Published in final edited form as:
Environ Res. 2009 October ; 109(7): 891–899. doi:10.1016/j.envres.2009.07.014.

Residential Proximity to Agricultural Pesticide Applications and Childhood Acute Lymphoblastic Leukemia

Rudolph P. Rull[1,2], **Robert Gunier**[1], **Julie Von Behren**[1], **Andrew Hertz**[1], **Vonda Crouse**[3], **Patricia A. Buffler**[4], and **Peggy Reynolds**[1,2]

[1]Northern California Cancer Center, Berkeley, CA

[2]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA

[3]Children's Hospital Central California, Madera, CA

[4]School of Public Health, University of California, Berkeley, CA

Abstract

Ambient exposure from residential proximity to applications of agricultural pesticides may contribute to the risk of childhood acute lymphoblastic leukemia (ALL). Using residential histories collected from the families of 213 ALL cases and 268 matched controls enrolled in the Northern California Childhood Leukemia Study, the authors assessed residential proximity within a half-mile (804.5 meters) of pesticide applications by linking address histories with reports of agricultural pesticide use. Proximity was ascertained during different time windows of exposure, including the first year of life and the child's lifetime through the date of diagnosis for cases or reference for controls. Agricultural pesticides were categorized *a priori* into groups based on similarities in toxicological effects, physicochemical properties, and target pests or uses. The effects of moderate and high exposure for each group of pesticides were estimated using conditional logistic regression. Elevated ALL risk was associated with lifetime moderate exposure, but not high exposure, to certain physicochemical categories of pesticides, including organophosphates, cholorinated phenols, and triazines, and with pesticides classified as insecticides or fumigants. A similar pattern was also observed for several toxicological groups of pesticides. These findings suggest future directions for the identification of specific pesticides that may play a role in the etiology of childhood leukemia.

Keywords

Agricultural pesticides; cancer; childhood leukemia; environmental exposure; geographic information systems

Address correspondence to: Rudolph P. Rull, PhD, Northern California Cancer Center, 2001 Center Street, Suite 700, Berkeley, CA 94704, Phone number: (510) 608-5181, Fax: (510) 510-666-0693, rrull@nccc.org.

Human Subjects Protections: The research activities described in this manuscript have been reviewed and approved by the Institutional Review Board of the Northern California Cancer Center, the University of California, Berkeley, Committee for Protection of Human Subjects, and the Committee for the Protection of Human Subjects of the State of California.

disclaimers

The authors declare that they have no competing interests.

INTRODUCTION

Previous case-control studies have observed an increased risk of childhood leukemia associated with household pesticide use and parental exposures to pesticides in occupational settings (Alderton et al., 2006; Belson et al., 2007; Buffler et al., 2005; Daniels et al., 1997; Infante-Rivard and Weichenthal, 2007; Infante-Rivard et al., 1999; Jurewicz and Hanke, 2006; Ma et al., 2002; Meinert et al., 2000; Menegaux et al., 2006; Monge et al., 2007). Agricultural pesticides applied near the home are another important source of exposure, particularly in rural communities. Pesticide concentrations in ambient air have been demonstrated to be higher in agricultural communities and near treated fields (Whitmore et al., 1994; Baker et al., 1996; Woodrow et al., 1997; Teske et al., 2002; Weppner et al., 2006). In studies of house dust measurements, concentrations of pesticide residues have been shown to be higher in residences closest to an crops (Simcox et al., 1995; Lu et al., 2000; Fenske et al., 2002), in farm residences compared to non-farm residences (Curwin et al., 2005; Obendorf et al., 2006), and in residences with increasing acreage of crops within 750 meters of the home (Ward et al., 2006). The few studies that have evaluated the association between proximity to agricultural pesticide use and childhood leukemia observed limited evidence for an etiologic relationship (Reynolds et al., 2005a; Reynolds et al., 2005b; Reynolds et al., 2002). These previous analyses only characterized pesticide use around a single residence at the time of birth or diagnosis, and thus did not account for multiple addresses during the subject's lifetime. Furthermore, these studies did not evaluate the effects of pesticide exposures during critical time periods such as gestation, the first year of life, or the child's lifetime from birth to the time of case diagnosis.

In this case-control study of childhood leukemia, we linked children's residential histories with available agricultural pesticide-use reporting data to characterize exposures to specific pesticides and groupings of pesticides during specific time periods of interest. We then examined whether residential proximity to agricultural applications of these agents is associated with acute lymphoblastic leukemia (ALL), the most common subtype of this childhood cancer.

MATERIALS AND METHODS

Study Population

The study population was derived from the first two phases of the Northern California Childhood Leukemia Study, an ongoing case-control study; the design of the study is discussed in detail elsewhere (Chang et al., 2006; Ma et al., 2004). Briefly, Phase I of the study consisted of cases diagnosed between August 1995 and November 1999 in one of 17 counties in the Greater San Francisco Bay Area. Cases in Phase II of the study were diagnosed between December 1999 and June 2002 in the Phase I area or one of 18 additional counties in the California Central Valley. In both phases, cases were ascertained within 72 hours of diagnosis. For each Phase I case, one control subject with matching age, sex, Hispanic ethnicity, maternal race, and maternal county of residence at the case's time of birth was randomly selected from birth certificates through the California Office of Vital Records. Phase II cases were matched to one or two controls using the same matching criteria except for county of residence. Eligibility criteria for cases and controls included: 1) residence in the study area; 2) age less than 15 at the time of diagnosis for cases or reference for controls; 3) no prior cancer diagnosis; and 4) having an English- or Spanish-speaking parent. If the first choice control could not be located or declined to participate, another birth certificate control was chosen. Overall, 382 cases and 482 controls were enrolled in Phases I and II of the study. These participating controls represent 58% of the total number of 837 eligible potential control subjects and 84% of the controls who were actually contacted (Chang et al., 2006).

Extensive demographic and exposure information, including a complete residential history, was collected from the parents or guardians (most often the mother) using a self-administered questionnaire and a follow-up in-person interview. Addresses obtained from the residential histories were geocoded using ArcInfo (ESRI, Redlands, California) geographic information system (GIS) software and Dynamap/2000 (Geographic Data Technology, Inc., Lebanon, New Hampshire) and NAVTEQ Standard (Navigational Technologies, Chicago, Illinois) street geocoding databases.

Because comprehensive pesticide-use reporting was initiated in 1990, we restricted the study population for this analysis to those cases and controls born in or after 1990. Of these, we excluded 37 cases of acute myeloid leukemia (AML) and 2 cases with other rarer subtypes as well as their matched controls. Of the remaining 271 ALL cases and their matched controls, we only included subjects for whom geocodable address information was available for ≥90% of the time period of interest. We further excluded incomplete matched sets without at least one case and one control, resulting in a study population of 213 ALL cases and 268 matched controls for the lifetime analyses and 191 ALL cases and 244 matched controls for the first year of life analyses.

Exposure Assessment

Potential exposures to specific pesticides were ascertained by linking subjects' residential history information with available pesticide-use reports maintained by the California Department of Pesticide Regulation (CDPR) since 1990 to track all statewide commercial agricultural pesticide applications (California Department of Pesticide Regulation, 2000). Each pesticide-use report provides detailed information on the name of the active ingredient in the pesticide, the amount applied, the crop and acreage treated, and the date and location of the application. Locations are reported according to the Public Land Survey System, a grid that parcels land into sections with an area of approximately 1 mi^2 (2.6 km^2). For this study, we obtained pesticide-use report data from 1990 through 2002. We edited these data to remove data entry errors such as those in reports including invalid sections of the Public Land Survey System and to adjust the number of pounds of pesticides applied in records that were flagged by CDPR as having extremely high application rates (pounds applied ÷ acres treated) to the number of pounds corresponding to the acres treated multiplied by the mean application rate for that pesticide and crop combination.

Because over 600 different pesticide active ingredients were applied near residences during the time period covered by this study, we selected 118 agents on the basis of frequent use (i.e., total crop acres treated and total pounds applied between 1990 and 2002) and available evidence of toxicological effects (Table 1). These effects included probable or possible carcinogenicity (IARC, 1991;National Toxicology Program, US Department of Health and Human Services, 2005;Office of Pesticide Programs, US Environmental Protection Agency, 2002), developmental or reproductive toxicity (Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 2008), and anti-cholinesterase activity based on laboratory animal studies (California Department of Pesticide Regulation, 1997). In addition, pesticides with suspected genotoxicity (i.e., directly damaging DNA) were identified on the basis of at least 2 positive results in genetic toxicity assays (Gold and Zeiger, 1997;Office of Pesticide Programs, US Environmental Protection Agency, 2002) as well as suspected endocrine disruptors (Colborn, et al. 1993;Illinois Environmental Protection Agency, 1997;Keith, 1997). Based on these a priori assignments, we categorized each of these selected pesticides into 6 toxicological classes. In addition, we categorized each pesticide into five classes of target pests or uses (insecticides, herbicides, fungicides, plant growth regulators, and fumigants) and 12 classes of physicochemical properties. Krieger's Handbook of Pesticide Toxicology (2001), the Compendium of Pesticide Common Names (Wood, 2008), and the

Pesticide Action Network Pesticides Database (Kegley et al., 2008) were consulted to verify the correct listing of each pesticide.

For each subjects' time period of interest (e.g., lifetime or first year of life), we identified the subjects' residences during that period and created a ½-mi (804.5 m) radius buffer around each residence and then intersected the buffers with the square-mile sections of the Public Land Survey System. This ½-mi buffer radius was selected in order to represent the distance where maximum exposure is likely to occur based on studies of pesticide drift (AgDRIFT Task Force, 1997; Frost and Ware, 1970; Ward et al., 2006; Woods et al., 2001). For each specific pesticide or pesticide group, we aggregated the total pesticide pounds applied proportional to the percentage area of each section within the buffer. Next, we summed the area-weighted pounds for all residences during the time period of interest and divided by the buffer area (0.8 mi^2 or 2.0 km^2) to obtain the total pounds applied per square mile. Finally, we divided the total pounds per square mile by the number of years in the exposure period of interest to estimate the average annual area-weighted use density for each specific pesticide or pesticide group.

For each analysis of pesticide groups or individual agents, we defined a subject as unexposed if their respective pesticide use density during the time period of interest was less than 1 lb/mi^2 for that group. For the remaining subjects, we derived two categories of pesticide exposure based on the distribution of pesticide use density among control subjects with greater than 1 lb/mi^2 of use density; these categories were defined as moderate (1^{st} to 49^{th} percentile) and high (50^{th} percentile and above) exposure. To maintain consistency, exposure categories for each time period of interest are based on the distribution of the controls' lifetime estimated exposure. Where we observed suggestive associations, and where numbers of exposed cases and controls permitted, we repeated the analysis using exposure categories based on the quartile distribution among controls with greater than 1 lb/mi^2 of use density.

Statistical Analysis

We employed conditional logistic regression to estimate the effects of residential proximity to use of specific agricultural pesticides listed in Table 2. Effect estimates are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Due to the small numbers of cases and controls exposed to specific pesticides and the possibility that related pesticides act by a common mechanism, we also estimated effects for exposures to groups of agents by physicochemical, toxicological, and target pest classes. Household income was included in all models as a covariate on the basis of its observed negative associations with case status (Table 1) and pesticide exposure (results not shown). All statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, North Carolina).

We initially evaluated each agent and pesticide group in separate single-pesticide or single-group models. Because pesticides are often applied in combination on similar crops and during similar seasonal periods, we also explored the use of a single multiple-pesticide or multiple-group model to account for the high degree of correlation observed between pesticide exposures. We also used this approach to estimate the effects of each the physicochemical classes of pesticides while simultaneously accounting for the other mutually exclusive classes and a group of other pesticides not categorized into any of these classes.

RESULTS

Table 2 lists the distributions of the matching factors and annual household income. Because subject eligibility for this analysis was limited to those born in or after 1990, all subjects were less than ten years old, with over half of the subjects under the age of five. Males accounted for 56% of the subjects, and 39% of the study subjects were Hispanic. The distribution of annual

household income differed between case and control subjects with controls (38%) being more likely than cases (24%) to be in the highest income group (≥$75,000).

In analyses of specific pesticide active ingredients, we did not observe elevated risks for ALL associated with moderate or high levels of exposure during the time windows of interest (results not shown). For many of these agents, the small numbers of exposed cases and controls limited our ability to detect associations and, in some instances, were not sufficient for analysis (i.e., exposed cases <4 or exposed controls <4). This paper presents effect estimates for moderate and high exposure to classes of pesticides grouped by physicochemical, toxicological, and target pest classes during two time periods: 1) subject's lifetime between the date of birth and the date of diagnosis or corresponding reference date and 2) subject's first year of life.

Table 3 lists effect estimates from single-group logistic regression models for exposures to pesticides grouped into five classes of target pests or uses over the course of the subjects' lifetime and during the first year of life. Elevated risks for ALL were observed for moderate lifetime exposure to fumigants (OR = 1.7; 95% CI: 1.0, 3.1) or insecticides (OR = 1.5; 95% CI: 0.9, 2.4). For these target pest classes, however, the estimates for the high-exposure categories did not appear to differ from the unexposed subjects. Effect estimates for exposure during the first year of life did not suggest an increased ALL risk with high or moderate exposure to any of these target pest or use groups.

Grouping pesticides by toxicological properties, we observed a consistent non-monotonic exposure-response pattern for lifetime exposure to each of the pesticide classes, with elevated risks in the moderate-exposure categories and shrinkage toward the null in the high-exposure categories (table 4). This same pattern was observed for exposure during the first year of life to probable or possible carcinogens, developmental or reproductive toxins, and cholinesterase inhibitors, while odds ratios for suspected genotoxins or endocrine disruptors did not suggest an elevation in risk for either moderate or high exposure.

Effect estimates from single-group models and a multiple-group model for lifetime exposure to physicochemical classes of pesticides are listed in table 5. Similar to the results for toxicological classes, elevated risks were observed in the moderate exposure groups for chlorinated phenols (OR = 2.0; 95% CI: 1.0, 3.8), organophosphates (OR = 1.6; 95% CI: 1.0, 2.7), and triazines (OR = 1.9; 95% CI: 1.0, 3.7), but not in the respective high-exposure groups. Other notable but less precise results include an elevated risk for high exposure to azole fungicides (OR = 2.1; 95% CI: 0.8, 5.4) and a reduced risk for high exposure to benzimidazole fungicides (OR = 0.5; 95% CI: 0.2, 1.0). Adjusting for exposure to other physicochemical classes and other uncategorized pesticides in a multiple-group model resulted in a general loss of precision. However, odds ratios remained elevated for high azole exposure (OR = 3.9; 95% CI: 1.0, 15.7) and moderate triazine exposure (OR = 4.1; 95% CI: 1.5, 11.1).

Exposures to physicochemical classes of pesticides during the first-year of life were also evaluated using single-group models (results not shown). Point estimates for moderate (OR = 1.6; 95% CI: 0.9, 2.8) and high (OR = 0.8; 95% CI: 0.4, 1.5) organophosphate exposure were similar to those observed for lifetime exposure. This non-monotonic exposure response was also observed for moderate (OR = 2.3; 95% CI: 1.0, 5.3) and high (OR = 0.9; 95% CI: 0.3, 2.5) exposure to ureas during the first year of life. In contrast to elevated risks observed for moderate lifetime exposure, we did not observe similar associations for moderate exposure to chlorinated phenols (OR = 1.6; 95% CI: 0.7, 3.6) or triazines (OR = 0.8; 95% CI: 0.3, 1.6) during the first year of life. Using a multiple-group model to adjust for exposures to other physicochemical groups yielded imprecise effect estimates (results not shown), although we observed an increased risk for moderate exposure to urea pesticides (OR = 3.6; 95% CI: 1.0, 12.7).

In general, effect estimates for exposure categories based on the quartile distribution among controls with greater than 1 lb/mi^2 of use density suggested a similar pattern to the respective effect estimates for moderate or high categories of exposure, but with considerably less precision (results not shown). For those pesticide categories that suggested an elevated risk associated with moderate exposure and no elevated risk associated with high exposure (e.g., lifetime exposure to chlorinated phenols, organophosphates, or fumigants), effect estimates for either or both the lower quartiles of exposure suggested an elevated risk while estimates for both the upper quartiles suggested no increased risk.

DISCUSSION

We observed an increased risk of childhood ALL associated with moderate lifetime exposure to several categories of agricultural pesticides, including the target-pest classes of insecticides or fumigants and the toxicological classes of probable or possible carcinogens, developmental or reproductive toxins, genotoxins, suspected endocrine disruptors and anti-cholinesterases. Increased risks were not observed in the highest categories of exposure. A similar exposure-response pattern was observed in single-class models of chlorinated phenols, organophosphates, and triazines. Mutual adjustment for all physicochemical classes led to an overall decrease in precision, but effect estimates tended to remain elevated in the moderate exposure categories. In this model, only azoles suggested an increased risk at the highest level of exposure.

Previous studies of ambient agricultural pesticide exposure and childhood leukemia have observed few elevated risks associated with exposure. An ecologic study in California that used pesticide-use reporting data to estimate pesticide use for census block groups at the time of diagnosis found only an increased incidence of childhood leukemia in areas with the highest use of the herbicide propargite (Reynolds et al., 2002). In a subsequent case-control study in California that used pesticide-use reporting data to characterize exposure at the birth residence, an increased risk of childhood leukemia was observed in the highest categories of exposure to the thiocarbamate fungicide metam sodium and the organochlorine insecticide dicofol. Effect estimates for exposures to pesticides listed as probable or possible carcinogens also suggested an elevated risk (Reynolds et al., 2005b). A recent US ecological study of childhood cancer in 25 states (excluding California) found an increased risk of childhood leukemia in counties with greater than 60% of acreage devoted to farming compared with counties with less than 20% acreage devoted to farming (Carozza et al., 2008). However, this study relied only on crop acreage and was unable to differentiate risks for specific pesticides.

The toxic effects of certain pesticides include oxidative stress, genotoxicity, endocrine disruption, and cholinesterase inhibition, but little is known about what role these effects may play in inducing ALL. There is limited toxicological evidence of a leukemogenic effect from exposure to specific types of agricultural pesticides such as organophosphates (Perry and Soreq, 2004; Williams et al., 2004). Previous toxicological studies observed a leukemogenic effect from exposure to isofenphos, an organophosphate insecticide (Boros and Williams, 2001; Williams et al., 2004). By design, organophosphates and other anti-cholinesterase compounds inhibit the ability of the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) to regulate acetylcholine, leading to an over-accumulation of this neurotransmitter (Krieger, 2001). Emerging evidence suggests that change in AChE and BuChE activity is associated with tumor development and may play a role in cell proliferation and differentiation, although it is not clear whether this is a cause or consequence of neoplastic processes (Vidal, 2005). Futhermore, cholinesterase inhibitors may induce amplification of the ACHE and BuChE genes in developing blood cells, a phenomenon associated with the development of leukemia (Lapidot-Lifson et al., 1989). However, it is unlikely that the organophosphate exposures in this study occurred at levels sufficiently high to induce

cholinesterase inhibition, especially when applications of these pesticides in agricultural settings are designed to minimize potential exposure.

The non-monotonic exposure-response pattern observed for some pesticide groups in this study may be due to biological effects related to endocrine disruption and/or competing risks. For endocrine-disrupting chemicals, moderate exposure increases the receptor-mediated response, but the response decreases with high exposure as receptors become saturated (Phillips et al., 2008; Welshons et al., 2003). Within the context of competing risks, ALL is only one outcome affected by exposure along a continuum ranging from subfertility to congenital malformations to fetal loss. In this framework, an elevated risk of ALL would be observed at a moderate level of exposure, but at higher levels of exposure, the observed risk would decrease as the risks of more severe outcomes such as malformation or fetal death increase (Selevan and Lemasters, 1987). However, the lack of an observed association with high exposure may be due to artifacts of the study design such as misclassification in the high exposure category or the use of overly broad categories for grouping pesticides, especially by toxicological class. The classification of pesticides as suspected genotoxins or endocrine disruptors is based on less evidence than in the classification of probable carcinogens, developmental or reproductive toxins, and cholinesterase inhibitors. Consequently, this lower specificity may bias effect estimates for these categories of pesticides toward the null.

Among the unique features of this study was the use of detailed residential histories and existing agricultural pesticide application data to improve the spatial and temporal resolution of exposure assessment, focus on specific exposure time windows, and distinguish exposures between specific pesticide compounds or categories. By integrating these data, we were able to minimize potential exposure misclassification arising from using only a single address (e.g., at birth or diagnosis) to characterize exposure during the time period of interest. The average number of residences between birth and the date of diagnosis or reference among subjects was 2.0 (range: 1-10) and did not appear to differ between cases (mean = 2.1) and controls (mean = 1.9). To minimize the potential for error when assigning locations to residential addresses, we used multiple street geocoding databases. However, residential histories were self-reported by mothers and maybe subject to recall error, especially among residentially mobile older children whose earliest addresses would have preceded the interview by several years. Although we were able to characterize residential mobility during children's lifetimes, we did not have sufficient prenatal address data available to assess agricultural pesticide exposures during gestation which may be the most critical time period for exposure (Birnbaum and Fenton, 2003). While we were able to estimate the effects of potential exposure to pesticides grouped into categories of target pests, toxicity, and physicochemical properties, we lacked sufficient power to do so for rarer exposures to specific pesticides.

Our exposure metric assumes that only pesticides applied in sections located within ½-mi of the residence of interest have the potential to drift to the residence and that all pesticides applied in sections within ½-mi resulted in exposure at the residence. We did not include factors that affect the fate and drift potential of pesticides in the environment, such as wind speed and direction at the time of application, the mixing of solvents and adjuvants that may affect the persistence and volatility of the active ingredient, and the application method. We also did not utilize available crop maps that could have improved the spatial resolution of pesticide applications beyond the one square-mile section. Future studies utilizing GIS and existing environmental databases to estimate exposure to agricultural pesticides should incorporate land use and meteorological data in the models (Nuckols et al., 2007; Rull and Ritz, 2003; Rull et al., 2006; Ward et al., 2006; Ritz and Rull, 2008).

Proximity to treated crops has been associated with higher pesticide concentrations in ambient air and house dust (Whitmore et al., 1994; Baker et al., 1996; Woodrow et al., 1997; Teske et

al., 2002; Harnly, 2005; Weppner et al., 2006). Whether residential proximity is related to an increased body burden of specific agricultural pesticides is not as clear. Urinary metabolite levels were higher for people living in farm compared to non-farm residences for atrazine and chlorpyrifos, but not glyphosate or metolachlor (Curwin, 2007). Among children living near treated farmland, one study observed higher urinary concentrations of organophosphate metabolites (Lu, 2000), but this was not observed in other studies (Fenske et al., 2002; Koch et al., 2002; Royster, 2002). An analysis of urine collected from children of farm workers found that organophosphate metabolites were moderately correlated with house dust levels of the insecticide diazinon but not chlorpyrifos (Bradman et al., 2007). In other studies, children's urinary organophosphate metabolite levels were observed to be more strongly correlated with hand wipe samples than house dust (Shalat et al., 2003; Weppner et al., 2006). A recent study observed that urinary organophosphate metabolites levels from pregnant women in an agricultural community were significantly higher than those from the general U.S. population. Although diet was found to be the dominant source of organophosphate exposure, the authors attributed this increase to non-dietary exposures from local agricultural pesticide use (McKone, 2007).

In summary, our study detected a modest increase in ALL risk with residential proximity to moderate levels of agricultural use of several types of pesticides, but not at higher levels of use. The observed consistency of this association across toxicological and physicochemical classes warrants further exploration in future studies. These studies should have a larger pool of cases and controls to allow for the evaluation of the effects of specific pesticides on ALL, AML, and other leukemia subtypes. Pesticide exposure assessment should account for crop locations and be further refined by including factors that influence the drift potential of agricultural pesticides in the environment, and integrating pesticide exposure from other sources such as diet and home use. In addition, prenatal residential histories should be collected and geocoded in order to characterize exposure during the critical gestational period.

Acknowledgements

The authors thank the children and their families for their participation in the Northern California Childhood Leukemia Study, and clinical investigators at the collaborating hospitals for help in recruiting patients including University of California, Davis, Medical Center (Dr. Jonathan Ducore), University of California San Francisco (Drs. Mignon Loh and Katherine Matthay), Children's Hospital of Central California (Dr. Vonda Crouse), Lucile Packard Children's Hospital (Dr. Gary Dahl), Children's Hospital Oakland (Dr. James Feusner), Kaiser Permanente Sacramento (Dr. Vincent Kiley), Kaiser Permanente Santa Clara (Drs. Carolyn Russo and Alan Wong), Kaiser Permanente San Francisco (Dr. Kenneth Leung), and Kaiser Permanente Oakland (Dr. Stacy Month). We also acknowledge the entire study staff and the Survey Research Center for their effort and dedication.

Funding support: This work was supported by the National Institute of Environmental Health Sciences (R01-ES09137) and the National Cancer Institute (R01-CA92674).

Abbreviations

AChE, acetylcholinesterase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BuChE, butyrylcholinesterase; CDPR, California Department of Pesticide Regulation; CI, confidence interval; GIS, geographic information system; OR, odds ratio.

References

AgDRIFT Task Force. A summary of ground application studies. AgDRIFT Task Force; Macon, MO: 1997 [accessed 1 March 2008]. Available: http://www.agdrift.com/PDF_FILES/Ground.pdf

Alderton LE, Spector LG, Blair CK, Roesler M, Olshan AF, Robison LL, Ross JA. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: a report from the Children's Oncology Group. Am. J. Epidemiol 2006;164:212–221. [PubMed: 16760223]

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 1996;30:1365–1368.

Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. Environ. Health Perspect 2007;115:138–145. [PubMed: 17366834]

Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ. Health Perspect 2003;111:389–394. [PubMed: 12676588]

Boros LG, Williams RD. Isofenphos induced metabolic changes in K562 myeloid blast cells. Leuk. Res 2001;25:883–890. [PubMed: 11532522]

Bradman A, Whitaker D, Quirós L, Castorina R, Henn BC, Nishioka M, Morgan J, Barr DB, Harnly M, Brisbin JA, Sheldon LS, McKone TE, Eskenazi B. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. J. Expo. Sci. Environ. Epidemiol 2007;17:331–349. [PubMed: 16736054]

Buffler PA, Kwan ML, Reynolds P, Urayama KY. Environmental and genetic risk factors for childhood leukemia: appraising the evidence. Cancer Invest 2005;23:60–75. [PubMed: 15779869]

California Department of Pesticide Regulation. Pesticide Use Reporting: an Overview of California's Unique Full Reporting System. California Department of Pesticide Regulation; Sacramento, CA: 2000.

California Department of Pesticide Regulation. Summaries of Toxicology Data. California Department of Pesticide Regulation; Sacramento, CA: 2008 [accessed 1 October 2008]. Available: http://www.cdpr.ca.gov/docs/risk/toxsums/toxsumlist.htm

Carozza SE, Li B, Elgethun K, Whitworth R. Risk of childhood cancers associated with residence in agriculturally intense areas in the United States. Environ. Health Perspect 2008;116:559–565. [PubMed: 18414643]

Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am. J. Epidemiol 2006;163:1091–1100. [PubMed: 16597704]

Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ. Health Perspect 1993;101:378–384. [PubMed: 8080506]

Curwin BD, Hein MJ, Sanderson WT, Nishioka MG, Reynolds SJ, Ward EM, Alavanja MC. Pesticide contamination inside farm and nonfarm homes. J. Occup. Environ. Hyg 2005;2:357–367. [PubMed: 16020099]

Curwin BD, Hein MJ, Sanderson WT, Striley C, Heederik D, Kromhout H, Reynolds SJ, Alavanja MC. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann. Occup. Hyg 2007;51:53–65. [PubMed: 16984946]

Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ. Health Perspect 1997;105:1068–1077. [PubMed: 9349828]

Fenske RA, Lu C, Barr D, Needham L. Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. Environ. Health Perspect 2002;110:549–553. [PubMed: 12003762]

Frost KR, Ware GW. Pesticide drift from aerial and ground applications. Agric. Eng 1970;51:460–467.

Gold, LS.; Zeiger, E., editors. Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press; New York: 1997.

Harnly M, McLaughlin R, Bradman A, Anderson M, Gunier R. Correlating agricultural use of organophosphates with outdoor air concentrations: A particular concern for children. Environ. Health Perspect 2005;113:1184–1189. [PubMed: 16140625]

IARC (International Agency for Research on Cancer). Occupational exposures in insecticide application, and some pesticides. IARC Monogr. Eval. Carcinog. Risk Hum 1991;53:5–586.

Illinois Environmental Protection Agency. Endocrine Disruptors Strategy. Illinois Environmental Protection Agency; Springfield, IL: 1997.

Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J. Toxicol. Environ. Health B. Crit. Rev 2007;10:81–99. [PubMed: 18074305]

Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. Epidemiology 1999;10:481–487. [PubMed: 10468419]

Jurewicz J, Hanke W. Exposure to pesticides and childhood cancer risk: has there been any progress in epidemiological studies? Int. J. Occup. Med. Environ. Health 2006;19:152–169. [PubMed: 17252666]

Kegley, SE.; Hill, BR.; Orme, S.; Choi, AH. PAN Pesticide Database. Pesticide Action Network; North America, San Francisco: 2008 [accessed March 1, 2008]. Available: http://www.pesticideinfo.org

Keith, L. Environmental Endocrine Disruptors: A Handbook of Property Data. Wiley & Sons; New York: 1997.

Koch D, Lu C, Fisker-Andersen J, Jolley L, Fenske RA. Temporal association of children's pesticide exposure and agricultural spraying: report of a longitudinal biological monitoring study. Environ. Health Perspect 2002;110:829–833. [PubMed: 12153767]

Krieger, R., editor. Handbook of pesticide toxicology. Vol. 2nd ed.. Academic Press; San Diego: 2001.

Lapidot-Lifson Y, Prody CA, Ginzberg D, Meytes D, Zakut H, Soreq H. Coamplification of human acetylcholinesterase and butyrylcholinesterase genes in blood cells: correlation with various leukemias and abnormal megakaryocytopoiesis. Proc. Natl. Acad. Sci. U. S. A 1989;86:4715–4719. [PubMed: 2734315]

Lu C, Fenske RA, Simcox NJ, Kalman D. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ. Res 2000;84:290–302. [PubMed: 11097803]

Ma X, Buffler PA, Gunier RB, Dahl G, Smith MT, Reinier K, Reynolds P. Critical windows of exposure to household pesticides and risk of childhood leukemia. Environ. Health Perspect 2002;110:955–960. [PubMed: 12204832]

Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am. J. Epidemiol 2004;159:915–921. [PubMed: 15128601]

McKone TE, Castorina R, Harnly ME, Kuwabara Y, Eskenazi B, Bradman A. Merging models and biomonitoring data to characterize sources and pathways of human exposure to organophosphorus pesticides in the Salinas Valley of California. Environ. Sci. Technol 2007;41:3233–3240. [PubMed: 17539531]

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 2000;151:639–646. [PubMed: 10752791]

Menegaux F, Baruchel A, Bertrand Y, Lescoeur B, Leverger G, Nelken B, Sommelet D, Hémon D, Clavel J. Household exposure to pesticides and risk of childhood acute leukaemia. Occup. Environ. Med 2006;63:131–134. [PubMed: 16421392]

Monge P, Wesseling C, Guardado J, Lundberg I, Ahlbom A, Cantor KP, Weiderpass E, Partanen T. Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica. Scand. J. Work Environ. Health 2007;33:293–303. [PubMed: 17717622]

National Toxicology Program. US Department of Health and Human Services. 11th Report on Carcinogens. National Toxicology Program, US Department of Health and Human Services; Washington, D.C.: 2005 [accessed 1 March 2008]. Available: http://ntp.niehs.nih.gov/?objectid=035E5806-F735-FE81-FF769DFE5509AF0A

Nuckols JR, Gunier RB, Riggs P, Miller R, Reynolds P, Ward MH. Linkage of the California Pesticide Use Reporting Database with spatial land use data for exposure assessment. Environ. Health Perspect 2007;115:684–689. [PubMed: 17520053]

Obendorf SK, Lemley AT, Hedge A, Kline AA, Tan K, Dokuchayeva T. Distribution of pesticide residues within homes in central New York State. Arch. Environ. Contam. Toxicol 2006;50:31–44. [PubMed: 16237496]

Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Chemicals Known to the State to Cause Cancer or Reproductive Toxicity, September 12, 2008. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency; Sacramento, CA: 2008 [accessed 1 October 2008]. Available: http://www.oehha.org/Prop65/prop65_list/files/P65single091208.pdf

Office of Pesticide Programs. US Environmental Protection Agency. List of Chemicals Evaluated for Carcinogenic Potential. Office of Pesticide Programs, US Environmental Protection Agency; Washington, D.C.: 2002.

Perry C, Soreq H. Organophosphate risk of leukemogenesis. Leuk. Res 2004;28:905–906. [PubMed: 15234565]

Phillips KP, Foster WG, Leiss W, Sahni V, Karyakina N, Turner MC, Kacew S, Krewski D. Assessing and managing risks arising from exposure to endocrine-active chemicals. J. Toxicol. Environ. Health B. Crit. Rev 2008;11:351–372. [PubMed: 18368561]

Reynolds P, Von Behren J, Gunier R, Goldberg DE, Hertz A. Agricultural pesticides and lymphoproliferative childhood cancer in California. Scand. J. Work Environ. Health 2005a;31(Suppl 1):46–54. [PubMed: 16190149]

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A. Agricultural pesticide use and childhood cancer in California. Epidemiology 2005b;16:93–100. [PubMed: 15613951]

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Harnly ME. Childhood cancer and agricultural pesticide use: an ecologic study in California. Environ. Health Perspect 2002;110:319–24. [PubMed: 11882484]

Royster MO, Hilborn E, Barr D, Carty CL, Rhoney S, Walsh D. A pilot study of global positioning system/geographical information system measurement of residential proximity to agricultural fields and urinary organophosphate metabolite concentrations in toddlers. J. Expo. Sci. Environ. Epidemiol 2002;12:433–440.

Ritz B, Rull RP. Assessment of environmental exposures from agricultural pesticides in childhood leukaemia studies: challenges and opportunities. Radiat. Prot. Dosimetry 2008;132:148–155. [PubMed: 18930927]

Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. Environ. Health Perspect 2003;111:1582–1589. [PubMed: 14527836]

Rull RP, Ritz B, Shaw GM. Neural tube defects and maternal residential proximity to agricultural pesticide applications. Am. J. Epidemiol 2006;163:743–753. [PubMed: 16495467]

Selevan SG, Lemasters GK. The dose-response fallacy in human reproductive studies of toxic exposures. J. Occup. Med 1987;29:451–454. [PubMed: 3598737]

Shalat SL, Donnelly KC, Freeman NC, Calvin JA, Ramesh S, Jimenez M, Black K, Coutinho C, Needham LL, Barr DB, Ramirez J. Nondietary ingestion of pesticides by children in an agricultural community on the US/Mexico border: preliminary results. J. Expo. Anal. Environ. Epidemiol 2003;13:42–50. [PubMed: 12595883]

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 1995;103:1126–1134. [PubMed: 8747019]

Teske ME, Bird SL, Esterly DM, Curbishley TB, Ray SL, Perry SG. AgDRIFT: a model for estimating near-field spray drift from aerial applications. Environ. Toxicol. Chem 2002;21:659–671. [PubMed: 11878480]

Vidal CJ. Expression of cholinesterases in brain and non-brain tumours. Chem. Biol. Interact 2005;157-158:227–32. [PubMed: 16256970]

Ward MH, Lubin J, Giglierano J, Colt JS, Wolter C, Bekiroglu N, Camann D, Hartge P, Nuckols JR. Proximity to crops and residential exposure to agricultural herbicides in Iowa. Environ. Health Perspect 2006;114:893–897. [PubMed: 16759991]

Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ. Health Perspect 2003;111:994–1006. [PubMed: 12826473]

Weppner S, Elgethun K, Lu C, Hebert V, Yost MG, Fenske RA. The Washington aerial spray drift study: children's exposure to methamidophos in an agricultural community following fixed-wing aircraft applications. J. Expo. Sci. Environ. Epidemiol 2006;16:387–396. [PubMed: 16249796]

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 1994;26:47–59. [PubMed: 8110023]

Williams RD, Boros LG, Kolanko CJ, Jackman SM, Eggers TR. Chromosomal aberrations in human lymphocytes exposed to the anticholinesterase pesticide isofenphos with mechanisms of leukemogenesis. Leuk. Res 2004;28:947–958. [PubMed: 15234572]

Wood, A. Compendium of pesticide common names. Alan Wood; London: 2008 [accessed March 1, 2008]. Available:http://www.alanwood.net/pesticides

Woodrow JE, Seiber JN, Baker LW. Correlation techniques for estimating pesticide volatilization flux and downwind concentrations. Environ. Sci. Technol 1997;31:523–529.

Woods N, Craig IP, Dorr G, Young B. Spray drift of pesticides arising from aerial application in cotton. J. Environ. Qual 2001;30:697–701. [PubMed: 11401259]

Table 1

Physicochemical, target pest[a], and toxicological[b,c,d,e,f,g] classifications of 118 agricultural pesticides applied in California, 1990-2002

Azoles
Fenbuconazole (F)[c,f]
Propiconazole (F)[c,d]
Terrazole (F)[b]
Triadimefon (F)[c,d,f]
Benzimidazoles
Benomyl (F)[c,d,e,f]
Thiabendazole (F)[b,d]
Thiophanate-methyl (F)[b,d]
Chlorinated phenols
2′4-D and related (H)[c,d,e,f]
Diclofop-methyl (H)[b,d]
MCPA (H)[c]
MCPP (H)[c]
Dinitroanilines
Ethalfluralin (H)[c]
Norflurazon (H)[c]
Oryzalin (H)[b]
Pendimethalin (H)[c,f]
Trifluralin (H)[c,e,f]
N-methyl carbamates
Aldicarb (I)[e,f,g]
Carbaryl (I)[b,e,f,g]
Carbofuran (I)[e,g]
Methiocarb (I)[f,g]
Methomyl (I)[f,g]
Mexacarbate (I)[g]
Oxamyl (I)[g]
Thiodicarb (I)[b,g]
Organochlorines
Dicofol (I)[c,f]
Endosulfan (I)[f]
Lindane (I)[c,f]
Methoxychlor (I)[f]
Organophosphates
Acephate (I)[c,e,g]
Azinphos-methyl (I)[g]
Bensulide (H)[g]
Chlorpyrifos (I)[e,f,g]

Diazinon (I)[d,e,g]

Dimethoate (I)[c,d,g]

Disulfoton (I)[g]

Ethephon (P)[g]

Fenamiphos (I)[g]

Fonofos (I)[g]

Malathion (I)[c,e,f,g]

Methamidophos (I)[g]

Methidathion (I)[c,g]

Methyl parathion (I)[e,f,g]

Mevinphos (I)[e,g]

Naled (I)[d,g]

Oxydemeton-methyl (I)[d,e,g]

Parathion (I)[c,f,g]

Phorate (I)[g]

Phosmet (I)[c,g]

Profenofos (I)[g]

Trichlorfon (I)[b,g]

Pyrethroids

Bifenthrin (I)[c,d,f]

Cypermethrin (I)[c,f]

Esfenvalerate (I)[f]

Lambda-cyhalothrin (I)[f]

Permethrin (I)[c,f]

Pyrethrins (I)[c]

Resmethrin (I)[d]

Tau-fluvalinate (I)[d,f]

Substituted benzenes

Chlorothalonil (F)[b,e]

PCNB (F)[c,f]

Thiocarbamates

Butylate (H),[g]

Cycloate (H)[d,g]

EPTC (H)[d,g]

Mancozeb (F)[b,d,f]

Maneb (F)[b,d,f]

Metam-sodium (F, H, FUM)[b,d,e]

Molinate (H)[c,d]

Pebulate (H) [g]

Thiobencarb (H) [g]

Thiram (F)[d,f]

Zineb (F)[d,f]

Ziram (F)[c,d,e,f]

Triazines

Atrazine (H)[c,e,f]

Cyanazine (H)[c,d,f]

Prometryn (H)[d]

Pymetrozine (I)[b]

Simazine (H)[c,d,f]

Ureas

Diuron (H)[b,d]

Linuron (H)[c,d,f]

Other pesticides

(Not grouped by physicochemical class)

1′3-dichloropropene (N, FUM)[b,e]

Alachlor (H) [b,d,e,f]

Amitraz (I)[c,d]

Benefin (H)[c]

Bromacil (H)[c]

Bromoxynil octanoate (H)[d]

Cacodylic acid (H)[b]

Captan (F)[b,e]

Chloropicrin (N, FUM)[e]

Chlorthal-dimethyl (H)[c]

Daminozide (P)[b]

Dicamba (H)[d]

Dioctyl phthalate (A)[b,d,f]

Diquat dibromide (H)[e]

Fenarimol (F)[f]

Fenbutatin-oxide (I)[d]

Fluazifop-butyl (H)[d]

Glyphosate (H)

Hexythiazox (I)[c]

Hydrogen cyanamide (H, P)[c]

Iprodione (F)[b,f]

Methyl bromide (F, H, I, FUM)[d,e]

Metolachlor (H)[c,f]

Metribuzin (H)[d,f]

MSMA (H)[c]

Myclobutanil (F)[d]

Ortho-phenylphenol (M)[b,d,e]

Oxadiazon (H)[b,d]

Oxyfluorfen (H)[c]

Oxythioquinox (F, I, FUM)[b,d]

Paraquat dichloride (H)[e]

Piperonyl butoxide (S)[c]

Propanil (H)[c]

Propargite (I)[b,d]

Propyzamide (H)[b]

S'S'S-tributyl (P)[b,g]

Sodium cacodylate (H)[b]

Triforine (F)[c,d]

Vinclozolin (F)[c,d,f]

---

[a] Target pest classifications: A, adjuvant; FUM, fumigant; F, fungicide; H, herbicide; I, insecticide; M, microbiocide; N, nematocide; P, plant growth regulator; S, synergist.

[b] Probable carcinogen.

[c] Possible carcinogen.

[d] Developmental or reproductive toxin.

[e] Suspected genotoxin.

[f] Suspected endocrine disruptor.

[g] Cholinesterase inhibitor.

Table 2

Characteristics of childhood acute lymphoblastic leukemia (ALL) cases and matched controls, the Northern California Childhood Leukemia Study, California, 1990-2002

	Cases		Controls	
Characteristics	**No.**	**%**	**No.**	**%**
Age[a]				
<3	70	33	90	34
3-4	81	38	103	38
5-10	62	29	75	28
Sex[a]				
Male	120	56	148	55
Female	93	44	120	45
Race/ethnicity[a]				
Hispanic	83	39	104	39
Non-Hispanic White	94	44	115	43
Non-Hispanic Black	8	4	10	4
Asian or other	28	13	39	14
Annual household income				
<$15,000	21	10	22	8
$15,000-29,999	43	20	35	13
$30,000-44,999	33	15	37	14
$45,000-59,999	37	17	29	11
$60,000-74,999	23	11	33	12
$75,000+	51	24	103	38
Refused or unknown	5	2	9	3
Total	213		268	

[a]Matching criterion.

Table 3

Effect estimates[a] for target pest classes of agricultural pesticides applied within ½-mi of residences on childhood acute lymphoblastic leukemia, the Northern California Childhood Leukemia Study, California, 1990-2002

Target pest class	Exposure range[b] (lb/mi^2)	Exposure: Lifetime				Exposure: First year of life			
		Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Insecticides	<1	123	163	1.0		124	162	1.0	
	1 - 72	59	52	1.5	0.9, 2.4	38	38	1.2	0.7, 2.2
	72 - 3,218	31	53	0.8	0.5, 1.4	29	44	0.8	0.5, 1.5
Herbicides	<1	125	160	1.0		126	166	1.0	
	1 - 57	51	54	1.2	0.8, 1.9	34	39	1.3	0.8, 2.3
	57 - 2,186	37	54	0.9	0.5, 1.5	31	39	1.0	0.6, 1.9
Fungicides	<1	141	181	1.0		138	175	1.0	
	1 - 64	40	43	1.2	0.7, 2.4	27	33	0.9	0.5, 1.7
	64 - 2,779	32	44	0.9	0.5, 1.6	26	36	0.9	0.5, 1.5
Plant growth regulators	<1	197	243	1.0		178	226	1.0	
	1 - 13	9	12	0.9	0.4, 2.4	9	5	2.5	0.7, 8.6
	13 - 447	7	13	0.7	0.2, 1.9	4	13	0.4	0.1, 1.3
Fumigants	<1	154	202	1.0		157	199	1.0	
	1 - 549	41	33	1.7	1.0, 3.1	18	18	1.0	0.4, 2.2
	549 - 42,342	18	33	0.8	0.4, 1.4	16	37	0.7	0.4, 1.4

CI, confidence interval; OR, odds ratio.

[a] Estimated by using conditional logistic regression, adjusting for household income.

[b] Moderate and high exposure categories are based on the median pesticide-use density among the controls with density ≥1 lb/mi^2.

Table 4

Effect estimates[a] for toxicological classes of agricultural pesticides applied within ½-mi of residences on childhood acute lymphoblastic leukemia, the Northern California Childhood Leukemia Study, California, 1990-2002

Toxicological class	Exposure range[b] (lb/mi^2)	Exposure: Lifetime				Exposure: First year of life			
		Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Probable carcinogens	<1	130	167	1.0		127	172	1.0	
	1 - 106	54	50	1.5	0.9, 2.4	41	29	1.9	1.0, 3.4
	106 - 13,371	29	51	0.7	0.4, 1.3	23	43	0.7	0.4, 1.3
Possible carcinogens	<1	126	168	1.0		125	169	1.0	
	1 - 83	60	50	1.6	1.0, 2.6	36	31	1.6	0.9, 2.8
	83 - 2,166	27	50	0.7	0.4, 1.2	30	44	0.9	0.5, 1.7
Probable or possible carcinogens	<1	116	157	1.0		115	160	1.0	
	1 - 161	67	55	1.6	1.0, 2.5	48	37	1.7	1.0, 3.4
	161 - 14,235	30	56	0.8	0.4, 1.3	28	47	0.8	0.4, 1.3
Developmental or reproductive toxins	<1	116	156	1.0		121	162	1.0	
	1 - 221	63	56	1.5	0.9, 2.3	39	36	1.4	0.8, 2.5
	221 - 30,500	34	56	0.8	0.5, 1.4	31	46	0.9	0.5, 1.6
Suspected genotoxins	<1	116	155	1.0		120	155	1.0	
	1 - 263	62	56	1.6	1.0, 2.6	42	45	1.1	0.6, 2.0
	263 - 45,593	35	57	0.8	0.5, 1.4	29	44	0.8	0.5, 1.5
Suspected endocrine disruptors	<1	121	162	1.0		125	161	1.0	
	1 - 93	58	53	1.5	0.9, 2.4	37	38	1.2	0.7, 2.2
	93 - 4,067	34	53	0.9	0.5, 1.6	29	45	0.8	0.4, 1.5
Cholinesterase inhibitors	<1	125	170	1.0		124	167	1.0	
	1 - 79	60	49	1.6	1.0, 2.7	38	35	1.4	0.8, 2.5
	79 - 3,364	28	49	0.8	0.4, 1.4	29	42	0.9	0.5, 1.7

CI, confidence interval; OR, odds ratio.

[a] Estimated using conditional logistic regression, adjusting for household income.

[b] Moderate and high exposure categories are based on the median pesticide-use density among the controls with density ≥1 lb/mi^2.

Table 5

Effect estimates for physiochemical classes of agricultural pesticides applied within ½-mi of lifetime residences on childhood acute lymphoblastic leukemia, the Northern California Childhood Leukemia Study, California, 1990-2002

Physicochemical class	Exposure range[a] (lb/mi^2)	Cases	Controls	Single-class model[b] OR	Single-class model[b] 95% CI	Multiple-class model[c] OR	Multiple-class model[c] 95% CI
Azoles	<1	197	251	1.0		1.0	
	1 - 2	5	8	1.0	0.3, 3.3	1.8	0.4, 7.8
	2 - 21	10	8	2.1	0.8, 5.4	3.9	1.0, 15.7
Benzimidazoles	<1	176	213	1.0		1.0	
	1 - 9	25	27	1.0	0.6, 2.0	0.6	0.2, 1.5
	9 - 96	12	28	0.5	0.2, 1.0	0.4	0.1, 1.3
Chlorinated phenols	<1	172	225	1.0		1.0	
	1 - 7	28	21	2.0	1.0, 3.8	1.5	0.6, 3.6
	7 - 83	13	22	0.7	0.3, 1.6	0.8	0.3, 2.1
Dinitroaniline	<1	162	202	1.0		1.0	
	1 - 20	31	33	1.1	0.6, 2.0	0.6	0.2, 1.4
	20 - 350	20	33	0.7	0.4, 1.4	0.6	0.2, 2.3
Methyl carbamates	<1	165	198	1.0		1.0	
	1 - 23	32	35	1.1	0.6, 1.9	0.7	0.3, 1.6
	23 - 778	16	35	0.6	0.3, 1.1	0.2	0.1, 1.1
Organochlorines	<1	182	225	1.0		1.0	
	1 - 9	19	21	1.0	0.5, 2.1	0.8	0.3, 2.3
	9 - 237	12	22	0.8	0.4, 1.7	0.7	0.2, 2.3
Organophosphates	<1	130	176	1.0		1.0	
	1 - 79	56	46	1.6	1.0, 2.7	1.6	0.7, 3.7
	79 - 2,572	27	46	0.8	0.4, 1.5	2.5	0.4, 14.8
Pyrethroids	<1	174	220	1.0		1.0	
	1 - 227	22	24	1.0	0.5, 2.0	2.1	0.7, 6.3
	227 - 43,810	17	24	1.0	0.5, 2.0	1.3	0.3, 5.6
Substituted benzenes	<1	182	235	1.0		1.0	
	1 - 19	20	16	1.7	0.8, 3.7	2.1	0.7, 6.6
	19 - 484	11	17	0.9	0.4, 2.0	2.8	0.7, 11.3
Thiocarbamates	<1	158	193	1.0		1.0	

Physicochemical class	Exposure range[a] (lb/mi^2)	Cases	Controls	Single-class model[b] OR	Single-class model[b] 95% CI	Multiple-class model[c] OR	Multiple-class model[c] 95% CI
	1 - 86	32	37	1.1	0.6, 1.9	0.7	0.3, 1.8
	86 - 13,152	23	38	0.7	0.4, 1.4	0.5	0.1, 2.3
Triazines	<1	170	219	1.0		1.0	
	1 - 27	31	24	1.9	1.0, 3.7	4.1	1.5, 11.1
	27 - 292	12	25	0.7	0.3, 1.4	2.0	0.4, 9.4
Ureas	<1	184	227	1.0		1.0	
	1 - 14	20	20	1.3	0.7, 2.7	1.3	0.4, 3.6
	14 - 274	9	21	0.5	0.2, 1.3	0.9	0.2, 3.9

CI, confidence interval; OR, odds ratio.

[a] Moderate and high exposure categories are based on the median pesticide-use density among the controls with density ≥1 lb/mi^2.

[b] Estimated using conditional logistic regression, adjusting for household income.

[c] Estimated using conditional logistic regression, adjusting for household income and all other physicochemical categories listed.