Childhood Cancer and Agricultural Pesticide Use: An Ecologic Study in California

Peggy Reynolds,[1] Julie Von Behren,[1] Robert B. Gunier,[1] Debbie E. Goldberg,[2] Andrew Hertz,[3] and Martha E. Harnly[1]

[1]California Department of Health Services, Environmental Health Investigations Branch, Oakland, California, USA; [2]Public Health Institute, Berkeley, California, USA; [3]Impact Assessment Inc., Oakland, California, USA

We analyzed population-based childhood cancer incidence rates throughout California in relation to agricultural pesticide use. During 1988–1994, a total of 7,143 cases of invasive cancer were diagnosed among children under 15 years of age in California. Building on the availability of high-quality population-based cancer incidence information from the California Cancer Registry, population data from the U.S. Census, and uniquely comprehensive agricultural pesticide use information from California's Department of Pesticide Regulation, we used a geographic information system to assign summary population, exposure, and outcome attributes at the block group level. We used Poisson regression to estimate rate ratios (RRs) by pesticide use density adjusted for race/ethnicity, age, and sex for all types of childhood cancer combined and separately for the leukemias and central nervous system cancers. We generally found no association between pesticide use density and childhood cancer incidence rates. The RR for all cancers was 0.95 [95% confidence interval (CI), 0.80–1.13] for block groups in the 90th percentile and above for use of pesticides classified as probable carcinogens, compared to the block groups with use of < 1 lb/mi^2. The RRs were similar for leukemia and central nervous system cancers. Childhood leukemia rates were significantly elevated (RR = 1.48; 95% CI, 1.03–2.13) in block groups with the highest use of propargite, although we saw no dose–response trend with increasing exposure categories. Results were unchanged by further adjustment for socioeconomic status and urbanization. *Key words*: **agriculture, childhood cancer, ecologic study, epidemiologic study, exposure assessment, geographic information system, pesticides, risk assessment.** *Environ Health Perspect* **110:319–324(2002). [Online 14 February 2002]**
http://ehpnet1.niehs.nih.gov/docs/2002/110p319-324reynolds/abstract.html

Cancer is the second leading cause of death among children 5–14 years of age in the United States (*1*). Few risk factors have been established for childhood cancers other than ionizing radiation (*2,3*), chemotherapy agents (*2*), and certain inherited genetic disorders (*4,5*). Positive associations have been observed in case–control studies between pesticide use in the home or garden and childhood leukemia (*6–9*) and brain cancer (*10,11*). Parental occupational exposure to pesticides, determined by occupation from birth certificates or questionnaire, has also been associated with childhood cancer (*6,7,12–15*). Two recent reviews of childhood cancer and pesticides concluded that multiple studies show a modest increased risk, particularly for leukemia and brain cancer, but these studies have been limited by small numbers, nonspecific pesticide information, and potential case-response bias (*16,17*).

California is the largest agricultural state in the nation, with an average of $20 billion per year in farm revenues during the 1990s (*18,19*). California also consistently ranked highest in agricultural pesticide use based on national surveys conducted in the 1990s, accounting for about 25% of use nationwide (*20,21*). The potential for pesticide exposure in agricultural communities has been a major source of public concern (*22–24*). Children living in agricultural communities have a broad range of potential exposure pathways to pesticides, including inhalation of ambient air, ingestion of contaminated household dust, parental occupational "take-home" exposures, and playing in or eating produce from treated fields (*25–30*). Proximity to treated fields has been correlated with pesticide concentrations in ambient air (*31*) and to pesticide metabolite levels in biologic monitoring of children (*32,33*).

In 1990, the California Department of Pesticide Regulation began the Pesticide Use Report (PUR) system, requiring growers and applicators to report all agricultural pesticide use. Previously, we used the PUR data and a geographic information system (GIS) to prioritize and classify the over 850 chemicals reported to the PUR and to assess the geographic distribution of agricultural pesticide use (*34*). Although pesticide use in most block groups (77%) averaged < 1 lb/mi^2 for 1991 through 1994, approximately 170,000 children under 15 years of age were living in block groups with ≥ 569 lbs of probable carcinogens per square mile of block group. The range of values reported was suitable for a statewide study of childhood cancer incidence rates by agricultural pesticide use density.

The California Department of Health Services has undertaken a number of childhood cancer cluster investigations in agricultural communities where pesticide use was a concern, but these studies have typically not had sufficient power to detect moderate increases in cancer rates (*35*). The current study is designed to take a broader perspective on those concerns by conducting a statewide study of childhood cancer and pesticide use, using case data from the population-based cancer registry. It also takes advantage of the specificity in the PUR, examining potential exposures to specific pesticides. This is the first study to assess population-based childhood cancer incidence rates by agricultural pesticide use density.

Materials and Methods

Pesticide data. California's Department of Pesticide Regulation maintains a pesticide use reporting (PUR) database that includes detailed information on the active ingredient, quantity applied, acres treated, crop treated, and location (in square mile sections) for all agricultural pesticide applications in the state. For this study, we used reported PUR data from 1991 through 1994 to calculate the annual average pesticide use in each square mile section (*36*), and we used a GIS to identify all sections located within each census block group (*37*). If a section fell into more than one block group, we allocated the pesticide use based on the percentage of area of the section in each block group. In 1990, California block groups had a median land area of 0.2 mi^2, with a range between 0.0001 and 3,610 mi^2 (*38*). We estimated average annual agricultural pesticide use for the study period for each block group by summing the average pounds applied in all relevant sections, then dividing by the block group area to obtain pesticide use density in pounds per square mile.

We combined pesticides reported to the PUR system during the study period into four toxicologic groups (probable carcinogens, possible carcinogens, genotoxic compounds, and reproductive or developmental toxicants)

Address correspondence to P. Reynolds, Environmental Health Investigations Branch, 1515 Clay Street, Suite 1700, Oakland, CA 94612 USA. Telephone: (510) 622-4500. Fax: (510) 622-4505. E-mail: preynold@dhs.ca.gov

This study was funded by grant R01 CA71745 from the National Cancer Institute.

Received 9 May 2001; accepted 7 August 2001.

and four chemical classes (organochlorides, organophosphates, carbamates, and dithiocarbamates). All pesticides classified as known human carcinogens were banned or severely restricted in California before the time of this study. Probable and possible carcinogens are determined almost exclusively from laboratory animal studies (*39*). Genotoxic chemicals directly damage DNA and may be important for a study of childhood cancer. We chose pesticides with at least two positive results in genetic toxicity assays for this analysis (*40*). We selected reproductive and developmental toxicants based on studies conducted in laboratory animals (*41*).

We prioritized individual pesticides for analysis on the basis of a combination of statewide use in pounds, the U.S. Environmental Protection Agency cancer class, the carcinogenic potency, field volatilization flux, and persistence (*34*). The top seven ranked pesticides that had a use density of > 1 lb/mi^2 in at least 1,000 block groups were selected for individual evaluation: propargite, methyl bromide, trifluralin, simazine, metam sodium, dicofol, and chlorothalonil.

Cancer incidence data. We obtained all cases of invasive cancer diagnosed in children under 15 years of age from California's population-based cancer registry for 1988 through 1994 (reported by April 1997). The statewide registry routinely records race, age, sex, and residence at the time of diagnosis. We assigned census block group designations to cases based on the geocoded location of residence at the time of diagnosis. We completed this task using a GIS to automatically match addresses with a road network and determine the corresponding census block group. We reviewed all addresses that could not be automatically linked and manually located them when possible.

Census data. We obtained population data for each census block group from the 1990 census (*42*) and multiplied population estimates by 7 to account for the person-risk time during the pericensal time period of the study. However, during this time period the population growth rate varied by age groups and race/ethnicity groups. To calculate the different rates of growth by age group and race/ethnicity, we determined the statewide population changes that occurred in each group between 1988 and 1994 (*43*) and then multiplied the age- and race-specific population for each census block group in 1990 by 7 and the applicable growth factor for that age/race group.

To examine potential confounding by socioeconomic status and urbanization, we used additional census information (*42*). We used quartiles of median family income in the block group as a proxy for neighborhood socioeconomic status and based the degree of urbanization of each block group on the census definition of an urbanized area and on census-defined metropolitan statistical areas.

Data analysis. We allocated block groups to agricultural pesticide use categories for four toxicologic groups, four chemical classes, and seven individual pesticides on the basis of statewide distributions of pesticide use density. We based these distributions on only those block groups with > 1 lb/mi^2 of use for that group or pesticide. For each analysis, the reference group was all block groups with no applications or with < 1 lb/mi^2 of pesticide use for that group or individual pesticide. We based the other three usage categories on the distributions of pesticide use densities among block groups in the state with > 1 lb/mi^2 of use density: 1st to 74th percentiles, 75th to 89th percentiles, and ≥ 90th percentile. We calculated age-, sex-, and race-adjusted rate ratios (RRs) for childhood cancer incidence and pesticide use density using Poisson regression. For these initial analyses, all types of childhood cancer were analyzed together and the two most common cancer types, leukemias and gliomas (brain cancer), were analyzed separately. We also examined these relationships for the two major leukemia subtypes, acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL), because associations with pesticides have been reported for these leukemia types. Although there have been suggestive studies for neuroblastoma, non-Hodgkin lymphoma, Wilms tumor, and Ewing sarcoma (*16*), the number of cases available for analysis was much smaller. We performed all analyses using SAS software (*44*).

Results

From 1988 to 1994, 7,143 cases of childhood cancer were diagnosed in California. We assigned 6,988 (97.8%) to a census block group. The study period included 46 million person-years of observation for children in California. Table 1 shows the number of geocoded cases by age, race/ethnicity, and sex for all sites, leukemias, and gliomas. Over one-third of the cases were leukemias, and 19% were gliomas; 36% of the total cases were Hispanic children, 47% were non-Hispanic white, and 7% were African American.

The number of block groups in the state with use density of > 1 lb/mi^2 for a given pesticide or group ranged from 1,072 (5% of all block groups) for metam sodium (Table 2) to 7,505 (35%) for genotoxic compounds (Table 3). The distributions of pesticide use density in these block groups were highly skewed, with order of magnitude differences between the median and 90th percentile values, and between the 90th percentile and the maximum. A significant number of block groups in the state had > 100 lb/mi^2 of pesticide use. For example, at the 75th percentile, 1,233 block groups in the state had > 162 lb/mi^2 of Class B (probable) carcinogenic pesticide use per year. The distributions of use density for the fumigants methyl bromide and metam sodium were much higher than those of the other individual pesticides. We mapped the geographic distribution of pesticide use density by block group for all probable carcinogens using the percentiles of the statewide distribution. By way of illustration, Figure 1 shows details of these distributions for one highly agricultural county in California (San Joaquin County). These distributions are described in greater detail elsewhere (*34*).

The RRs obtained from the Poisson regression analysis for all cancer sites, all leukemias, and all gliomas are presented in Tables 2, 3, and 4. The age-, race-, and sex-adjusted RRs for all childhood cancer sites combined were close to 1 for all four toxicologic groups at each usage level. For all cancer sites combined, the RR for areas with high propargite usage had a slightly elevated but not statistically significant RR (1.25). For leukemia, the results were statistically

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

	All sites		Leukemias		Gliomas	
	No.	(%)	No.	(%)	No.	(%)
Age group (years)						
0–4	3,515	(50)	1,351	(55)	604	(45)
5–9	1,752	(25)	673	(27)	421	(31)
10–14	1,721	(25)	419	(17)	326	(24)
Race/ethnicity						
African American	491	(7)	108	(4)	114	(8)
Hispanic	2,535	(36)	1,013	(41)	390	(29)
Asian, Native American, other	694	(10)	262	(11)	117	(9)
Non-Hispanic white	3,268	(47)	1,060	(44)	730	(54)
Sex						
Male	3,809	(55)	1,349	(55)	733	(54)
Female	3,179	(45)	1,094	(45)	618	(46)
Total	6,988	(100)	2,443	(100)	1,351	(100)

significant ($p < 0.05$) at the highest usage level for propargite (RR = 1.48). For the gliomas, the adjusted RRs were ≤ 1 for all the groups and individual pesticides examined. The RR for glioma in the highest usage areas for genotoxic pesticides was statistically significantly < 1 [RR = 0.71; 95% confidence interval (CI), 0.52–0.96].

We also examined these relationships for the two major leukemia subtypes, ALL and ANLL. In general, the point estimates for the two subtypes were very similar. The RR for ALL in the highest use areas for propargite was elevated (RR = 1.46), but the CI included 1. Very few cases of block groups with high pesticide use density had cases of ANLL, and the resulting point estimates have wide CIs that all included 1 (data not shown).

When we added an additional term for median family income of the block group to the multivariate models to assess the potential for confounding by socioeconomic status, the results were unchanged (data not shown). When we added an additional term for degree of urbanization, all point estimates increased slightly (data not shown).

Table 2. Childhood cancer RRs[a] [and 95% confidence intervals (CIs)] by block group agricultural pesticide use density for individual pesticides.

Percentile (lb/mi^2)	No. block groups	All sites No. cases	All sites RR (95% CI)	Leukemias No. cases	Leukemias RR (95% CI)	Gliomas No. cases	Gliomas RR (95% CI)
Propargite							
< 1 lb/mi^2	18,907	6,278	Ref	2,191	Ref	1,223	Ref
1st–74th			0.92		0.92		0.82
(1–69)	1,520	542	(0.83–1.10)	191	(0.78–1.08)	95	(0.66–1.02)
75th–89th			0.81		0.68		1.04
(70–171)	304	86	(0.64–1.02)	26	(0.45–1.04)	21	(0.66–1.62)
≥ 90th			1.25		1.48		0.98
(172–926)	204	82	(0.99–1.59)	35	(1.03–2.13)	12	(0.54–1.76)
Methyl bromide							
< 1 lb/mi^2	17,574	5,720	Ref	1,981	Ref	1,122	Ref
1st–74th			1.01		1.02		0.99
(1–836)	2,524	956	(0.93–1.09)	335	(0.90–1.16)	186	(0.84–1.16)
75th–89th			0.98		1.15		0.77
(837–2,667)	502	177	(0.83–1.16)	73	(0.89–1.48)	27	(0.52–1.14)
≥ 90th			1.01		1.13		0.63
(2,668–45,185)	335	135	(0.83–1.22)	54	(0.84–1.52)	16	(0.38–1.05)
Metam Sodium							
< 1 lb/mi^2	19,777	6,575	Ref	2,293	Ref	1,282	Ref
1st–74th			0.95		0.98		0.87
(1–499)	871	319	(0.85–1.07)	116	(0.78–1.24)	57	(0.64–1.20)
75th–89th			0.95		0.87		0.77
(500–1,502)	173	58	(0.73–1.23)	19	(0.50–1.53)	9	(0.35–1.67)
≥ 90th			0.81		0.92		0.37
(1,502–14,480)	114	36	(0.58–1.12)	15	(0.48–1.73)	3	(0.09–1.41)
Trifluralin							
< 1 lb/mi^2	19,597	6,547	Ref	2,286	Ref	1,279	Ref
1st–74th			0.94		0.96		0.80
(1–51)	1,005	354	(0.84–1.07)	127	(0.79–1.17)	58	(0.65–0.98)
75th–89th			0.80		0.73		0.75
(52–117)	205	55	(0.59–1.08)	18	(0.44–1.23)	10	(0.46–1.22)
≥ 90th			0.85		0.87		0.58
(118–784)	128	32	(0.57–1.26)	12	(0.46–1.63)	4	(0.27–1.25)
Simazine							
<1 lb/mi^2	18,853	6,255	Ref	2,198	Ref	1,205	Ref
1st–74th			1.02		0.92		1.02
(1–44)	1,561	563	(0.92–1.12)	179	(0.76–1.12)	111	(0.85–1.22)
75th–89th			0.94		1.37		1.08
(45–111)	314	92	(0.74–1.19)	47	(0.95–1.98)	21	(0.72–1.60)
≥ 90th			1.17		0.79		1.12
(112–582)	207	78	(0.91–1.51)	19	(0.45–1.40)	14	(0.69–1.82)
Dicofol							
< 1 lb/mi^2	19,609	6,514	Ref	2,283	Ref	1,270	Ref
1st–74th			1.03		1.02		0.92
(1–25)	994	368	(0.90–1.17)	130	(0.84–1.24)	64	(0.71–1.20)
75th–89th			0.91		0.70		0.52
(26–72)	200	65	(0.68–1.23)	18	(0.42–1.17)	7	(0.24–1.13)
≥ 90th			0.89		0.72		1.16
(73–352)	132	41	(0.61–1.29)	12	(0.38–1.34)	10	(0.60–2.22)
Chlorothalonil							
< 1 lb/mi^2	18,603	6,115	Ref	2,119	Ref	1,198	Ref
1st–74th			0.99		1.02		0.95
(1–43)	1,749	672	(0.91–1.08)	243	(0.88–1.18)	126	(0.79–1.15)
75th–89th			0.89		0.92		0.83
(44–108)	352	108	(0.72–1.10)	40	(0.65–1.32)	19	(0.52–1.33)
≥ 90th			1.04		1.27		0.47
(109–2,537)	231	93	(0.83–1.30)	41	(0.90–1.80)	8	(0.23–0.97)

Ref, reference level.
[a]All RRs were adjusted for age, race, and sex.

Discussion

In this study, which we designed to give an initial overview of pesticide-associated risk relationships, there is little evidence to support an association between childhood cancer incidence rates and residence in areas of high agricultural pesticide use. The general lack of associations in these results stands in contrast to the positive associations reported in most published case–control studies of childhood cancer and pesticides, and in contrast to the general conclusions implicating a risk association (*16,17*). Importantly, most previous studies have relied on self-reported pesticide use in the home and garden or parental occupational exposure and have had no information on agricultural pesticide use outside the home. Our study, on the other hand, examined agricultural use and had no data on home use. Some frequently used agricultural pesticides, such as trifluralin, simazine, ziram, chlorpyrifos, and diazinon, have or have had significant home and garden use. We included these compounds in our toxicologic groups where appropriate. We did examine several pesticides (i.e., propargite, methyl bromide, dicofol, and metam sodium) that are either not marketed for domestic use or are legally restricted to agricultural use in California.

Census block groups with high use of propargite did have significantly elevated rates of childhood leukemia in this study, but we observed no dose–response trend over categories of increasing pesticide usage. In contrast, block groups with the highest use of genotoxic pesticides had significantly lower rates of glioma. In animal studies, chemical exposures have been shown to increase and decrease both the incidence and size of tumors (*45,46*). We incorporated a large number of multiple comparisons into these analyses by testing many pesticide categories and cancer sites, which increased the likelihood of observing at least one statistically significant finding by chance. It is interesting to note, however, that propargite was the highest ranked among individual pesticides for potential cancer hazard based on reported use in California weighted by exposure and carcinogenic potential (*34*). Propargite is an insecticide used primarily in

orchards and vineyards to control mites. Propargite is classified as a probable human carcinogen based on excess sarcomas of the jejunum observed in rats fed propargite in their diet, although excess tumors have not been found in studies in mice (*39*). Whether or not this agent may impart risk for childhood leukemia will require additional study.

Propargite use in California is concentrated in the Central Valley rather than in other agricultural areas of the state. Propargite use is very high in the areas around three Central Valley communities (including McFarland) which were the sites of childhood cancer "cluster" investigations (all ≥ the 97th percentile of use for all block groups) (*35*). In addition to propargite, two chemicals also used heavily in the Central Valley are ziram and azinphos-methyl. The "cluster" towns also ranked ≥ the 95th percentile of use for these pesticides among all block groups statewide. When we subsequently analyzed these two chemicals, ziram had an adjusted RR of 1.54 (95% CI, 0.89–2.66) for leukemia, and azinphos-methyl had an adjusted RR of 1.40 (95% CI, 0.86–2.28) for leukemia.

Childhood cancer rates and proximity to agricultural use of specific pesticides have not been previously analyzed, although several studies of adult cancer incidence and mortality have been conducted (*47–49*); one recent study using the California PUR has reported elevations of adverse reproductive outcomes in high pesticide use areas (*50*). Our study is the first to examine childhood cancer incidence in relation to pesticides using an ecologic study design. This type of study has several limitations, including the lack of data on potential confounding factors, lack of information on residential stability, and the opportunity for misclassification of group level exposures. However, the design also offers some research advantages. The pesticide data we used in this study were based on mandatory reporting by growers that was not subject to recall bias. The PUR data also provided specific pesticide active ingredients and the amount applied. We were able to summarize and evaluate the use of potentially high hazard individual pesticides and groups of pesticides with similar toxicologic properties. Furthermore, because of the records-based nature of the study, we could include nearly all cases occurring in the population and had no problem with response bias.

In this particular situation, an ecologic approach is particularly appealing because the exposures of interest are area specific and are not likely to be accurately reported by individual respondents. Nonetheless, there are improvements that could enhance the accuracy and completeness of exposure attributes from these kinds of data. Pesticide use at the block group level was used as a surrogate for exposure in this study. We did not conduct environmental or biologic monitoring to assess actual exposure to children. Pesticide use in homes, schools, and parks is not reported with information on location and could not be included in this analysis. To improve exposure classification, biologic or environmental monitoring needs to be conducted to measure the actual exposure to children from agricultural pesticide use and compare this to exposure from pesticide use in the home, in the garden, and at school. A GIS was essential in this study for geocoding cases and assigning pesticide use to census block groups. The PUR data could be improved for use in epidemiologic studies by improving spatial reporting or by incorporating existing GIS layers with land use or crop classifications to increase the spatial resolution of pesticide applications. Such a project has recently been completed in Kern

Table 3. Childhood cancer RRs[a] (and 95% CIs) by block group agricultural pesticide use density for toxicologic groups.

Percentile (lb/mi^2)	No. block groups	All sites No. cases	All sites RR (95% CI)	Leukemias No. cases	Leukemias RR (95% CI)	Gliomas No. cases	Gliomas RR (95% CI)
Class B (probable carcinogens)							
<1 lb/mi^2	16,099	5,204	Ref	1,834	Ref	1,007	Ref
1st–74th			0.98		0.91		1.03
(1–161)	3,626	1,373	(0.91–1.04)	455	(0.81–1.03)	283	(0.91–1.17)
75th–89th			0.96		1.05		0.74
(162–568)	725	239	(0.83–1.11)	95	(0.83–1.33)	35	(0.54–1.01)
≥ 90th			0.95		0.89		0.78
(569–14,935)	485	172	(0.80–1.13)	59	(0.66–1.20)	26	(0.54–1.12)
Class C (possible carcinogens)							
<1 lb/mi^2	14,694	4,660	Ref	1,639	Ref	896	Ref
1st–74th			1.00		0.98		1.05
(1–131)	4,682	1,807	(0.94–1.07)	620	(0.87–1.09)	369	(0.93–1.18)
75th–89th			0.95		0.92		0.84
(132–444)	940	329	(0.83–1.08)	114	(0.74–1.16)	56	(0.64–1.10)
≥ 90th			0.91		0.91		0.78
(445–5,043)	619	192	(0.77–1.08)	70	(0.68–1.21)	30	(0.54–1.12)
Genotoxins							
<1 lb/mi^2	13,549	4,260	Ref	1,495	Ref	808	Ref
1st–74th			0.96		0.93		1.09
(1–467)	5,541	2,043	(0.91–1.02)	691	(0.83–1.04)	443	(0.98–1.22)
75th–89th			1.00		0.97		0.81
(468–1,843)	1,111	419	(0.90–1.12)	145	(0.79–1.20)	64	(0.64–1.03)
≥ 90th			0.96		1.12		0.71
(1,844–70,670)	734	266	(0.84–1.10)	112	(0.89–1.41)	36	(0.52–0.96)
Developmental and reproductive toxicants							
<1 lb/mi^2	14,347	4,554	Ref	1,590	Ref	874	Ref
1st–74th			0.95		0.93		1.04
(1–481)	4,942	1,805	(0.90–1.01)	616	(0.84–1.03)	382	(0.93–1.17)
75th–89th			1.04		1.03		0.85
(482–1,788)	988	384	(0.93–1.17)	135	(0.84–1.26)	60	(0.66–1.10)
≥ 90th			0.99		1.15		0.76
(1,789–48,784)	658	245	(0.86–1.14)	102	(0.91–1.44)	35	(0.55–1.06)

Ref, reference level.
[a]All RRs were adjusted for age, race, and sex.

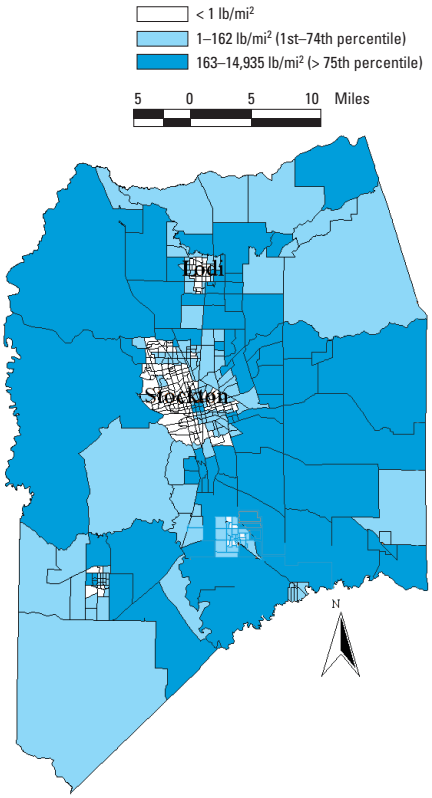

Figure 1. Annual average pesticide use density for 1991–1994 by census block group in San Joaquin County, California.

County, California. Because of the large number of pesticides reported in the PUR data, we were not able to evaluate each individual compound or all possible combinations of pesticides. Further study is needed in laboratory animals to direct future inquiries of possible interaction effects between combinations of pesticides.

The address at diagnosis may not be the most relevant time or place for exposure. Because we were limited to the use of registry data, however, we did not have information on residential history for the subjects. This should be less of a concern for childhood cancer than for adult cancer because of the shorter latency periods. We are currently conducting a case–control study using the address of mother's residence from birth certificates and the PUR data, which will allow us to evaluate these risk relationships for residences during another important time window. The exposure methods will be refined to assess pesticide use around a geocoded point rather than a census block group. Although follow-up studies that can better address timing of exposure will be important in assessing the etiologic significance of pesticide exposures, this study does address the public concern about whether rates of childhood cancer are higher in areas of heavy agricultural pesticide use.

This study is the first to examine RRs for childhood cancer associated with patterns of agricultural pesticide use. The observed lack of association in this study stands in contrast to evidence on household use from the case–control literature, but does not necessarily imply a lack of association with pesticide exposures in general. The current study focuses on residence in areas of high agricultural pesticide use. Little is known about timing of exposure and childhood cancer, and it may be that pesticide exposures during other windows of time such as the perinatal period are more important. Furthermore, although there is little detail on specific chemicals in the existing literature, it may be that proximity to agents used for household pest control is more important than to those used in agriculture. It may be reassuring that the overall incidence of these rare diseases in children does not appear to be associated with living in intensely agricultural areas, but it serves only as a preliminary overview. As for the associations of leukemia with propargite, azinphos-methyl, and ziram, whether or not these agents may impart risk will require additional study. There remain many issues to explore using other study designs before we can determine whether proximity to agricultural pesticide use is a risk factor for childhood cancers.

Table 4. Childhood cancer RRs[a] (and 95% CIs) by block group agricultural pesticide use density for chemical groups.

Percentile (lb/mi^2)	No. block groups	All sites No. cases	All sites RR (95% CI)	Leukemias No. cases	Leukemias RR (95% CI)	Gliomas No. cases	Gliomas RR (95% CI)
Organochlorides							
< 1 lb/mi^2	19,028	6,316	Ref	2,200	Ref	1,238	Ref
1st–74th			1.00		1.07		0.87
(1–32)	1,429	522	(0.89–1.12)	196	(0.90–1.26)	89	(0.69–1.09)
75th–89th			0.97		0.86		0.74
(33–85)	289	97	(0.75–1.25)	31	(0.57–1.29)	14	(0.42–1.30)
≥ 90th			0.84		0.70		0.86
(86–589)	189	53	(0.60–1.18)	16	(0.39–1.23)	10	(0.44–1.67)
Organophosphates							
< 1 lb/mi^2	14,866	4,734	Ref	1,662	Ref	905	Ref
1st–74th			1.00		0.97		1.09
(1–100)	4,554	1,752	(0.94–1.06)	601	(0.88–1.08)	368	(0.97–1.22)
75th–89th			0.94		0.93		0.80
(101–348)	909	309	(0.82–1.07)	109	(0.75–1.16)	50	(0.61–1.05)
≥ 90th			0.90		0.91		0.71
(349–7,129)	606	193	(0.76–1.06)	71	(0.70–1.18)	28	(0.50–1.02)
Carbamates							
< 1 lb/mi^2	16,921	5,449	Ref	1,917	Ref	1,051	Ref
1st–74th			1.05		1.00		1.12
(1–53)	3,001	1,213	(0.97–1.13)	411	(0.89–1.14)	251	(0.97–1.29)
75th–89th			0.86		0.79		0.73
(54–140)	609	180	(0.72–1.02)	60	(0.59–1.07)	29	(0.50–1.06)
≥ 90th			1.01		1.03		0.76
(141–1,706)	404	146	(0.83–1.23)	55	(0.75–1.41)	20	(0.48–1.19)
Dithiocarbamates							
< 1 lb/mi^2	17,768	5,844	Ref	2,035	Ref	1,156	Ref
1st–74th			0.99		1.00		0.85
(1–204)	2,375	879	(0.91–1.07)	313	(0.87–1.16)	150	(0.71–1.01)
75th–89th			0.90		0.91		0.93
(205–763)	475	160	(0.75–1.07)	58	(0.67–1.23)	32	(0.64–1.34)
≥ 90th			0.91		0.89		0.59
(764–14,931)	317	105	(0.73–1.13)	37	(0.61–1.30)	13	(0.33–1.04)

Ref, reference level.
[a]All RRs were adjusted for age, race, and sex.

References and Notes

1. Martin JA, Smith BL, Mathews TJ, Ventura SJ. Birth and Deaths: Preliminary Data for 1998. National Vital Statistics Reports, Vol 47, No. 25. Hyattsville, MD:National Center for Health Statistics, 1999.
2. Ross JA, Davies SM, Potter JD, Robinson LL. Epidemiology of childhood leukemia, with a focus on infants. Epidemiol Rev 16(2):243–272 (1994).
3. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. Br Med J 1:1495–1508 (1958).
4. Li FP, Fraumeni JF, Mulvihill JJ, Slattner WA, Dreyfus M, Tucker M, Miller R. A cancer family syndrome in twenty-four kindreds. Cancer Res 48:5358–5362 (1988).
5. Cowell JK. The genetics of retinoblastoma. Br J Cancer 63:333–336 (1991).
6. Meinert R, Schuz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am J Epidemiol 151(7):639–646 (2000).
7. Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. Eur J Cancer 32A(11):1943–1948 (1996).
8. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health 85(2):249–252 (1995).
9. Lowengart RA, Peters JM, Cicioni C, Buckley J, Bernstein L, Preston-Martin S, Rappaport E. Childhood leukemia and parents' occupational and home exposures. J Natl Cancer Inst 79(1):39–46 (1987).
10. Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. Environ Health Perspect 105:1214–1220 (1997).
11. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. Arch Environ Contam Toxicol 24:87–92 (1993).
12. Kristensen P, Andersen A, Irgens L, Bye A, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 65:39–50 (1996).
13. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, Nesbit ME, Odom L, Peters JM, Woods WG, et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Children's Cancer Study Group. Cancer Res 49:4030–4037 (1989).
14. Van Steensel-Moll HA, Valkenburg HA, Van Zanen GE. Childhood leukemia and parental occupation. Am J Epidemiol 121(2):216–224 (1985).
15. Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. Childhood cancer and parental occupation in Finland. J Epidemiol Community Health 35:11–15 (1981).
16. Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect 106(suppl 3):893–908 (1998).
17. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 105:1068–1077 (1997).
18. U.S. Department of Agriculture. 1992 Census of Agriculture. Vol 2. Subject Series. Coverage Evaluation. AC92-S-2. Washington, DC:U.S. Department of Commerce, Economics and Statistics Administration, 1994.
19. U.S. Department of Agriculture. 1997 Census of Agriculture. Vol. 2. Subject Series. Ranking of States and Counties. AC97-S-2. Washington, DC:U.S. Deptartment of Agriculture, National Agricultural Statistics Service, 1999.
20. Aspelin AL, Grube AH. Pesticide Industry Sales and Usage: 1996 and 1997 Market Estimates. 733-R-99–001. Washington, DC:U.S. Environmental Protection Agency, Office of Pesticide Programs, 1999.
21. Aspelin AL. Pesticides Industry Sales and Usage: 1994 and 1995 Market Estimates. 733-R-97-002. Washington, DC:U.S. Environmental Protection Agency, Office of Pesticide Programs, 1997.

22. Solomon GM, Mott L. Trouble on the Farm: Growing Up with Pesticides in Agricultural Communities. New York:Natural Resources Defense Council, 1998.
23. Ross Z, Kaplan J. Poisoning the Air: Airborne Pesticides in California. San Francisco:California Public Interest Research Group Charitable Trust, 1998.
24. Walker B, Wiles R, Hettenbach T, Campbell C, Davies K. What You Don't Know Could Hurt You: Pesticides in California's Air. Washington, DC:Environmental Working Group, 1999.
25. Simcox NJ, Fenske RA, Wolz SA, Lee I-C, Kalman DA. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environ Health Perspect 103:1126–1134 (1995).
26. Baker LW, Fitzell DL, Seiber JN, Parker TR, Shibamoto T, Poore MW, Longley KE, Tomlin RP, Propper R, Duncan DW. Ambient concentrations of pesticides in California. Environ Sci Technol 30:1365–1368 (1996).
27. Lewis RG, Fortmann RC, Camann DE. Evaluation of methods for monitoring the potential exposure of small children to pesticides in the residential environment. Arch Environ Contam Toxicol 26:37–46 (1994).
28. Whitmore RW, Immerman FW, Camann DE, Bond AE, Lewis RG, Schaum JL. Non-occupational exposures to pesticides for residents of two U.S. cities. Arch Environ Contam Toxicol 26:47–59 (1994).
29. Bradman MA, Harnly ME, Draper W, Seidel S, Teran S, Wakeham D, Neutra R. Pesticide exposures to children from California's central valley: results of a pilot study. J Expos Anal Environ Epidemiol 7(2):217–234 (1997).
30. Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse effects. Environ Health Perspect 107(suppl 3):409–419 (1999).
31. Woodrow JE, Seiber JN, Baker LW. Correlation techniques for estimating pesticide volatilization flux and downwind concentrations. Environ Sci Technol 31(2):523–529 (1997).
32. Loewenherz C, Fenske RA, Simcox NJ, Bellamy G, Kalman D. Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central Washington State. Environ Health Perspect 105:1344–1353 (1997).
33. Fenske RA, Kissel JC, Lu C, Kalman DA, Simcox NJ, Allen EH, Keifer MC. Biologically based pesticide dose estimates for children in an agricultural community. Environ Health Perspect 108:515–520 (2000).
34. Gunier RB, Harnly ME, Reynolds P, Hertz A, Von Behren J. Agricultural pesticide use in California: pesticide prioritization, use densities, and population distributions for a childhood cancer study. Environ Health Perspect 109:1071–1078 (2001).
35. Reynolds P, Smith DF, Satariano E, Nelson DO, Goldman LR, Neutra RR. The four county study of childhood cancer: clusters in context. Stat Med 15(7–9):683–697 (1996).
36. California Department of Pesticide Regulation. Pesticide Use Report System Data, 1991–1994 (Data File). Sacramento, CA:California Department of Pesticide Regulation, 1996.
37. Environmental Systems Research Institute. ArcView, version 3.0. Redlands, CA:Environmental Systems Research Institute, 1994.
38. U.S. Bureau of the Census. TIGER Line Files (Data File). Washington, DC:U.S. Bureau of the Census, 1995.
39. U.S. EPA. Office of Pesticide Programs. The U.S. EPA Reference Dose Tracking Report. Available: http://npic.orst.edu/tracking.htm [cited 8 March 2001].
40. Gold LS, Zeiger E. Handbook of Carcinogenic Potency and Genotoxicity Databases. New York:CRC Press, 1997.
41. California Department of Pesticide Regulation. Summaries of Toxicology Data. Sacramento, CA:California Department of Pesticide Regulation, Medical Toxicology Branch, 1997.
42. U.S. Bureau of the Census. Census of Population and Housing, 1990: Modified Age/Race, Sex and Hispanic Origin (MARS) State and County File. Washington, DC:U.S. Bureau of the Census, 1992.
43. California Department of Finance. Race/Ethnic Population with Age and Sex Detail, 1970–2040. Sacramento, CA:State of California, Department of Finance, 1998.
44. SAS Institute. SAS Version 7.00. Cary, NC:SAS Institute, 1998.
45. Lee K, Johnson V, Blakley B. The effect of exposure to a commercial 2,4-D herbicide formulation during gestation on urethan-induced lung adenoma formation in CD-1 mice. Vet Hum Toxicol 42(3):129–132 (2000).
46. Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 108(suppl 3):573–594 (2000).
47. Mills PK. Correlation analysis of pesticide use data and cancer incidence rates in California counties. Arch Environ Health 53(6):410–413 (1998).
48. Kettles MA, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. Environ Health Perspect 105:1222–1227 (1997).
49. Schreinemachers DM, Creason JP, Garry VF. Cancer mortality in agricultural regions of Minnesota. Environ Health Perspect 107:205–211 (1999).
50. Bell EM, Hertz-Picciotto I, Beaumont JJ. A case-control study of pesticides and fetal death due to congenital anomalies. Epidemiology 12(2):148–56 (2001).