Title
Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort

Journal
Environmental Research, 96(2)

ISSN
0013-9351

Authors
Reynolds, Peggy
Hurley, Susan E
Goldberg, Debbie E
et al.

Publication Date
2004-10-01

DOI
10.1016/j.envres.2004.03.001

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Environmental Research 96 (2004) 206–218
Environmental Research
http://www.elsevier.com/locate/envres

Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort

Peggy Reynolds,[a,*] Susan E. Hurley,[b] Debbie E. Goldberg,[b] Sauda Yerabati,[c] Robert B. Gunier,[a] Andrew Hertz,[c] Hoda Anton-Culver,[d] Leslie Bernstein,[e] Dennis Deapen,[e] Pamela L. Horn-Ross,[f] David Peel,[d] Richard Pinder,[e] Ronald K. Ross,[e] Dee West,[f] William E. Wright,[g] and Argyrios Ziogas[d]

[a] *Environmental Health Investigations Branch, California Department of Health Services, 1515 Clay Street, Suite 1700, Oakland, CA 94612, USA*
[b] *Public Health Institute, Oakland, CA, USA*
[c] *Impact Assessment, Inc., Oakland, CA, USA*
[d] *School of Medicine, University of California, Irvine, CA, USA*
[e] *Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*
[f] *Northern California Cancer Center, Union City, CA, USA*
[g] *Cancer Surveillance Section, California Department of Health Services, Sacramento, CA, USA*

Received 11 July 2003; received in revised form 21 January 2004; accepted 2 March 2004

Abstract

We examined the association between residential proximity to agricultural pesticide use and breast cancer incidence among members of the California Teachers Study cohort, a large study of professional school employees with extensive information on breast cancer risk factors, followed for cancer incidence since 1995. We identified 1552 invasive breast cancer cases, diagnosed between 1996 and 1999, among 114,835 cohort members. We used California Pesticide Use Reporting data to select pesticides for analysis based on use volume, carcinogenic potential, and exposure potential; a Geographic Information System was used to estimate pesticide applications within a half-mile radius of subjects' residences. We applied Cox proportional hazard models to estimate hazard rate ratios (HR) for selected pesticides, adjusting for age, race, and socioeconomic status. We saw no association between residential proximity to recent agricultural pesticide use and invasive breast cancer incidence. HR estimates for the highest compared to the lowest exposure categories for groups of agents were as follows: probable or likely carcinogens (1.07, 95% confidence interval (CI): 0.86–1.32), possible or suggestive carcinogens (1.06, 95% CI: 0.87–1.29), mammary carcinogens (1.15, 95% CI: 0.90–1.48), and endocrine disruptors (1.03, 95% CI: 0.86–1.25). HR estimates for other groups and individual pesticides did not differ from unity, nor was there a trend for any groupings of or individual pesticides examined. Stratifying by menopausal status or family history of breast cancer did not substantially affect our results. Our analyses suggest that breast cancer incidence is not elevated in areas of recent, high agricultural pesticide use in California.

Keywords: Breast neoplasms; Pesticides; Cohort studies; California teachers study; Geographic information system; Incidence

1. Introduction

Breast cancer is the most common form of cancer among adult women in the United States (US) (Kosary et al., 1997; Ries et al., 1998) and known risk factors are thought to explain only about half of the cases occurring nationwide (Madigan et al., 1995). Observations that breast cancer incidence has been increasing over the past several decades, tending to be higher in industrialized nations, have fueled speculation that environmental contaminants may play a role in breast cancer etiology (John and Kelsy, 1993; Johnson-Thompson and Guthrie, 2000; Laden and Hunter, 1998; Wolff et al., 1996).

Agricultural pesticides may be one of the most ubiquitous environmental contaminants. In 1991, 2.7 billion pounds of agricultural pesticides were used in the US (US Environmental Protection Agency, Office of Pesticides and Toxic Substances, 1991) and population-based biomonitoring data indicate that most Americans

*Corresponding author. Fax: +1-510-622-4505.
E-mail address: preynold@dhs.ca.gov (P. Reynolds).

0013-9351/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.envres.2004.03.001

have detectable levels of many such pesticides in their bodies (Adgate et al., 2001; Gordon et al., 1999; Hill et al., 1995; Lu et al., 2000; US Centers for Disease Control and Prevention, National Center for Environmental Health, 2001). While animal studies provide ample evidence that many currently used pesticides are carcinogenic and tumor promoters (Crisp et al., 1997; Dich et al., 1997; Oregon State University, 1998; Sherman, 1994), relatively little is known about the risk to human populations from chronic low-level environmental exposures to these compounds. Occupational studies of female agricultural workers are sparse and tend not to observe a positive relationship between breast cancer and pesticide exposures (Davis et al., 1993; Kristensen et al., 1996; Pukkala and Notkola, 1997; Ronco et al., 1992; Settimi et al., 1999; Wiklund and Dich, 1994). Population-based studies are even fewer and have primarily been ecologic in design (Kettles et al., 1997; Mills, 1998; Waterhouse et al., 1996; Zahm et al., 1997). Recently, considerable research has focused on the potential relationship between breast cancer and body burden levels of organochlorine pesticides (Aronson et al., 2000; Bagga et al., 2000; Dello Iacovo et al., 1999; Dewailly et al., 1994; Dorgan et al., 1999; Guttes et al., 1998; Helzlsouer et al., 1999; Hoyer et al., 2000; Hunter et al., 1997; Liljegren et al., 1998; Mendonca et al., 1999; Millikan et al., 2000; Moysich et al., 1998; Mussalo-Rauhamaa et al., 1990; Olaya-Contreras et al., 1998; Romieu et al., 2000; Schecter et al., 1997; Stellman et al., 2000; Unger et al., 1984; van't Veer et al., 1997; Wolff et al., 1993, 2000; Zheng et al., 1999a-c). Results from these studies have been conflicting and methodologic differences in study design and measurement issues have hampered resolution of their differing results (Adami et al., 1995; Azevedo e Silva Mendonca, 1998; Gammon et al., 1998; Longnecker et al., 2000; Santodonato, 1997; Wassermann et al., 1976).

Potential pesticide exposure to agricultural community residents has been a major source of public concern (Solomon and Mott, 1998). California is the largest agricultural state in the US, boasting an annual average of 20 billion dollars in farm revenues during the 1990s (US Department of Agriculture, 1994; US Department of Agriculture, National Agricultural Statistics Service, 1999). The state also has some of the highest breast cancer incidence rates in the nation (Blot et al., 1977; Kwong et al., 2001; Parkin et al., 1997; Ries et al., 1998; Sturgeon et al., 1995; Walker et al., 1999). In 1990, the California Department of Pesticide Regulation expanded its Pesticide Use Reporting (PUR) system requiring the reporting of all agricultural pesticide use in the state. This database provides a unique opportunity to examine statewide environmental exposures to agricultural pesticide use and breast cancer incidence in California. We designed our study to look at the relationship between residential proximity to agricultural pesticide use, as reported in the PUR, and breast cancer incidence within a large, well-defined cohort of women residing throughout California.

2. Methods

2.1. Study population

Our study population, the California Teachers Study (CTS) cohort, was established from respondents to a 1995 mailing to all 329,000 active and retired female enrollees in the State Teachers Retirement System (STRS). STRS members are California public school employees, kindergarten through community college level, who teach, are involved in the selection and preparation of instructional materials, or supervise persons engaged in those activities. All California public school employees must pay into and receive retirement benefits through STRS and membership is in effect as long as retirement contributions remain on deposit with the program. STRS members are employed in approximately 1160 public school districts, community college districts, county offices of education, and state reporting entities throughout California. A total of 133,479 women (approximately 40% of those approached) returned the 1995 baseline questionnaire and chose to join the CTS cohort. The creation and characteristics of the cohort are described in detail elsewhere (Bernstein et al., 2002). A comparison of the cohort's geographic and age distributions to the STRS membership in that analysis revealed very similar distributions (Bernstein et al., 2002). Use of human subjects data in this study was reviewed by the California Health and Human Services Agency, Committee for the Protection of Human Subjects and found to be in compliance with their ethical standards and with the US Code of Federal Regulations, Title 24, Part 46 on the Protection of Human Subjects.

2.2. Follow-up and cancer incidence data

The CTS follows its cohort members annually for deaths, changes of address, and cancer diagnoses. The study uses mortality files and confirmed reports from relatives to ascertain date and cause of death. It obtains cohort members' address changes through annual mailings, participant responses, and record linkage with multiple sources, including the California Department of Motor Vehicles (DMV) and the US Postal Service National Change of Address database. The CTS identifies cancer outcomes for its members through annual linkage with the California Cancer Registry (CCR), a legally mandated, statewide, population-based cancer reporting system (California Cancer Registry, Data Standards and Quality Control Unit, 2000).

Modeled after the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, the CCR maintains high standards for data quality and completeness; their data is estimated to be 99% complete (Kwong et al., 2001). Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address, and social security number and includes manual review of possible matches. For our analyses, we defined a case as any woman diagnosed with invasive breast cancer following her completion of the baseline questionnaire through December 31, 1999. We excluded women diagnosed with breast cancer prior to completing their baseline questionnaire ($N = 6131$).

2.3. Geocoding

The CTS baseline questionnaire collected residential address information for all respondents living in California at baseline ($N = 123,925$). CTS investigators sent these addresses to Geographic Data Technology (GDT) (Geographic Data Technologies, 2002) for geocoding. All addresses not geocoded by GDT were submitted to the (California) Teale Data Center (Teale Data Center, 2002) for manual geocoding. Geographic Information System (GIS) specialists at the California Department of Health Services (CDHS) geocoded the remaining addresses. Following these efforts, most (89%) of the remaining 2328 ungeocodable addresses were post office boxes. For these records, CTS investigators accessed DMV, Experian (Experian, 2002), and California Property Tax Roll data to trace actual residential addresses.

We used ZP4 software (Semaphore Corp., 2002) to standardize and validate the addresses of cohort members and geocoded them using ArcView GIS software (Environmental Systems Research Institute, Inc., 2000) and street databases from GDT (Geographic Data Technologies, 2002) US Census Bureau (TIGER2000) (US Census Bureau, 2002a), and NavTech (Navagational Technologies, 2002). Ultimately, we geocoded 121,597 (98.1%) of the CTS respondents' addresses to a latitude and longitude.

2.4. Pesticide data

California's Department of Pesticide Regulation maintains a PUR database containing detailed information, reported at the level of Sections of the Public Land Survey System (PLSS), on active ingredient, quantity applied, acres treated, crop treated, and location (in square mile sections) for all agricultural pesticide applications in the state (California Department of Pesticide Regulation, 1997). For our study, we used PUR data from 1993 through 1995 because they represented the most complete data available for the time immediately preceding the start of our study's follow-up period. Our study is based on all compounds reported in the PUR database (including fungicides, herbicides, and insecticides). For simplicity, we hereafter will refer to all such compounds simply as "pesticides". For this analysis, we combined pesticides into six toxicological groups and selected five individual pesticides for examination based on their carcinogenic and exposure potential, as described below.

Toxicological groups of pesticides. Our purpose in grouping the pesticides was to study exposures with similar toxicity end points relevant to breast cancer, since true exposure occurs for mixtures of pesticides and total risk may be underestimated by studying only exposures to individual agents. We combined pesticides reported to the PUR system, during our study's period of interest (1993–1995), into six toxicological groups: probable or likely human carcinogens, possible or suggestive human carcinogens, mammary carcinogens, endocrine disruptors, anticholinesterases, and organochlorines. Some pesticides fell into more than one group. A full listing of the chemicals included in each of these toxicological groups appears in Table 1.

California banned or severely restricted the use of all known human carcinogens prior to the time of our study. As a result, the carcinogenic evidence for the pesticides that we assessed is based almost exclusively on laboratory animal studies (Crisp et al., 1997). The United States Environmental Protection Agency (US EPA) evaluates pesticides for their human carcinogenic potential and has recently updated the guidelines to move away from the A–E letter system toward more descriptive ratings such as likely or suggestive human carcinogens (US Environmental Protection Agency, Office of Pesticide Programs, 2002). For this analysis, we combined 17 pesticides classified as probable (Class B) or likely human carcinogens (US Environmental Protection Agency, Office of Pesticide Programs, 2002). Similarly, we grouped 35 pesticides classified as possible carcinogens (Class C) or with suggestive evidence of human carcinogenicity (US Environmental Protection Agency, Office of Pesticide Programs, 2002). We also identified four pesticides associated with excess mammary tumors in laboratory animal studies (Oregon State University, 1998; US Environmental Protection Agency, Office of Pesticide Programs, 2002).

We defined endocrine disruptors as those pesticides which have the potential to directly or indirectly increase estrogenic effects leading to mammary cell proliferation (Crisp et al., 1997; Illinois Environmental Protection Agency, 1997; National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, 2001; Oregon State University, 1998) and identified a total of 34 endocrine-disrupting pesticides used in California (Illinois Environmental Protection Agency, 1997). We included anticholinesterases as a toxicological group because they represent

Table 1
Toxicologic categorization[a] of agricultural pesticides reported to the California Pesticide Use Reporting system, 1993–1995

Toxicologic group	Individual agricultural pesticides		
Probable or likely human carcinogens	Cacodylic acid	Ethoprop	Orthophenylphenol
	Captan		
	Cholorothalonil	Iprodione	Propargite[b]
	1,3-Dichloropropene	Mancozeb	Propyzamide
	Diclofop-methyl	Maneb	Thiophanate-methyl
	Diuron[b]	Metam sodium	Ziram
Possible or suggestive human carcinogens	Acephate	Dicofol	Parathion
	Acrolein	Dimethoate	Pendimethalin
	Alachlor	Ethalfluralin	Permethrin
	Amitraz	Hydrogen cyanamide	Phosmet
	Benomyl	Lindane	Piperonyl butoxide
	Bifenthrin	Linuron	Propanil
	Bromacil	Malathion	Simazine[b]
	Bromoxynil octanoate	Methidathion	Triadimefon
	Carbaryl	Metolachlor	Trifluralin
	Chlorthal-dimethyl	Molinate	Vinclozolin
	Cyanazine	Norflurazon	
	Cypermethrin	Oryzalin[b]	
		Oxyfluorfen	
Mammary carcinogens	Atrazine	Oryzalin[b]	Simazine[b]
	Diuron[b]		
Endocrine disruptors	2,4-D	Hydrogen cyanamide	Oryzalin[b]
	Acrolein	Iprodione	Paraquat dichloride
	Alachlor	Lindane	Parathion
	Aldicarb	Malathion	Pendimethalin
	Atrazine	Mancozeb	Permethrin
	Benomyl	Maneb	Simazine[b]
	Bromacil	Methidathion	Thiophanate-methyl
	Cacodylic acid	Methomyl	Trifluralin
	Captan	Methyl bromide[b]	Vinclozolin
	Dicofol	Metribuzin	Ziram
	Diuron[b]	Mevinphos	
	Endosulfan	Molinate	
Anticholinesterases	Acephate	Disulfoton	Methyl parathion
	Aldicarb	Ethephon	Mevinphos
	Azinophos methyl	Fenamiphos	Naled
	Carbaryl	Malathion	Parathion
	Chlorpyrifos	Methamidophos	Phorate
	Diazinon	Methidathion	Phosmet
	Dimethoate	Methomyl	
Organochlorines	Dicofol	Endrin	Lindane

[a] Some pesticides fall into more than one group.
[b] Pesticide also chosen for individual analysis.

two specific groups of pesticides (organophosphates and carbamates) that potentially increase estrogenic activity by acting on the hypothalamic–pituitary axis (Oregon State University, 1998). We selected organochlorines because of their persistence in the body and the environment and because of the extensive evidence for their estrogenicity (Snedeker, 2001). Use of organochlorines has been consistently declining in California; we could identify only three organochlorine pesticides used between 1993 and 1995.

Selection of individual pesticides. We selected five pesticides for individual analysis: simazine, diuron, oryzalin, propargite, and methyl bromide. The first three have established toxicological data from laboratory animal studies implicating their role in mammary tumorigenesis and they are considered endocrine disruptors (Crisp et al., 1997; Illinois Environmental Protection Agency, 1997; National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, 2001; Oregon State

University, 1998; US Environmental Protection Agency, Office of Pesticide Programs, 2002). We selected propargite and methyl bromide because they ranked highest in a cancer hazard ranking system that we developed for a previous study of childhood cancer (Reynolds et al., 2002). Since the carcinogenic potential used in the ranking system is based on laboratory animal studies and includes tumors at multiple sites, these methods are applicable to a study of breast cancer and childhood cancer.

The detailed methods for the pesticide cancer hazard ranking system are presented elsewhere (Gunier et al., 2001). Briefly, each pesticide was assigned a hazard score based on two measures of carcinogenicity (cancer class and potency) and two measures of exposure potential (field volatilization flux and half-life). We then multiplied the hazard score for each pesticide with the average annual pounds of the pesticide applied statewide from 1993 through 1995 to derive the cancer hazard-adjusted use. We identified 57 pesticides used at or above 100,000 pounds per year in California for which all the necessary toxicity and environmental data were available. Methyl bromide and propargite ranked highest among these 57 pesticides for hazard-adjusted use during the time period of interest (1993–1995).

Pesticide exposure assessment. We calculated the CTS cohort members' residential pesticide exposure potential by determining the amount of pesticide applied (in pounds per square mile) within a half-mile radius (buffer) of each woman's residential baseline address. We chose to use a distance of one half mile for our buffer because the highest environmental concentrations of pesticides are likely to occur near the application site (Lu et al., 2000; Simcox et al., 1995). We used a GIS to identify PLSS Sections and the proportion of land area within the half-mile buffers. For each subject, we estimated the average annual agricultural pesticide use for 1993–1995 by summing the average pounds applied in all relevant PLSS Sections of the buffer, weighted by the proportion of land area in the buffer, and then dividing by the buffer area. From this calculation, we obtained a measure of pesticide use density in pounds per square mile (lb/mi^2). To evaluate the sensitivity of our exposure assessment methods to the use of a half-mile radius buffer, we also calculated the pesticide use density for two individual agents, simazine and diuron, only in each subject's PLSS Section of residence similar to the methods used in a previous study of fetal death (Bell et al., 2001).

2.5. Census data

We used 1990 US Census data to characterize the socioeconomic status (SES) and the degree of urbanization of cohort members' neighborhoods. We created a summary SES metric based on the study participants' census block group and incorporated measures of their occupation, education, and income (US Bureau of the Census, 1992). To do this, we first ranked all California block groups by education level (percentage of adults over age 25 years having completed a college degree or higher), income (median family income), and occupation (percentage of adults employed in managerial/professional occupations) according to quartiles based on the statewide adult population. This resulted in a score of one through four for each of these SES attributes. We then created a summary SES metric by summing the scores across each of these attributes and categorizing them into four groups based on the quartiles of this score for the statewide population.

To define degree of urbanization we used a combination of census-based information. The US Census Bureau defines an urbanized area as a centralized area, with a population of 50,000 or more people and a population density of at least 1000 people per square mile (US Census Bureau, 2002b). Since, by this definition, 85% of California residents live in an urban area, we used additional information to further refine our urbanization variable. We assigned Metropolitan Statistical Area (MSA) or Consolidated Metropolitan Statistical Area (CMSA) size codes to each tract that fell within a census-designated urban area. In addition, we assigned each tract to a census place size code, which represents the population size of the town or city in which the tract is located. If a tract was split between places, we assigned it the size code of the most populous place. Initially, we created four urban/rural categories by combining MSA/CMSA size and place size. We defined the first category, "most urban," as cities of greater than or equal to 100,000 people within MSA/CMSA areas of greater than or equal to one million people. Cities of less than 100,000 people in MSA/CMSA areas of greater than or equal to one million people fell into our second category, defined as "suburban." Our third category included tracts in MSA/CMSAs of less than one million people and was defined as "medium and small metropolitan areas." Our fourth category included small towns (less than 50,000 people) and rural areas outside of census-designated urbanized areas. Because of the sparseness of cohort members living in these last two categories, we combined them into an "other" category representing all those living outside urban and suburban areas.

2.6. Calculation of follow-up

We based our person-months at risk calculations on the first 4 years of follow-up, January 1, 1996 through December 31, 1999. For women who remained in California during the entire follow-up period, we calculated person-months at risk as the number of months between the date that each woman joined the

CTS cohort (the date that she completed the baseline questionnaire) and either the date of her breast cancer diagnosis, the date of her death, or December 31, 1999 (the end of the CTS follow-up period). Women who moved out of California during the follow-up period and did not develop breast cancer prior to leaving were presumed to have lived in California for one-half of the time that had elapsed between their entry into the cohort and the date associated with their first non-California address. We assigned these women person-months up to the midpoint of that time period.

2.7. Data analysis

Because our toxicological groupings and individual pesticides were highly correlated and not necessarily mutually exclusive, we looked at the six pesticide groupings and five individual pesticides using separate models. For each group or individual pesticide analysis, we considered subjects with exposures of $<1\,\text{lb/mi}^2$ to have negligible exposure potential; we used these as our reference category or unexposed group. We based our other three exposure categories on the distributions of pesticide use densities among subjects with $\geqslant 1\,\text{lb/mi}^2$ of use density: 1st to 49th percentiles, 50th to 74th percentiles, and $\geqslant$75th percentile. We used Cox proportional hazard models to calculate hazard rate ratios (HR) and 95% confidence intervals (CI) for breast cancer associated with pesticide use density, adjusting for age, race, SES, and urbanization. We also repeated these analyses with stratification for menopausal status, family history of breast cancer, and degree of urbanization. We performed all analyses using SAS software (SAS Institute, Inc., 2000), limiting all our analyses to the 114,835 respondents who had been successfully geocoded and had no prior history of breast cancer.

3. Results

Table 2 shows the characteristics of the 114,835 CTS cohort members included in our analysis. Half of these women were between the ages of 40 and 59 years. Most were non-Hispanic White (86.2%) and lived in urban or suburban areas (73.8%). Almost one-third were in the highest SES category (32.2%). Approximately half the cohort members were postmenopausal (50.7%) and most had no family history of breast cancer (86.6%).

Table 3 shows the distribution of potential agricultural pesticide exposures among the CTS cohort members included in our analyses. The number of women living in areas of pesticide use density $\geqslant 1\,\text{lb/mi}^2$ for a given pesticide or group of pesticides ranged from 7259 (6% of all women) for organochlorines to 44,292 (36%) for endocrine disruptors. Among the individual pesticides, methyl bromide represented the most prevalent potential exposure; 16% of teachers lived in areas with $\geqslant 1\,\text{lb/mi}^2$ annual use of the pesticide. The distribution of use density for methyl bromide was much higher than that of the other individual pesticides with a median application rate near study subjects' residences of $181\,\text{lb/mi}^2$. A substantial number of women lived in residential areas with pesticide use density $>100\,\text{lb/mi}^2$ applied per year. For example, 7913 women in our study lived in areas with a per-year use density $\geqslant 175\,\text{lb/mi}^2$ for probable or likely carcinogens and 10,492 women lived in areas with a per-year use density $\geqslant 324\,\text{lb/mi}^2$ for endocrine-disrupting pesticides.

Table 2
Selected characteristics of the California Teachers Study cohort members included in the present analysis ($N = 114,835$)

	Number	Percent
Age group (years)		
20–29	5322	4.6
30–39	15,421	13.4
40–49	30,810	26.8
50–59	27,969	24.4
60–69	18,461	16.1
70–79	11,908	10.4
$\geqslant 80$	4944	4.3
Race/ethnicity		
Non-Hispanic White	99,003	86.2
African American	3096	2.7
Hispanic	5013	4.4
Asian, Pacific Islander	4201	3.7
Native American, other	2484	2.1
Not reported	1038	0.9
Socioeconomic status[a]		
1st quartile (low)	2020	1.8
2nd quartile	23,264	20.3
3rd quartile	52,523	45.7
4th quartile (high)	37,028	32.2
Urbanization[b]		
Urban	42,996	37.4
Suburban	41,770	36.4
Other	30,069	26.2
Menopausal status		
Pre-menopausal	43,971	38.3
Post-menopausal	58,192	50.7
Unable to determine	12,672	11.0
Family history of breast cancer		
Yes	13,485	11.8
No	99,479	86.6
Adopted or not known	1871	1.6

[a] Socioeconomic status quartiles are based on the distribution of the California census block group levels of a census-based socioeconomic summary metric incorporating education, income, and occupation (see text for further explanation).

[b] Urbanization is based on the distribution of the California census block group levels of an urban/suburban/rural measurement (see text for further explanation).

Table 3
Annual average pesticide use density in the California Teachers Study cohort, 1993–1995

	Teachers with $\geqslant 1$ lb/mi^2 pesticide applied		Median (lb/mi^2)[a]	75th Percentile (lb/mi^2)[a]	Maximum (lb/mi^2)
	Number	Percentage			
Toxicologic category					
Probable or likely human carcinogens	33,476	28	33	175	43,813
Possible or suggestive human carcinogens	40,525	33	21	99	5256
Mammary carcinogens	20,667	17	17	58	1947
Endocrine disruptors	44,292	36	54	324	57,410
Anticholinesterases	39,058	32	22	111	5157
Organochlorines	7259	6	5	18	921
Individual pesticides					
Simazine	13,411	11	14	41	1704
Simazine—section only	11,342	9	20	56	2067
Diuron	10,099	8	11	33	909
Diuron—section only	7536	6	20	55	1139
Oryzalin	12,012	10	8	23	615
Propargite	12,403	10	15	52	1490
Methyl bromide	19,136	16	181	917	52,844

[a] Among those with $\geqslant 1$ lb/mi^2.

Our estimates of relative risk (hazard rate ratios) were based on 113,283 women, with more than 5.31 million months of follow-up, who did not develop breast cancer during the follow-up period and 1552 women, with 39,520 months of follow-up, who did develop invasive breast cancer. Table 4 contains HRs obtained from the Cox proportional hazard analysis for breast cancer. After adjusting for age, race, SES, and urbanization, HRs revealed no evidence that residential proximity to recent agricultural pesticide use was related to invasive breast cancer incidence. HR estimates for the highest quartile of area use were as follows: probable or likely carcinogens (1.07, 95% CI: 0.86–1.32), possible or suggestive carcinogens (1.06, 95% CI: 0.87–1.29), mammary carcinogens (1.15, 95% CI: 0.90–1.48), endocrine disruptors (1.03, 95% CI: 0.86–1.25), anticholinesterases (1.09, 95% CI: 0.89–1.33), and organocholorines (0.99, 95% CI: 0.63–1.55). HR estimates for the individual pesticides examined also did not differ from unity with HR estimates for the highest quartiles of exposure ranging from 1.11 (95% CI: 0.81–1.50) for simazine to 0.95 (95% CI: 0.67–1.35) for oryzalin. HRs were similar for the two pesticides selected for sensitivity analysis, simazine and diuron, when pesticide use only in the section of residence was used for exposure assessment, although the point estimates for the highest exposure category increased slightly in both cases (data not shown). HRs showed no linear increase or decrease with increasing level of exposure for any of the groupings or individual pesticides analyzed. Additional adjustment of the models for established breast cancer risk factors (including family history of breast cancer, age at menarche, pregnancy history, lifetime duration of

Table 4
Adjusted hazard ratio[a] estimates of invasive breast cancer associated with residential proximity to agricultural pesticide use among members of the California Teachers Study cohort with no prior history of breast cancer

Percentile (lb/mi^2)	Breast cancer cases (N)	Person-years at RISK	Hazard ratio	95% CI
Probable or likely human carcinogens				
<1 lb/mi^2	1157	322,446	1.00	Ref.
1st–49th (1–32 lb/mi^2)	199	61,850	0.95	0.81, 1.10
50th–74th (33–174 lb/mi^2)	93	30,815	0.93	0.75, 1.15
$\geqslant$75th ($\geqslant$175 lb/mi^2)	103	30,820	1.07	0.86, 1.32
Possible or suggestive human carcinogens				
<1 lb/mi^2	1078	296,461	1.00	Ref.
1st–49th (1–20 lb/mi^2)	246	74,385	0.96	0.84, 1.11
50th–74th (21–98 lb/mi^2)	103	37,720	0.82	0.67, 1.01
$\geqslant$75th ($\geqslant$99 lb/mi^2)	125	37,367	1.06	0.87, 1.29
Mammary carcinogens				
<1 lb/mi^2	1326	369,680	1.00	Ref.
1st–49th (1–16 lb/mi^2)	104	38,494	0.82	0.67, 1.00
50th–74th (17–57 lb/mi^2)	52	18,673	0.86	0.65, 1.13
$\geqslant$75th ($\geqslant$58 lb/mi^2)	70	19,084	1.15	0.90, 1.48
Endocrine disruptors				
<1 lb/mi^2	1027	282,635	1.00	Ref.
1st–49th (1–53 lb/mi^2)	274	81,869	0.97	0.84, 1.11
50th–74th (54–323 lb/mi^2)	114	40,591	0.87	0.71, 1.05
$\geqslant$75th ($\geqslant$324 lb/mi^2)	137	40,837	1.03	0.86, 1.25
Anticholinesterases				
<1 lb/mi^2	1081	301,893	1.00	Ref.
1st–49th (1–21 lb/mi^2)	251	71,733	1.04	0.90, 1.19
50th–74th (22–110 lb/mi^2)	98	36,211	0.83	0.68, 1.03
$\geqslant$75th ($\geqslant$111 lb/mi^2)	122	36,096	1.09	0.89, 1.33

Table 4 (*continued*)

Percentile (lb/mi^2)	Breast cancer cases (*N*)	Person-years at RISK	Hazard ratio	95% CI
Organochlorines				
<1 lb/mi^2	1468	418,945	1.00	Ref.
1st–49th (1–4 lb/mi^2)	46	13,115	1.06	0.79, 1.43
50th–74th (5–17 lb/mi^2)	18	7,110	0.82	0.52, 1.32
⩾75th (⩾18 lb/mi^2)	20	6,761	0.99	0.63, 1.55
Simazine				
<1 lb/mi^2	1399	396,381	1.00	Ref.
1st–49th (1–13 lb/mi^2)	73	25,045	0.91	0.71, 1.15
50th–74th (14–40 lb/mi^2)	36	12,075	0.91	0.65, 1.28
⩾75th (⩾41 lb/mi^2)	44	12,430	1.11	0.81, 1.50
Diuron				
<1 lb/mi^2	1447	408,537	1.00	Ref.
1–49th (1–10 lb/mi^2)	46	19,069	0.77	0.57, 1.03
50–74th (11–32 lb/mi^2)	28	8,979	1.01	0.69, 1.47
⩾75th (⩾33 lb/mi^2)	31	9346	1.04	0.73, 1.49
Oryzalin				
<1 lb/mi^2	1436	401,570	1.00	Ref.
1st–49th (1–7 lb/mi^2)	48	22,035	0.65	0.48, 0.86
50th–74th (8–22 lb/mi^2)	34	11,130	0.96	0.68, 1.35
⩾75th (⩾23 lb/mi^2)	34	11,197	0.95	0.67, 1.35
Propargite				
<1 lb/mi^2	1417	399,956	1.00	Ref.
1st–49th (1–14 lb/mi^2)	63	22,990	0.84	0.65, 1.09
50th–74th (15–51 lb/mi^2)	35	11,367	1.00	0.71, 1.41
⩾75th (⩾52 lb/mi^2)	37	11,618	1.03	0.74, 1.45
Methyl Bromide				
<1 lb/mi^2	1311	375,381	1.00	Ref.
1st–49th (1–180 lb/mi^2)	125	35,325	1.09	0.91, 1.31
50th–74th (181–916 lb/mi^2)	61	17,690	1.08	0.83, 1.40
⩾75th (⩾917 lb/mi^2)	55	17,535	0.98	0.74, 1.28

[a] Hazard ratio estimates are derived from Cox proportional hazards models and are adjusted for age, race/ethnicity, socioeconomic status and urbanization.

breastfeeding, physical activity, alcohol consumption, body mass index, and use of hormone therapy) did not substantially alter our results (data not shown).

Stratifying the models by menopausal status and family history of breast cancer did not substantially affect the risk estimates, although analyses were hindered by small numbers (data not shown). Likewise, results from models stratified by urbanization were generally similar to those observed in the full sample, although among rural residents there was some suggestion of an increased risk associated with the highest level of simazine (HR = 1.17, 0.82–1.67 based on use within $\frac{1}{2}$ mile buffer; HR = 1.44, 95% CI: 1.01–2.05 based on use only in section of residence) and a reduced risk for the lowest quartile of oryzalin use (HR = 0.65, 95% CI: 0.43–1.00). These risk estimates, however, were based on very small numbers.

4. Discussion

Our analyses suggest that breast cancer incidence is not elevated among members of the CTS cohort living in areas of recent, high agricultural pesticide use. Interest in breast cancer risk associated with pesticide exposures has been largely predicated on the lipophilic, persistent, and carcinogenic characteristics of many such agents historically used in agriculture (Blair and Zahm, 1990; Dich et al., 1997). Evidence from case–control literature on body burden levels of pesticides and breast cancer risk has been mixed (Adami et al., 1995; Snedeker, 2001; Wolff et al., 1996) and, although observed differences in secular and geographic patterns have provoked questions about the potential for population exposure to these agents (Allen et al., 1997; Westin and Richter, 1990), few studies to date have specifically explored the risks among women living in agricultural areas (Hopenhayn-Rich et al., 2002; Kettles et al., 1997; Mills, 1998; Waterhouse et al., 1996; Wesseling et al., 1999; Zahm et al., 1997).

The few studies able to examine breast cancer outcomes among female agricultural workers have tended to report null associations (Davis et al., 1992; Inskip et al., 1996; Kristensen et al., 1996; Pukkala and Notkola, 1997; Ronco et al., 1992) or associations with HRs significantly below unity (Settimi et al., 1999; Singleton et al., 1989; Wiklund and Dich, 1994). In a California mortality study designed to evaluate standardized mortality ratios (SMRs) for various occupational groups, women employed in agricultural occupations had a significantly lower SMR for breast cancer (SMR = 45), which remained low after adjustment for SES and for alcohol and tobacco consumption (SMR = 59) (Singleton et al., 1989).

Few general population studies of pesticide-related cancer have been conducted in women and most are hampered by indirect assessments of exposure and a lack of information on other variables of interest (Zahm et al., 1997). The incidence of breast cancer was not elevated among women participating in the Tecumseh, Michigan study of rural farming area residents (Waterhouse et al., 1996); similarly, it was not elevated among women living in agricultural production areas of Belgium (Janssens et al., 2001). Higher breast cancer rates were observed among women living in an area of Kentucky with high levels of triazine herbicide use (Kettles et al., 1997). However, a follow-up study, using more refined measures of potential exposure and an additional 3 years of follow-up, failed to find an association between atrazine and breast cancer incidence in Kentucky (Hopenhayn-Rich et al., 2002). An ecologic

analysis of cancer rates and heavy pesticide use conducted in rural counties of Costa Rica reported an increase in all female hormonally related cancers, including breast cancer (RR = 1.25, 95% CI: 1.02–1.54) (Wesseling et al., 1999). This positive finding may partly be a function of exposure levels; pesticide use is considerably higher in Costa Rica than in areas with intensive agriculture in developed countries (Wesseling et al., 1999). A correlation analysis of countywide pesticide use and cancer incidence in some areas of California, from 1988 through 1992, suggested some potentially interesting risk associations for men of color but not for women (Mills, 1998). The lack of detail on chemical agents of interest and the inability to account for within-area exposure potential variability have proven to be the major shortcomings of these approaches.

The development of GIS applications for epidemiologic studies is providing new avenues for addressing such shortcomings (Gunier et al., 2001; Reynolds et al., 2002; Ward et al., 2000), though a great deal of methodologic work remains. Like our own study, an investigation of environmental risk factors for breast cancer in Cape Cod, Massachusetts utilizes a GIS to provide more spatially precise estimates of specific population exposures (Brody et al., 2002). This case–control study of breast cancer in Cape Cod area women assigns pesticide exposure information individually to its subjects. Results are not yet available from that study, but a comparison of their findings with those from our study will prove valuable.

In our study we did not see an overall association with simazine, the most commonly used triazine herbicide used in California. While we did see some suggestion of an increased breast cancer risk associated with simazine use among rural residents, it was based on small numbers ($N = 34$ cases) and there was no evidence of a trend. Given the large number of comparisons made in this study, such a finding may be due to chance although future study might be warranted.

Our study has a number of important limitations. We focused on examining residential proximity to agricultural pesticide use and had no information on other pesticide exposures such as house fumigation or pesticides applied in parks, on golf courses, along the sides of roadways, or in subjects' own households. We based exposure potential on residential proximity only and could not account for workplace or leisure time exposures. Additionally, we based our exposure classifications on reported pesticide use and not on environmental or biological measurements. Finally, we based exposure assignments on recent pesticide use near women's baseline residence and could not account for historic use patterns or for the residential mobility of our study subjects.

Historical California data indicate that recent pesticide use patterns generally reflect long-term patterns at the state and county level but may be less predictive at the neighborhood level. In California, agricultural pesticide use has been fairly consistent statewide (125–175 million pounds per year), with basically the same counties, crops, and pesticides ranking highest in use year after year since full reporting was implemented in 1990 (Wilhoit et al., 1999). Reporting was not required for all agricultural pesticide use in the 1980s, but the restricted PUR data indicate that the same counties, crops, and pesticides had the most use every year during the decade (California Department of Pesticide Regulation, 1997). However, GIS mapping of pesticide use patterns in the 1980s compared to the 1990s showed that there has been some change at the neighborhood level as former cropland and surrounding buffers have been turned into residential areas.

Although we did not have residential history information for the cohort, we have conducted two separate analyses that help to inform the issue of residential mobility. Preliminary data from a small substudy ($N = 328$) nested within the cohort, for whom complete lifetime residential histories were collected, suggest that the cohort may be somewhat residentially stable with participants reporting an average of 15 years at their current address (Hurley et al., 2004, unpublished). Additionally, we repeated the pesticides analyses in the full cohort, restricting it to only study subjects who had not moved during the follow-up period and found essentially the same results as those reported here (data not shown).

Another potential limitation of our study is that the PUR data are reported to square mile sections of a statewide grid system rather than to the actual field boundaries. We included agricultural pesticide use reported in any section within a half-mile of the subject's residence. Our methods are similar to the "broad" definition of exposure used in a previous study of fetal death that used PUR data (Bell et al., 2001). Recently, an assessment of potential exposure misclassification error resulting from this method of exposure assessment was published (Rull and Ritz, 2003). The authors of that study compared risk estimates generated from the use of square mile sections and the "broad" definition of exposure using PUR data, similar to the method used in our analyses, to a more refined measure using 500-m buffers and crop maps combined with PUR data. They reported that while the sensitivity of the "broad" definition was 100%, the specificity was only 62–94%, resulting in an attenuation of a true risk ratio from 1.5 to 1.1 (Rull and Ritz, 2003). They also reported that the specificity was better when exposure estimates were based only on use within the section of residence. In our study, the hazard ratios for simazine and diuron were similar when we considered pesticide use in the section of residence only, although the point estimates were slightly higher for the highest exposure category and became significant for simazine among rural residents.

The reduced specificity and ability to detect risk reported by these investigators (Rull and Ritz, 2003) was based on the assumption that no exposure occurs beyond 500 m from a treated field. However, a health evaluation using measured concentrations of pesticides in outdoor air from agricultural counties around California found that there were potential health risks associated with the levels measured at distances much greater than 500 m from treated fields (Lee et al., 2002). The environmental transport of pesticides from the application site depends on many factors including wind speed, physical properties of the pesticide, droplet size and application method (Raupach et al., 2001; Teske et al., 2002; Woodrow et al., 1997). In future studies, improved exposure assessment methods are needed that can combine meteorological data, field-level pesticide application information, and the physical properties of each pesticide into a dispersion model to predict ambient concentrations are needed. The resulting ambient concentrations could then be adjusted for potency before summing across all pesticides with similar health effects as has been done previously for pesticides and other hazardous air pollutants (Lee et al., 2002; Morello-Frosch et al., 2000; Pratt et al., 2000; Woodruff et al., 2000).

Our study offers a number of advantages over those that examine risk relationships based on population exposures. With the extensive information available from California's PUR system, we were able to evaluate our subjects' residential proximity to quantified use estimates of pesticides within specific toxicological groups and to individual agents. Since these exposure attributes were independently assessed, they were not subject to recall bias or dependent on the knowledge of study participants. Because our study is based on exposure estimates assigned to individuals in a well-defined cohort, it is not subject to the limitations of purely ecologic analyses. Additionally, as residents of California, a very large and geographically heterogeneous state, the cohort members experienced considerable variability in exposure opportunity.

Our study was exploratory in nature and designed to evaluate whether breast cancer rates are higher in areas of recent high agricultural pesticide use, an issue of great public concern. The results presented here suggest that no such association exists. Whether pesticide exposures are etiologically implicated in the development of breast cancer will require study designs that better characterize lifetime exposures to these agents.

Acknowledgments

We express our appreciation to all of the participants in the California Teachers Study and to the analysts and staff who have contributed so much to the success of this research project. The authors thank the following people for technical or administrative support: Mark Allen, Gretchen Agha, Rachna Nivas, Theresa Saunders, Frank Stasio, Jan Schaefer, Susan Stewart, Andrea Subotic, and Jane Sullivan-Halley. The ideas and opinions expressed are those of the authors and no endorsement by the California Department of Health Services should be inferred. This project was funded by grants from the California Breast Cancer Research Program (6JB-0111) and the National Cancer Institute (R01 CA77398).

References

Adami, H.O., Lipworth, L., Titus-Ernstoff, L., Hsieh, C.C., Hanberg, A., Ahlborg, U., Baron, J., Trichopoulos, D., 1995. Organochlorine compounds and estrogen-related cancers in women. Cancer Causes Control 6, 551–566.

Adgate, J.L., Barr, D.B., Clayton, C.A., Eberly, L.E., Freeman, N.C., Lioy, P.J., Needham, L.L., Pellizzari, E.D., Quackenboss, J.J., Roy, A., Sexton, K., 2001. Measurement of children's exposure to pesticides: analysis of urinary metabolite levels in a probability-based sample. Environ. Health Perspect. 109, 583–590.

Allen, R.H., Gottlieb, M., Clute, E., Pongsiri, M.J., Sherman, J., Obrams, G.I., 1997. Breast cancer and pesticides in Hawaii: the need for further study. Environ. Health Perspect. 105 (Suppl. 3), 679–683.

Aronson, K.J., Miller, A.B., Woolcott, C.G., Sterns, E.E., McCready, D.R., Lickley, L.A., Fish, E.B., Hiraki, G.Y., Holloway, C., Ross, T., Hanna, W.M., SenGupta, S.K., Weber, J.P., 2000. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol. Biomarkers Prevent. 9, 55–63.

Azevedo e Silva Mendonca, G., 1998. Measuring exposure of organochlorinated pesticides. Cad Saude Publica 14 (Suppl. 3), 177–179.

Bagga, D., Anders, K.H., Wang, H.J., Roberts, E., Glaspy, J.A., 2000. Organochlorine pesticide content of breast adipose tissue from women with breast cancer and control subjects. J. Natl. Cancer Inst. 92, 750–753.

Bell, E.M., Hertz-Picciotto, I., Beaumont, J.J., 2001. A case–control study of pesticides and fetal death due to congenital anomalies. Epidemiology 12, 148–156.

Bernstein, L., Allen, M., Anton-Culver, H., Deapen, D., Horn-Ross, P.L., Peel, D., Pinder, R., Reynolds, P., Sullivan-Halley, J., West, D., Wright, W., Ziogas, A., Ross, R.K., 2002. High breast cancer incidence rates among California teachers: results from the California teachers study (United States). Cancer Causes Control 13, 625–635.

Blair, A., Zahm, S.H., 1990. Methodologic issues in exposure assessment for case–control studies of cancer and herbicides. Am. J. Ind. Med. 18, 285–293.

Blot, W.J., Fraumeni, J.F., Stone, B.J., 1977. Geographic patterns of breast cancer in the United States. J. Natl. Cancer. Inst. 59, 1407–1411.

Brody, J.G., Vorhees, D.J., Melly, S.J., Swedis, S.R., Drivas, P.J., Rudel, R.A., 2002. Using GIS and historical records to reconstruct residential exposure to large-scale pesticide application. J. Expo Anal. Environ. Epidemiol. 12, 64–80.

California Cancer Registry, Data Standards and Quality Control Unit, 2000. California Cancer Reporting System Standards: Abstracting and Coding Procedures for Hospitals. California Department of Health Services, Sacramento, CA.

California Department of Pesticide Regulation, 1997. Pesticide Use Report System Data, 1991–1994 (data file). California Department of Pesticide Regulation, Sacramento, CA.

Crisp, T., Glegg, E., Cooper, R., Anderson, D., Baetcke, K., Hoffmann, J., et al., 1997. Special report on environmental endocrine disruption: an effects assessment and analysis. EPA/630/R096/012, US Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

Davis, J.R., Brownson, R.C., Garcia, R., 1992. Family pesticide use in the home, garden, orchard, and yard. Arch. Environ. Contam. Toxicol. 22, 260–266.

Davis, D.L., Bradlow, H.L., Wolff, M., Woodruff, T., Hoel, D.G., Anton-Culver, H., 1993. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. Environ. Health Perspect. 101, 372–377.

Dello Iacovo, R., Celentano, E., Strollo, A.M., Iazzetta, G., Capasso, I., Randazzo, G., 1999. Organochlorines and breast cancer. A study on Neapolitan women. Adv. Exp. Med. Biol. 472, 57–66.

Dewailly, E., Dodin, S., Verreault, R., Ayotte, P., Sauve, L., Morin, J., Brisson, J., 1994. High organochlorine body burden in women with estrogen receptor-positive breast cancer. J. Natl. Cancer Inst. 86, 232–234.

Dich, J., Zahm, S.H., Hanberg, A., Adami, H.O., 1997. Pesticides and cancer. Cancer Causes Control 8, 420–443.

Dorgan, J.F., Brock, J.W., Rothman, N., Needham, L.L., Miller, R., Stephenson Jr., H.E., Schussler, N., Taylor, P.R., 1999. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control 10, 1–11.

Environmental Systems Research Institute, Inc., 2000. ArcView, Version 3.3 (computer program). ESRI, Redlands, CA.

Experian, 2002. Home Page. Experian, Costa Mesa, CA. Available: http://www.experian.com/consumer/index.html [accessed 15 December 2002].

Gammon, M.D., Terry, M.B., Teitelbaum, S.L., Britton, J.A., Levin, B., 1998. Organochlorine residues and breast cancer. N. Engl. J. Med. 338, 989 (discussion 991).

Geographic Data Technologies, 2002. Home Page. GDT, Lebanon, NH. Available: http://www.geographic.com/home/index.cfm [accessed 15 December 2002].

Gordon, S.M., Callahan, P.J., Nishioka, M.G., Brinkman, M.C., O'Rourke, M.K., Lebowitz, M.D., Moschandreas, D.J., 1999. Residential environmental measurements in the national human exposure assessment survey (NHEXAS) pilot study in Arizona: preliminary results for pesticides and VOCs. J. Expo. Anal. Environ. Epidemiol. 9, 456–470.

Gunier, R.B., Harnly, M.E., Reynolds, P., Hertz, A., Von Behren, J., 2001. Agricultural pesticide use in California: pesticide prioritization, use densities, and population distributions for a childhood cancer study. Environ. Health Perspect. 109, 1071–1078.

Guttes, S., Failing, K., Neumann, K., Kleinstein, J., Georgii, S., Brunn, H., 1998. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. Arch. Environ. Contam. Toxicol. 35, 140–147.

Helzlsouer, K.J., Alberg, A.J., Huang, H.Y., Hoffman, S.C., Strickland, P.T., Brock, J.W., Burse, V.W., Needham, L.L., Bell, D.A., Lavigne, J.A., Yager, J.D., Comstock, G.W., 1999. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol. Biomarkers Prevent. 8, 525–532.

Hill Jr., R.H., Head, S.L., Baker, S., Gregg, M., Shealy, D.B., Bailey, S.L., Williams, C.C., Sampson, E.J., Needham, L.L., 1995. Pesticide residues in urine of adults living in the United States: reference range concentrations. Environ. Res. 71, 99–108.

Hopenhayn-Rich, C., Stump, M.L., Browning, S.R., 2002. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch. Environ. Contam. Toxicol. 42, 127–136.

Hoyer, A.P., Jorgensen, T., Brock, J.W., Grandjean, P., 2000. Organochlorine exposure and breast cancer survival. J. Clin. Epidemiol. 53, 323–330.

Hunter, D.J., Hankinson, S.E., Laden, F., Colditz, G.A., Manson, J.E., Willett, W.C., Speizer, F.E., Wolff, M.S., 1997. Plasma organochlorine levels and the risk of breast cancer. N. Engl. J. Med. 337, 1253–1258.

Illinois Environmental Protection Agency, 1997. Illinois EPA endocrine disruptors strategy (Table 1 Preliminary List of Chemicals Associated With Endocrine System Effects in Animals and Humans (*) or In Vitro (+) 1996/10/16). Illinois Environmental Protection Agency, Springfield, IL.

Inskip, H., Coggon, D., Winter, P., Pannett, B., 1996. Mortality of farmers and farmers' wives in England and Wales 1979–80, 1982–90. Occup. Environ. Med. 53, 730–735.

Janssens, J.P., Van Hecke, E., Geys, H., Bruckers, L., Renard, D., Molenberghs, G., 2001. Pesticides and mortality from hormone-dependent cancers. Eur. J. Cancer Prev. 10, 459–467.

John, E., Kelsy, J., 1993. Radiation: other environmental exposures and breast cancer. Epidemiol. Rev. 15, 157–162.

Johnson-Thompson, M.C., Guthrie, J., 2000. Ongoing research to identify environmental risk factors in breast carcinoma. Cancer 88, 1224–1229.

Kettles, M.K., Browning, S.R., Prince, T.S., Horstman, S.W., 1997. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. Environ. Health Perspect. 105, 1222–1227.

Kosary, C., Hankey, B., Miller, B., Harras, A., Edwards, B., 1997. SEER Cancer Statistics Review, 1973–1994. National Cancer Institute, Bethesda, MD.

Kristensen, P., Andersen, A., Irgens, L.M., Bye, A.S., Sundheim, L., 1996. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int. J. Cancer 65, 39–350.

Kwong, S.L., Perkins, C.I., Morris, C.R., Cohen, R., Allen, M., Wright, W.E., 2001. Cancer in California: 1988–1999. California Department of Health Services, Cancer Surveillance Section, Sacramento, CA.

Laden, F., Hunter, D.J., 1998. Environmental risk factors and female breast cancer. Annu. Rev. Public Health 19, 101–123.

Lee, S., McLaughlin, R., Harnly, M., Gunier, R., Kreutzer, R., 2002. Community exposures to airborne agricultural pesticides in California: ranking of inhalation risks. Environ. Health Perspect. 110, 1175–1184.

Liljegren, G., Hardell, L., Lindstrom, G., Dahl, P., Magnuson, A., 1998. Case–control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur. J. Cancer Prevent. 7, 135–140.

Longnecker, M.P., Ryan, J.J., Gladen, B.C., Schecter, A.J., 2000. Correlations among human plasma levels of dioxin-like compounds and polychlorinated biphenyls (PCBs) and implications for epidemiologic studies. Arch. Environ. Health 55, 195–200.

Lu, C., Fenske, R.A., Simcox, N.J., Kalman, D., 2000. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ. Res. 84, 290–302.

Madigan, M.P., Ziegler, R.G., Benichou, J., Byrne, C., Hoover, R.N., 1995. Proportion of breast cancer cases in the United States explained by well-established risk factors. J. Natl. Cancer Inst. 87, 1681–1685.

Mendonca, G.A., Eluf-Neto, J., Andrada-Serpa, M.J., Carmo, P.A., Barreto, H.H., Inomata, O.N., Kussumi, T.A., 1999. Organochlorines and breast cancer: a case–control study in Brazil. Int. J. Cancer 83, 596–600.

Millikan, R., DeVoto, E., Duell, E.J., Tse, C.K., Savitz, D.A., Beach, J., Edmiston, S., Jackson, S., Newman, B., 2000. Dichlorodiphenyldichloroethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Cancer Epidemiol. Biomarkers Prevent. 9, 1233–1240.

Mills, P.K., 1998. Correlation analysis of pesticide use data and cancer incidence rates in California counties. Arch. Environ. Health 53, 410–413.

Morello-Frosch, R.A., Woodruff, T.J., Axelrad, D.A., Caldwell, J.C., 2000. Air toxics and health risks in California: the public health implications of outdoor concentrations. Risk Anal. 20, 273–291.

Moysich, K.B., Ambrosone, C.B., Vena, J.E., Shields, P.G., Mendola, P., Kostyniak, P., Greizerstein, H., Graham, S., Marshall, J.R., Schisterman, E.F., Freudenheim, J.L., 1998. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prevent. 7, 181–188.

Mussalo-Rauhamaa, H., Hasanen, E., Pyysalo, H., Antervo, K., Kauppila, R., Pantzar, P., 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. Cancer 66, 2124–2128.

National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program, 2001. National Toxicology Program's Report of the Endocrine Disruptors Low Dose Peer Review. US Department of Health and Human Services, Research Triangle Park, NC.

Navagational Technologies, 2002. Home Page. NavTech, Chicago, IL. Available: http://www.navtech.com/ [accessed 15 December 2002].

Olaya-Contreras, P., Rodriguez-Villamil, J., Posso-Valencia, H.J., Cortez, J.E., 1998. Organochlorine exposure and breast cancer risk in Colombian women. Cad Saude Publica 14 (Suppl. 3), 125–132.

Oregon State University, 1998. The EXtension TOXicology NETwork (EXTOXNET). Oregon State University, Corvallis, OR, Available: http://ace.orst.edu/info/extoxnet/ [accessed 5 November 2002].

Parkin, D., Whelan, S., Ferlay, J., Raymond, L., Young, J., 1997. Cancer Incidence in Five Continents, 143. World Health Organization, International Agency for Research on Cancer, Lyon, France.

Pratt, G.C., Palmer, K., Wu, C.Y., Oliaei, F., Hollerbach, C., Fenske, M.J., 2000. An assessment of air toxics in Minnesota. Environ. Health Perspect. 108, 815–825.

Pukkala, E., Notkola, V., 1997. Cancer incidence among Finnish farmers, 1979–93. Cancer Causes Control 8, 25–33.

Raupach, M.R., Briggs, P.R., Ahmad, N., Edge, V.E., 2001. Endosulfan transport: II. Modeling airborne dispersal and deposition by spray and vapor. J. Environ. Qual. 30, 729–740.

Reynolds, P., Von Behren, J., Gunier, R.B., Goldberg, D.E., Hertz, A., Harnly, M.E., 2002. Childhood cancer and agricultural pesticide use: an ecologic study in California. Environ. Health Perspect. 110, 319–324.

Ries, L., Kosary, C., Hankey, B., Miller, B., Edwards, B., 1998. SEER Cancer Statistics Review, 1973–1995. National Cancer Institute, Bethesda, MD.

Romieu, I., Hernandez-Avila, M., Lazcano-Ponce, E., Weber, J.P., Dewailly, E., 2000. Breast cancer, lactation history, and serum organochlorines. Am. J. Epidemiol. 152, 363–370.

Ronco, G., Costa, G., Lynge, E., 1992. Cancer risk among Danish and Italian farmers. Br. J. Ind. Med. 49, 220–225.

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

Santodonato, J., 1997. Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. Chemosphere 34, 835–848.

SAS Institute, Inc., 2000. SAS, Version 8.0e (computer program). SAS Institute, Inc., Cary, NC.

Schecter, A., Toniolo, P., Dai, L.C., Thuy, L.T., Wolff, M.S., 1997. Blood levels of DDT and breast cancer risk among women living in the north of Vietnam. Arch. Environ. Contam. Toxicol. 33, 453–456.

Semaphore Corporation, 2002. ZP4, Version 46 (computer program). Semaphore Corp, Aptos, CA.

Settimi, L., Comba, P., Carrieri, P., Boffetta, P., Magnani, C., Terracini, B., Andrion, A., Bosia, S., Ciapini, C., De Santis, M., Desideri, E., Fedi, A., Luccoli, L., Maiozzi, P., Masina, A., Perazzo, P.L., Axelson, O., 1999. Cancer risk among female agricultural workers: a multi-center case–control study. Am. J. Ind. Med. 36, 135–141.

Sherman, J.D., 1994. Structure-activity relationships of chemicals causing endocrine, reproductive, neurotoxic, and oncogenic effects: a public health problem. Toxicol. Ind. Health 10, 163–179.

Simcox, N.J., Fenske, R.A., Wolz, S.A., Lee, I.C., Kalman, D.A., 1995. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environ. Health Perspect. 103, 1126–1134.

Singleton, J.A., Beaumont, J.J., Doebbert, G., 1989. A computer program for analyses of vital statistics-based occupational mortality data. Comput. Biomed. Res. 22, 488–496.

Snedeker, S.M., 2001. Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin. Environ. Health Perspect. 109 (Suppl. 1), 35–47.

Solomon, G.M., Mott, L., 1998. Trouble on the Farm: Growing up with Pesticides in Agricultural Communities. Natural Resources Defense Council, New York, NY.

Stellman, S.D., Djordjevic, M.V., Britton, J.A., Muscat, J.E., Citron, M.L., Kemeny, M., Busch, E., Gong, L., 2000. Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York. Cancer Epidemiol. Biomarkers Prevent. 9, 1241–1249.

Sturgeon, S.R., Schairer, C., Gail, M., McAdams, M., Brinton, L.A., Hoover, R.N., 1995. Geographic variation in mortality from breast cancer among white women in the United States. J. Natl. Cancer Inst. 87, 1846–1853.

Teale Data Center, 2002. Home Page. Teale Data Center, Sacramento, CA, Available: http://www.gislab.teale.ca.gov/ [accessed 15 January 2003].

Teske, M.E., Bird, S.L., Esterly, D.M., Curbishley, T.B., Ray, S.L., Perry, S.G., 2002. AgDRIFT: a model for estimating near-field spray drift from aerial applications. Environ. Toxicol. Chem. 21, 659–671.

Unger, M., Kiaer, H., Blichert-Toft, M., Olsen, J., Clausen, J., 1984. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. Environ. Res. 34, 24–28.

US Bureau of the Census, 1992. Census of Population and Housing, 1990: Modified Age/Race, Sex and Hispanic Origin (MARS) State and County File (data file). US Bureau of the Census, Washington, DC.

US Census Bureau, 2002a. TIGER2000 (data file). US Census Bureau, Washington, DC.

US Census Bureau, 2002b. Census 2000 Urban and Rural Classification. US Census Bureau, Washington, DC. Available: http://www.census.gov/geo/www/ua/ua_2k.html [accessed 22 January 2003b].

US Centers for Disease Control and Prevention, National Center for Environmental Health, 2001. National Report on Human Exposure to Environmental Chemicals. 01-0164, US Centers for Disease Control and Prevention, Atlanta, GA.

US Department of Agriculture, 1994. 1992 Census of Agriculture. AC92-S-2, US Department of Commerce, Economics and Statistics Administration, Washington, DC.

US Department of Agriculture, National Agricultural Statistics Service, 1999. 1997 Census of Agriculture. AC97-S-2, US Department of Agriculture, Washington, DC.

US Environmental Protection Agency, Office of Pesticide Programs, 2002. Chemicals Evaluated for Carcinogenic Potential. EPA-20020508A, US Environmental Protection Agency, Washington, DC.

US Environmental Protection Agency, Office of Pesticides and Toxic Substances, 1991. EPA's Pesticide Programs. 21T-1005, US Environmental Protection Agency, Washington, DC.

van't Veer, P., Lobbezoo, I.E., Martin-Moreno, J.M., Guallar, E., Gomez-Aracena, J., Kardinaal, A.F., Kohlmeier, L., Martin, B.C., Strain, J.J., Thamm, M., van Zoonen, P., Baumann, B.A., Huttunen, J.K., Kok, F.J., 1997. DDT (dicophane) and postmenopausal breast cancer in Europe: case–control study. Br. Med. J. 315, 81–85.

Walker, B., Wiles, R., Hettenbach, T., Campbell, C., Davies, K., 1999. What You Don't Know Could Hurt You: Pesticides in California's Air. Environmental Working Group, Washington, DC.

Ward, M.H., Nuckols, J.R., Weigel, S.J., Maxwell, S.K., Cantor, K.P., Miller, R.S., 2000. Identifying populations potentially exposed to agricultural pesticides using remote sensing and a geographic information system. Environ. Health Perspect. 108, 5–12.

Wassermann, M., Nogueira, D.P., Tomatis, L., Mirra, A.P., Shibata, H., Arie, G., Cucos, S., Wassermann, D., 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull. Environ. Contam. Toxicol. 15, 478–484.

Waterhouse, D., Carman, W.J., Schottenfeld, D., Gridley, G., McLean, S., 1996. Cancer incidence in the rural community of Tecumseh, Michigan: a pattern of increased lymphopoietic neoplasms. Cancer 77, 763–770.

Wesseling, C., Antich, D., Hogstedt, C., Rodriguez, A., Ahlbom, A., 1999. Geographical differences of cancer incidence in Costa Rica in relation to environmental and occupational pesticide exposure. Int. J. Epidemiol. 28, 365–374.

Westin, J.B., Richter, E., 1990. The Israeli breast-cancer anomaly. Ann. N. Y. Acad. Sci. 609, 269–279.

Wiklund, K., Dich, J., 1994. Cancer risks among female farmers in Sweden. Cancer Causes Control 5, 449–457.

Wilhoit, L., Davidson, N., Supkoff, D., Steggall, J., Braun, A., Simmons, S., et al., 1999. Pesticide Use Analysis and Trends from 1991 to 1996. PM 99-01, California Department of Pesticide Regulation, Sacramento, CA.

Wolff, M.S., Toniolo, P.G., Lee, E.W., Rivera, M., Dubin, N., 1993. Blood levels of organochlorine residues and risk of breast cancer. J. Natl. Cancer Inst. 85, 648–652.

Wolff, M.S., Collman, G.W., Barrett, J.C., Huff, J., 1996. Breast cancer and environmental risk factors: epidemiological and experimental findings. Annu. Rev. Pharmacol. Toxicol. 36, 573–596.

Wolff, M.S., Zeleniuch-Jacquotte, A., Dubin, N., Toniolo, P., 2000. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol. Biomarkers Prevent. 9, 271–277.

Woodrow, J.E., Seiber, J.N., Baker, L.W., 1997. Correlation techniques for estimating pesticide volatilization flux and downwind concentrations. Environ. Sci. Technol. 31, 523–529.

Woodruff, T.J., Caldwell, J., Cogliano, V.J., Axelrad, D.A., 2000. Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. Environ. Res. Sect. A 82, 194–206.

Zahm, S.H., Ward, M.H., Blair, A., 1997. Pesticides and cancer. Occup. Med. 12, 269–289.

Zheng, T., Holford, T.R., Mayne, S.T., Owens, P.H., Ward, B., Carter, D., Dubrow, R., Zahm, S.H., Boyle, P., Tessari, J., 1999a. Beta-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. Cancer 85, 2212–2218.

Zheng, T., Holford, T.R., Mayne, S.T., Tessari, J., Owens, P.H., Zahm, S.H., Zhang, B., Dubrow, R., Ward, B., Carter, D., Boyle, P., 1999b. Environmental exposure to hexachlorobenzene (HCB) and risk of female breast cancer in Connecticut. Cancer Epidemiol. Biomarkers Prevent. 8, 407–411.

Zheng, T., Holford, T.R., Mayne, S.T., Ward, B., Carter, D., Owens, P.H., Dubrow, R., Zahm, S.H., Boyle, P., Archibeque, S., Tessari, J., 1999c. DDE and DDT in breast adipose tissue and risk of female breast cancer. Am. J. Epidemiol. 150, 453–458.