class to assess compounds that behave similarly in the environment and human body. The classification of the US Environmental Protection Agency (EPA) for cancer class was used, although class B (probable carcinogen) and class C (possible carcinogen) are roughly equivalent to IARC groups 2A and 2B, respectively [unpublished data of the International Agency for Research on Cancer (IARC). Preamble to the IARC monograph series, section 12: evaluation (homepage on the Internet). Accessed 6 March 2003; available at <http://monographs.iarc.fr>. IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans]. For the ecological analysis, yearly pounds of use were averaged for 1991 through 1994 (figure 2) and, with the use of a geographic information system, these averages were summed for each block group, based on

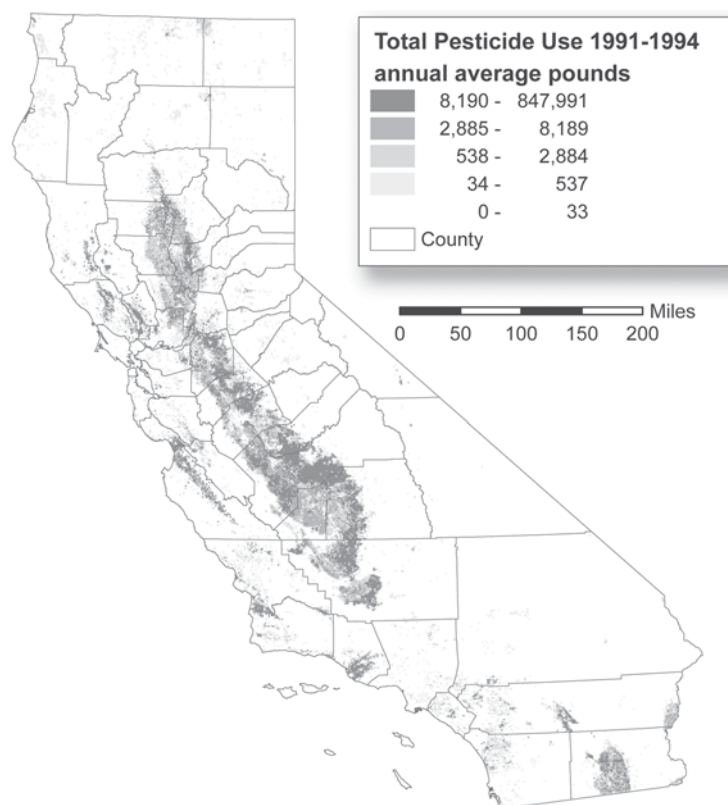


Figure 2. Annual average amount of pesticides applied in California, 1991–1994. (1 pound = 0.45 kg)

the percentage of the section within the block group boundaries, then divided by the area of the block group (12, 18).

Four toxicologic groups (probable carcinogens, possible carcinogens, genotoxic compounds and reproductive or developmental toxicants) and four chemical classes (organochlorines, organophosphates, carbamates and dithiocarbamates) were included in these analyses. Seven individual pesticides, ranked highest for toxicity and usage (propargite, methyl bromide, trifluralin, simazine, metam sodium, dicofol and chlorothalonil) (12), were separately analyzed. For each analysis, the reference group was comprised of all block groups with no applications or less than 1 pound (0.45 kg) per square mile of pesticide use for that group or individual pesticide. The other two usage categories were based on the distributions of pesticide-use densities among the block groups in the state with greater than 1 pound (0.45 kg) per square mile of use density: 1st to 74th percentiles and ≥ 75 th percentile.

Statistical methods

Rate ratios (RR) were estimated with the use of a Poisson regression and adjustment for age, race, and gender. Additional models were run to examine potential confounding by the socioeconomic or urbanization characteristics of the neighborhoods (block groups). All the analyses were performed using an SAS program (26).

Results

The CDHS study included 1938 cases of ALL, 258 cases of Hodgkin's disease, 275 cases of non-Hodgkin's

lymphoma, and 99 cases of Burkitt's lymphoma. The distribution of the cases by age group, race and ethnicity, and gender is shown in table 1. The majority of the ALL cases occurred among children <5 years of age, while the lymphomas, particularly Hodgkin's and non-Hodgkin lymphomas, were more common among older children. There were almost equal numbers of Hispanic and non-Hispanic white children among the cases for both ALL and Hodgkin's disease. However, for non-Hodgkin lymphoma, there were more non-Hispanic white cases than Hispanic cases. This finding is consistent with the significantly lower incidence rates for non-Hodgkin's lymphoma among California's Hispanic children as compared with its non-Hispanic white children in a previous report (27). For all four cancer types, there were more cases among the boys than among the girls.

An examination of the toxicologic and chemical groupings revealed no increased rates of ALL in high usage areas (tables 2 and 3). The rate ratios for the areas of highest class B carcinogen use, for example, was 0.99 [95% confidence interval (95% CI) 0.79–1.24]. Similarly, the rates of ALL were not significantly elevated in areas of the highest use for any of the individual pesticides examined (table 4). Most of the rate ratios for the highest categories of use were at or below 1. The only slightly elevated rate ratios observed for ALL were for methyl bromide (RR 1.16) and simazine (RR 1.21), but they were not statistically significant.

The rate ratios for Hodgkin's disease were somewhat elevated for the toxicologic and chemical groups. That for areas with the highest class B carcinogen use was 1.28 (95% CI 0.75–2.18) (table 2). For developmental and reproductive toxins, the rate ratio was 1.45 (95% CI 0.96–2.20), based on 33 cases in the highest use areas. Similarly, increased rate ratios were observed for high-use areas of organochlorines, carbamates, and

Table 1. Number of childhood cancer cases by age, race and ethnicity, and gender from 1988 through 1994 in California.

	Acute lymphoblastic leukemias		Hodgkin's disease		Non-Hodgkin's lymphoma		Burkitt's lymphoma	
	N	%	N	%	N	%	N	%
Age group								
0–4 years	1096	57	13	5	66	24	30	30
5–9 years	551	28	71	28	111	40	52	53
10–14 years	291	15	174	67	98	36	17	17
Race and ethnicity								
African-American	67	4	21	8	21	8	3	3
Hispanic	828	43	114	44	78	28	29	29
Asian, native American, other	182	9	11	4	33	12	14	14
Non-Hispanic, white	861	44	112	44	143	52	53	54
Gender								
Male	1097	57	163	63	186	68	75	76
Female	841	43	95	37	89	32	24	24
Total	1938	100	258	100	275	100	99	100

Table 2. Rate ratios ^a (RR) and 95% confidence intervals (95% CI) for childhood cancer by the density of pesticide use in the block groups, for the toxicologic groups. (lbs/mi² = pounds per square mile ^b)

	Block groups	Acute lymphoblastic leukemias			Hodgkin's disease			Non-Hodgkin's lymphoma		
		Cases (N)	RR	95% CI	Cases (N)	RR	95% CI	Cases (N)	RR	95% CI
Class B (probable carcinogens)										
<1st percentile	16 099	1462	1.00 ^c	..	182	1.00 ^c	..	218	1.00 ^c	..
1st–74th percentile (1–161 lbs/mi ²)	3 626	351	0.88	0.76–1.01	55	1.11	0.78–1.58	47	0.79	0.57–1.08
≥75th percentile (162–14 935 lbs/mi ²)	1 210	125	0.99	0.79–1.24	21	1.28	0.75–2.18	10	0.56	0.30–1.07
Class C (possible carcinogens)										
<1st percentile	14 694	1308	1.00 ^c	..	166	1.00 ^c	..	198	1.00 ^c	..
1st–74th percentile (1–131 lbs/mi ²)	4 682	479	0.94	0.83–1.06	64	0.99	0.72–1.36	59	0.76	0.54–1.05
≥75th percentile (132–5 043 lbs/mi ²)	1 559	151	0.93	0.76–1.13	28	1.28	0.82–1.99	18	0.76	0.44–1.32
Genotoxins										
<1st percentile	13 549	1194	1.00 ^c	..	149	1.00 ^c	..	184	1.00 ^c	..
1st–74th percentile (1–467 lbs/mi ²)	5 541	543	0.91	0.80–1.04	74	0.98	0.72–1.33	69	0.74	0.55–0.99
≥75th percentile (468–70 670 lbs/mi ²)	1 845	201	1.00	0.82–1.21	35	1.35	0.90–2.03	22	0.74	0.46–1.17
Developmental and reproductive toxins										
<1st percentile	14 347	1265	1.00 ^c	..	158	1.00 ^c	..	196	1.00 ^c	..
1st–74th percentile (1–481 lbs/mi ²)	4 942	491	0.93	0.82–1.05	67	1.00	0.73–1.38	58	0.70	0.51–0.96
≥75th percentile (482–48 784 lbs/mi ²)	1 646	182	1.03	0.85–1.24	33	1.45	0.96–2.20	21	0.79	0.49–1.28

^a All rate ratios were adjusted for age, race, and gender.^b 1 pound = 0.45 kilograms; mile = 1.6 kilometers.^c Reference group.**Table 3.** Rate ratios ^a (RR) and 95% confidence intervals (95% CI) for childhood cancer by the density of pesticide use in the block groups, for the chemical groups (lbs/mi² = pounds per square mile ^b)

	Block groups	Acute lymphoblastic leukemias			Hodgkin's disease			Non-Hodgkin's lymphoma		
		Cases (N)	RR	95% CI	Cases (N)	RR	95% CI	Cases (N)	RR	95% CI
Organochlorines										
<1st percentile	19 028	1746	1.00 ^c	..	232	1.00 ^c	..	253	1.00 ^c	..
1st–74th percentile (1–32 lbs/mi ²)	1 429	157	1.06	0.85–1.33	17	0.83	0.52–1.32	15	0.71	0.41–1.24
≥75th percentile (33–589 lbs/mi ²)	478	35	0.73	0.47–1.15	9	1.31	0.70–2.46	7	1.11	0.50–2.47
Organophosphates										
<1st percentile	14 866	1316	1.00 ^c	..	170	1.00 ^c	..	201	1.00 ^c	..
1st–74th percentile (1–100 lbs/mi ²)	4 554	475	0.97	0.86–1.09	64	1.01	0.74–1.36	55	0.73	0.53–1.00
≥75th percentile (101–7 129 lbs/mi ²)	1 515	147	0.94	0.77–1.14	24	1.12	0.71–1.76	19	0.83	0.50–1.37
Carbamates										
<1st percentile	16 921	1527	1.00 ^c	..	189	1.00 ^c	..	223	1.00 ^c	..
1st–74th percentile (1–53 lbs/mi ²)	3 001	320	0.98	0.84–1.13	51	1.26	0.90–1.76	40	0.84	0.62–1.14
≥75th percentile (54–1 706 lbs/mi ²)	1 013	91	0.87	0.67–1.13	18	1.30	0.77–2.20	12	0.84	0.49–1.43
Dithiocarbamates										
<1st percentile	17 768	1619	1.00 ^c	..	212	1.00 ^c	..	234	1.00 ^c	..
1st–74th percentile (1–204 lbs/mi ²)	2 375	241	0.96	0.82–1.13	30	0.91	0.60–1.40	35	0.97	0.68–1.40
≥75th percentile (205–14 931 lbs/mi ²)	792	78	0.92	0.70–1.19	16	1.38	0.78–2.44	6	0.52	0.23–1.19

^a All rate ratios were adjusted for age, race, and gender.^b 1 pound = 0.45 kilograms; mile = 1.6 kilometers.^c Reference group.

dithiocarbamates, but these rates were each based on fewer than 20 cases (table 3). The rates of Hodgkin's disease also appeared to be slightly elevated in areas with the highest use of several of the individual pesticides, including methyl bromide (RR 1.24), metam sodium (RR 1.17), trifluralin (RR 1.13), and dicofol (RR 1.43) (table 4). However, none of these rate ratios were statistically significant, and they were based on relatively small numbers of cases. For example, in the highest

use areas for dicofol, there were only seven cases of Hodgkin's disease.

The rate ratios for non-Hodgkin's lymphoma were <1 for most of the chemicals and groups examined. The rate ratios for all of the toxicologic groups were <1 (table 2). The rate ratio for non-Hodgkin's lymphoma in high-use areas of class B carcinogens, for example, was 0.56 (95% CI 0.30–1.07). The rate ratios for the chemical groups were also <1 with the exception of those of

Table 4. Rate ratios^a (RR) and 95% confidence intervals (95% CI) for childhood cancer by the density of pesticide use in the block groups, for the individual pesticides (lbs/mi² = pounds per square mile^b)

	Block groups	Acute lymphoblastic leukemias			Hodgkin's disease			Non-Hodgkin's lymphoma		
		Cases (N)	RR	95% CI	Cases (N)	RR	95% CI	Cases (N)	RR	95% CI
Propargite										
<1st percentile	18 907	1736	1.00 ^c	..	226	1.00 ^c	..	254	1.00 ^c	..
1st–74th percentile (1–69 lbs/mi ²)	1 520	151	0.91	0.76–1.09	26	1.18	0.80–1.74	19	0.78	0.52–1.17
≥75th percentile (70–926 lbs/mi ²)	508	51	1.03	0.76–1.39	6	0.85	0.39–1.86	2	0.29	0.09–0.96
Methyl bromide										
<1st percentile	17 574	1579	1.00 ^b	..	209	1.00 ^b	..	234	1.00 ^c	..
1st–74th percentile (1–836 lbs/mi ²)	2 524	255	0.97	0.83–1.13	34	0.96	0.66–1.40	30	0.76	0.52–1.13
≥75th percentile (837–45 185 lbs/mi ²)	837	104	1.16	0.92–1.45	15	1.24	0.72–2.13	11	0.86	0.46–1.60
Metam sodium										
<1st percentile	19 777	1821	1.00 ^c	..	243	1.00 ^c	..	265	1.00 ^c	..
1st–74th percentile (1–499 lbs/mi ²)	871	90	0.95	0.73–1.23	10	0.77	0.43–1.38	9	0.67	0.33–1.33
≥75th percentile (500–14 480 lbs/mi ²)	287	27	0.88	0.55–1.39	5	1.17	0.52–2.64	1	0.24	0.03–1.85
Trifluralin										
<1st percentile	19 597	1810	1.00 ^c	..	237	1.00 ^c	..	265	1.00 ^c	..
1st–74th percentile (1–51 lbs/mi ²)	1 005	103	0.97	0.76–1.25	16	1.08	0.60–1.95	8	0.52	0.21–1.29
≥75th percentile (52–784 lbs/mi ²)	333	25	0.81	0.49–1.34	5	1.13	0.40–3.17	2	0.47	0.08–2.78
Simazine										
<1st percentile	18 853	1739	1.00 ^c	..	232	1.00 ^c	..	244	1.00 ^c	..
1st–74th percentile (1–44 lbs/mi ²)	1 561	142	0.92	0.74–1.15	22	1.02	0.70–1.50	26	1.16	0.54–2.50
≥75th percentile (45–582 lbs/mi ²)	521	57	1.21	0.86–1.71	4	0.59	0.25–1.41	5	0.76	0.14–4.06
Dicofol										
<1st percentile	19 609	1812	1.00 ^c	..	240	1.00 ^c	..	259	1.00 ^c	..
1st–74th percentile (1–25 lbs/mi ²)	994	103	1.01	0.79–1.29	11	0.78	0.44–1.40	11	0.77	0.41–1.45
≥75th percentile (26–352 lbs/mi ²)	332	23	0.67	0.40–1.12	7	1.43	0.70–2.95	5	1.10	0.43–2.79
Chlorothalonil										
<1st percentile	18 603	1684	1.00 ^c	..	222	1.00 ^c	..	251	1.00 ^c	..
1st–74th percentile (1–43 lbs/mi ²)	1 749	190	0.99	0.83–1.19	28	1.10	0.75–1.62	17	0.61	0.39–0.97
≥75th percentile (44–2 537 lbs/mi ²)	583	64	1.05	0.78–1.43	8	0.98	0.49–1.97	7	0.83	0.42–1.67

^a All rate ratios were adjusted for age, race, and gender.^b 1 pound = 0.45 kilograms; mile = 1.6 kilometers.^c Reference group.

the organochlorine group, which had a rate ratio of 1.11 for the highest usage areas (95% CI 0.50–2.47) (table 3). For the highest use category of propargite, the observed rate ratio was 0.29 (95% CI 0.09–0.96), but this value was based on only two cases in the highest potential exposure category (table 4). The only individual pesticide that had a rate ratio of >1 for the highest category was dicofol (RR 1.10), but this value was not statistically significant and, again, was based on relatively small numbers of cases. The rate ratios for Burkitt's lymphoma were similar to those of non-Hodgkin's lymphoma, and none were statistically significant (data not shown).

The rate ratios for all of these analyses were essentially unchanged when terms for median family income were added to the models (data not shown). When adjusted for urbanization levels, the point estimates increased slightly, and the rate ratios for Hodgkin's disease and three of the toxicologic groupings became statistically significant (class C: RR 1.60, 95% CI 1.05–2.42; genotoxins: RR 1.54, 95% CI 1.08–2.20; developmental or reproductive toxins: RR 1.66, 95% CI 1.15–2.40).

Discussion

This CDHS study represents a first step in evaluating potential risk relationships for childhood lymphoproliferative malignancies and residential exposures to agricultural pesticides. Previous studies of pesticide-associated risks for childhood cancer have primarily relied on self-reported information on household pesticide use or information on parental occupational pesticide exposures. The analyses, along with earlier study findings for broader cancer groups (18), suggest little evidence that residence in areas of high agricultural pesticide use is associated with increased risks for cancer in children.

The single study with an exposure characterization similar to that used by CDHS is a large population-based cohort study of farming families from the agricultural censuses in Norway (28). This study, based on record linkage to the Cancer Registry of Norway, was primarily designed to evaluate risks associated with parental occupational exposures, but proximity to treated fields was also relevant, as many of these families also lived on the farms.

Interestingly, the Norway study also reported null findings for childhood leukemias, but positive results for the lymphomas, in association with agricultural pesticides.

It is of particular interest that the CDHS results stand in contrast to a generally positive pattern of suggested association between childhood cancer and household pesticide use found in the case-control literature. Reviews of this literature have noted both positive and null study findings, but were based on only a few studies (1, 2). Furthermore, most earlier reports relied on one or two indicator questions from case interviews and have limited information on leukemia or lymphoma subtypes. A 1997 review (1) reported positive risk associations for household pesticide use in the handful of published childhood leukemia studies including such information, but the few studies that had examined risk associations for farm residence, garden pesticide use, or home extermination found no elevated risks. While the evidence on this use is still mixed, more recent reports have been able to examine these risk associations in somewhat greater detail. A large German case-control study reported a stronger association between household pesticide use and childhood lymphoma than that between household pesticide use and childhood leukemia (29). The same study reported a suggestion of elevated leukemia risk in association with living on a farm. A recent California study of childhood leukemia, which focused on detailed household pesticide exposure opportunities, found a substantially elevated risk in association with the use of professional pest control services; the highest point estimates for insecticide exposures occurred during the in utero period (30). Similarly, a Canadian case-control study reported higher risk associations for ALL with household insecticide and pesticide use during the mother's pregnancy (31). These last two studies suggested that earlier life exposures may be more associated with outcome than are exposures occurring closer to the time of diagnosis.

Potential exposures associated with living and playing near agricultural pesticide applications differ from those associated with household treatments in at least two ways. First, agricultural pesticides represent a somewhat different collection of chemical agents. Active ingredients in many such pesticides are registered as restricted-use in California and can only be applied in agricultural settings [California Department of Pesticide Regulation. California product/label database queries & lists (homepage on the Internet). Accessed: 15 June 2002; available at <http://www.cdpr.ca.gov/docs/label/labelque.htm>]. Second, exposures resulting from home and garden pesticide use, particularly indoors, are likely to be much higher than the exposures resulting from living near areas of agricultural pesticide use.

Three recent studies underscore the finding that household exposures may be more important than agri-

cultural exposures. The Northern California Childhood Leukemia Study observed elevated odds ratios for reported indoor, but not outdoor, home pesticide use (30). Similarly, a report on non-Hodgkin's lymphoma from the Children's Cancer Group reported much higher risk estimates for household pesticide use than for parental occupations (32). In a very large, population-based, case-control study of childhood leukemias and lymphomas in Germany (29), reported use of household pesticides was more strongly associated with these outcomes than was reported garden pesticide use.

There are several important limitations to consider in an evaluation of the CDHS study findings. Chief among these is the assumption that residential proximity is a good indicator of exposure. The literature to date is somewhat mixed regarding how well proximity to agricultural fields correlates with environmental or biological measures of exposure. Studies from Washington State suggest that living in close proximity to treated orchards increases the level of pesticides in household dust and also increases metabolite levels in urine (33, 34). A smaller study in Imperial County, California, did not find an association between urinary organophosphate metabolite concentrations in toddlers and proximity to agricultural fields (35). The CDHS analyses, reported here, were based on summary measures of agricultural pesticide use near a single residential address and did not account for residential mobility or for time and activity patterns of the study children. This pesticide information, while remarkably detailed, was limited to agricultural applications and could not account for other area treatments, such as house fumigation or pesticides applied on nearby parks or golf courses. Similarly, there was no information on individual household or garden pesticide use. Exposure potential was exclusively based on reported applications, and there was no environmental or biological measurement of exposure. The CDHS study, by virtue of being entirely record-based, was also limited to information on demographic covariates. No information on personal risk factors or on residential history was available. The time window for exposure was limited to recent residence, and pesticide use information was averaged over the period of interest.

Even with these limitations, the CDHS approach offers several advantages over studies of pesticide use to date. Because of the richness of the California PUR database, it was possible to evaluate specific toxicologic groups of pesticides and to quantify pesticide-use levels. In contrast to the existing case-control literature, this study was population-based and not subject to response or reporting bias. Because of the large California child population and diversity of residential environments, the study data offered sufficient variability, scale, and power to detect even modest risk associations.

Some methodological challenges remain in the effort to assess children's potential exposure to the large family of chemical mixtures that characterize pesticides (29, 36, 37). Future study designs, which combine the advantages of a well-designed case-control study with approaches based on a geographic information system, will help advance the understanding of potential risks for children exposed to pesticides, whether agricultural or household. CDHS is spearheading two such efforts. In a statewide population-based case-control study of early childhood malignancies, CDHS researchers are tailoring information on pesticide exposure attributed to individual residences at the time of birth. This approach will examine time-specific pesticide use within a short distance of these residences, rather than characterizing general neighborhood use. In addition, a follow-up study is currently under way, in a joint effort between CDHS and the University of California at Berkeley, to integrate some of these study methods for area exposure attributes, the rich personal, biological, and environmental data being collected as part of the Northern California Childhood Leukemia Study.

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