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/mi². 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
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 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 (46), 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 significant.
significant ($p < 0.05$) at the highest usage level for propargite (RR = 1.48). For the gliomas, the adjusted RRs were $\leq 1$ 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).

### 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, 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 used heavily in the Central Valley are ziram percentiles of use for all block groups) (95% CI, 0.86–2.28) for leukemia. Phos-methyl had an adjusted RR of 1.40 (95% CI, 0.89–2.66) for leukemia, and azinphos-methyl 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.

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

| Percentile (lb/mi²) | No. block groups | All sites | Leukemias | Gliomas |
|---------------------|------------------|----------|-----------|---------|
|                     | No. cases        | No. cases | No. cases | No. cases |
|                     | (95% CI)         | (95% CI) | (95% CI) | (95% CI) |
| Class B (probable carcinogens) | | | | |
| <1 lb/mi²            | 16,099           | 5,204    | Ref       | 1,834    | Ref       | 1,007    | Ref       |
| 1st–74th             | 3,626            | 1,373    | (0.91–1.04) | 455     | (0.81–1.03) | 283     | (0.91–1.17) |
| 75th–89th            | 725              | 239      | (0.83–1.11) | 95      | (0.83–1.33) | 35       | (0.54–1.01) |
| ≥90th                | 485              | 172      | (0.80–1.13) | 59      | (0.66–1.20) | 26       | (0.54–1.12) |
| Class C (possible carcinogens) | | | | |
| <1 lb/mi²            | 14,694           | 4,660    | Ref       | 1,639    | Ref       | 896      | Ref       |
| 1st–74th             | 4,682            | 1,807    | (0.94–1.07) | 620     | (0.97–1.09) | 369     | (0.93–1.18) |
| 75th–89th            | 940              | 329      | (0.83–1.08) | 114     | (0.74–1.16) | 56       | (0.64–1.10) |
| ≥90th                | 619              | 192      | (0.77–1.08) | 70      | (0.68–1.21) | 30       | (0.54–1.12) |
| Genotoxins           | <1 lb/mi²        | 13,549   | 4,260     | Ref       | 1,495    | Ref       | 808      | Ref       |
| 1st–74th             | 5,541            | 2,043    | (0.91–1.02) | 691     | (0.83–1.04) | 443     | (0.98–1.22) |
| 75th–89th            | 1,111            | 419      | (0.90–1.12) | 145     | (0.79–1.20) | 64       | (0.64–1.03) |
| ≥90th                | 734              | 266      | (0.84–1.10) | 112     | (0.89–1.41) | 36       | (0.52–0.96) |
| Developmental and reproductive toxicants | <1 lb/mi² | 14,247 | 4,554     | Ref       | 1,590    | Ref       | 874      | Ref       |
| 1st–74th             | 4,942            | 1,805    | (0.90–1.01) | 616     | (0.84–1.03) | 382     | (0.93–1.17) |
| 75th–89th            | 988              | 384      | (0.93–1.17) | 135     | (0.84–1.26) | 60       | (0.66–1.10) |
| ≥90th                | 658              | 245      | (0.86–1.14) | 102     | (0.91–1.44) | 35       | (0.55–1.06) |

Ref. reference level.
*All RRs were adjusted for age, race, and sex.

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 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. 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 intensively 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* (and 95% CIs) by block group agricultural pesticide use density for chemical groups.

| Percentile (lb/m²) | No. block groups | No. cases | RR (95% CI) | No. cases | RR (95% CI) | No. cases | RR (95% CI) |
|-------------------|------------------|-----------|-------------|-----------|-------------|-----------|-------------|
| < 1 lb/m²         | 19,028           | 6,316     | Ref         | 2,200     | 1.238       | Ref       |             |
| 1st–74th          | 167              | 522       | (0.89–1.12) | 196       | (0.90–1.26)| 28        | (0.71–1.09)|
| 75th–89th         | 33              | 97        | (0.75–1.25) | 31        | (0.51–1.29)| 14        | (0.42–1.30)|
| ≥ 90th            | 38               | 53        | (0.60–1.18) | 16        | (0.39–1.23)| 10        | (0.44–1.67)|
| 1st–74th          | 11,486           | 4,734     | Ref         | 1,662     | 905         | Ref       |             |
| 75th–89th         | 4,554            | 1,752     | (0.94–1.06) | 601       | (0.88–1.07)| 366       | (0.97–1.22)|
| ≥ 90th            | 909              | 390       | (0.82–1.07) | 109       | (0.75–1.16)| 50        | (0.61–1.05)|
| 1st–74th          | 606              | 193       | (0.76–1.06) | 71        | (0.70–1.18)| 28        | (0.50–1.02)|
| 75th–89th         | 17,768           | 5,844     | Ref         | 2,035     | 1,156       | Ref       |             |
| ≥ 90th            | 2,375            | 879       | (0.91–1.07) | 313       | (0.87–1.16)| 150       | (0.71–1.01)|
| 75th–89th         | 475              | 160       | (0.75–1.07) | 58        | (0.67–1.23)| 32        | (0.64–1.34)|
| ≥ 90th            | 317              | 105       | (0.73–1.13) | 37        | (0.61–1.30)| 13        | (0.33–1.04)|

*All RRs were adjusted for age, race, and sex.

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