

Prostate Cancer Risk Associated with Ambient Pesticide Exposure in California's Central Valley

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Background

Rationale

- Other than age, family history, and hormonal factors, there are few established risk factors for prostate cancer.
- There is evidence that pesticide exposure is a risk factor for prostate cancer. Some pesticides, classified as endocrine-disrupting chemicals (EDCs), can affect normal hormone function, and the variations in hormone levels affect prostate cancer risk.
- The extremely strong risk associated with age (incidence after 45 increasing at a rate approaching the 9th power of age) is compatible with accumulated environmental exposure.

Objectives

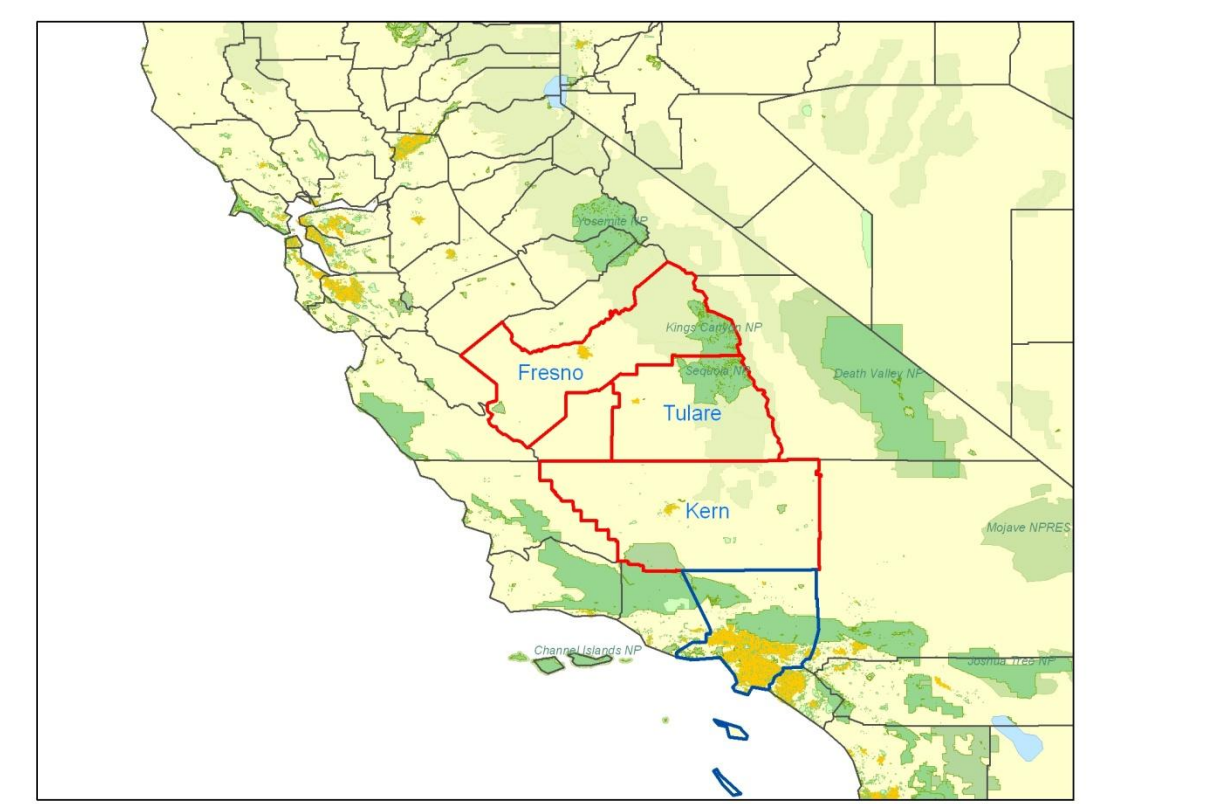
- Show that historical ambient pesticide exposure may be associated with the risk of prostate cancer.
- Show that historical residential and PUR/LU data provides substantial reduction in exposure misclassification in both prostate cancer cases and controls compared to estimates based only on current residential

Study Design

- Population based pilot case-control study in Central Valley area.

The Study Area

The study takes place in Central Valley of California which is the most agriculturally productive state in the United States. Growers in the Central Valley apply approximately 250 million pounds of pesticides annually, roughly a quarter of all pesticides used in the United States. Fresno, Kern and Tulare counties are ranked the top agricultural counties in California by value of production and intensive agricultural pesticide applications. A large proportion of residences in these three counties are potentially exposed to pesticides.



Case-Control Selection

Cases

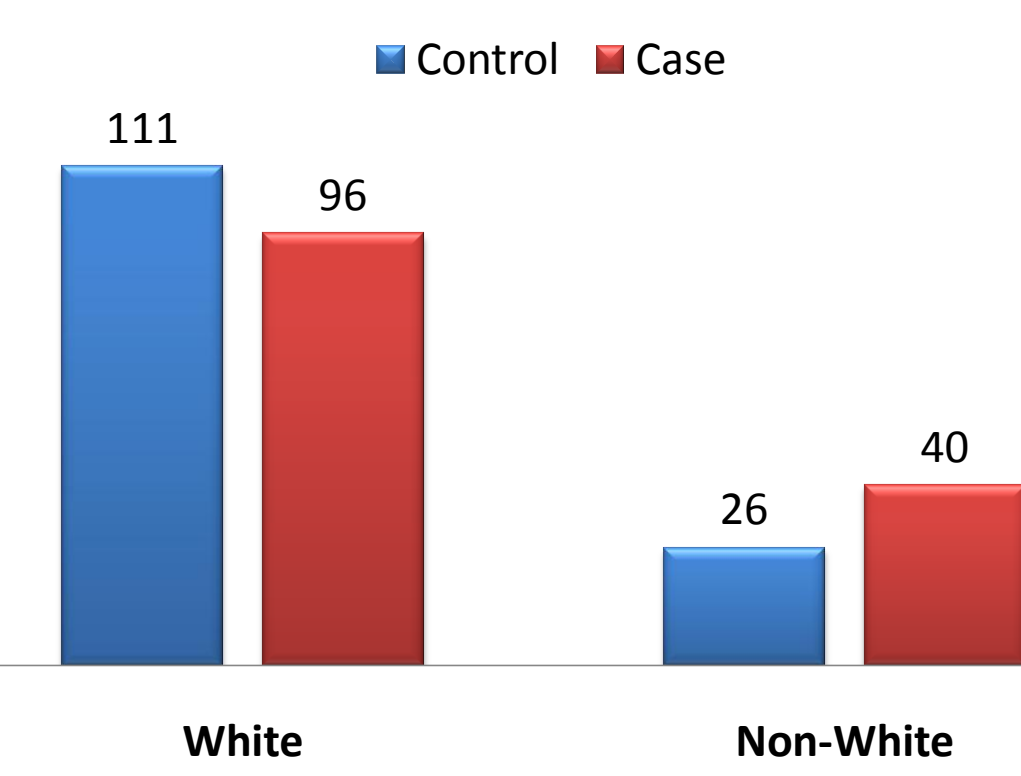
- Histologically confirmed prostate cancer cases diagnosed between July 2004 and January 2005 occurring in Cancer Registry.
- 65 to 74 years old at diagnosis.
- Non-Latino and Latino whites.
- Must be residing in Tulare, Fresno and Kern counties at diagnosis.
- Not using Rapid Case, likely biased towards earlier stage of disease.
- 784 selected

Controls

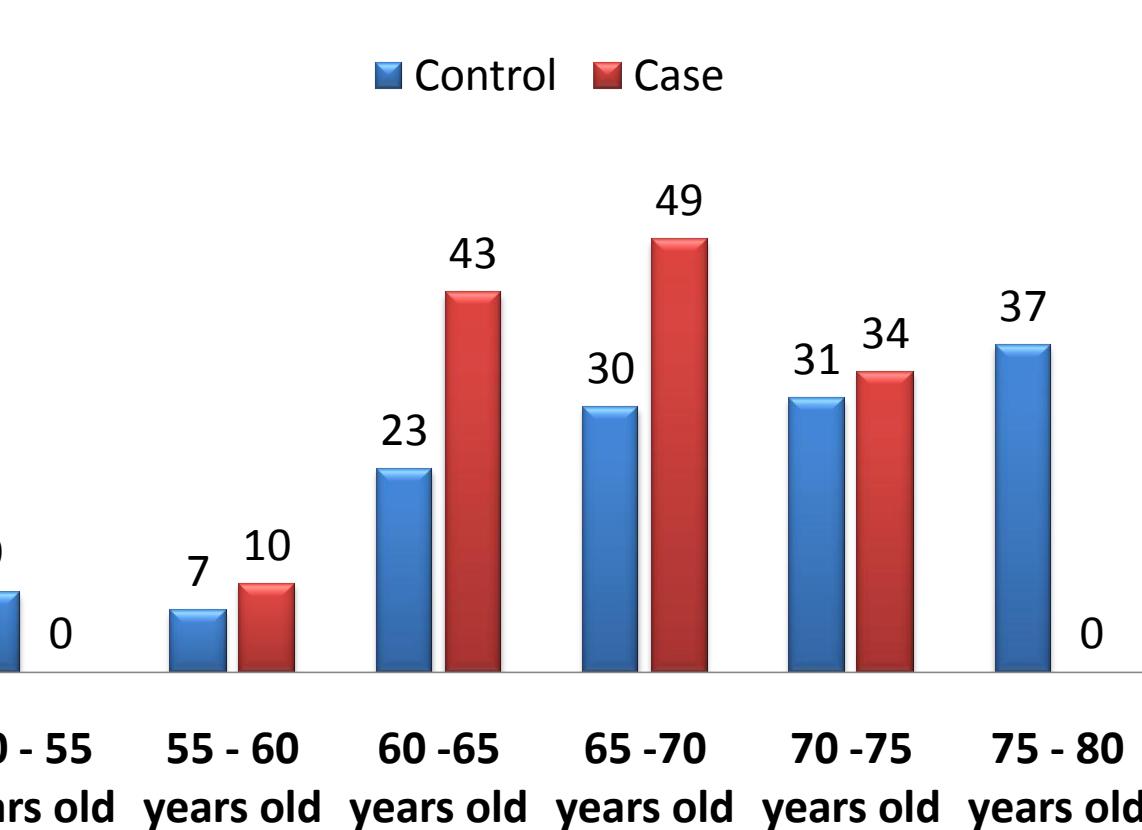
- Similar eligibility criterion as cases.
- 65 years or older, Medicare selection: Contact info lists obtained from Medicare, frequency-matched to cases by age.
- Under 65: "Parcel" selection: Residential info obtained from Tax Assessor, linked to reverse look-up to obtain personal info. "Cold calling" to assess whether the target is eligible for the study.
- 700 selected

With a target of 120 cases and 120 controls for the pilot study, 136 cases and 137 controls entered the final analysis stage, figures below show the case-control distribution by race and age.

Race distribution among cases and controls



Age distribution among cases and controls



Interview and Geo-coding

Interview and questionnaire

- Questions pertaining to residential history of pesticide exposure
- Questions pertaining to occupational history of pesticide exposure
- Questions pertaining to other prostate cancer risk factors (including FFQ)

Geo-coding

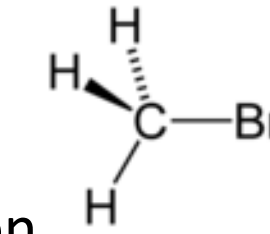
The complete residential history of each participant obtained in interview and questionnaire was manually geo-coded using Google Earth®. The figure on the left shows an example to geo-code "336 Lloyd St. Bakersfield, CA 93307" The resulting latitude and longitude values are shown under the foot.



The Four Pesticides in the Analysis

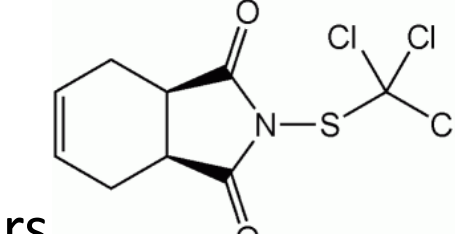
Methyl Bromide

- Everything-a-cide.
- Direct gaseous insecticide.
- 70-80% released into atmosphere.
- RR = 2.3 in AG Health Study for prostate cancer.



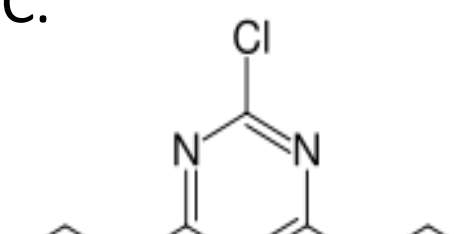
Captan

- Fungicide.
- Applied by sprayers.
- Dissipates rapidly in the environment.
- Probable human carcinogen (GI).
- Demonstrated EDC.



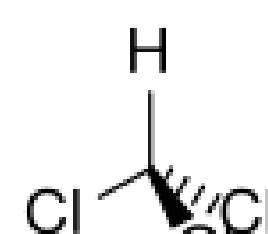
Simazine

- Herbicide of Triazine class.
- Applied to soil (spray) and absorbed through leaves and roots.
- May disrupt hypothalamic-pituitary-gonadal or HPG axis in humans, potentially causing changes to hormone levels and developmental delays.

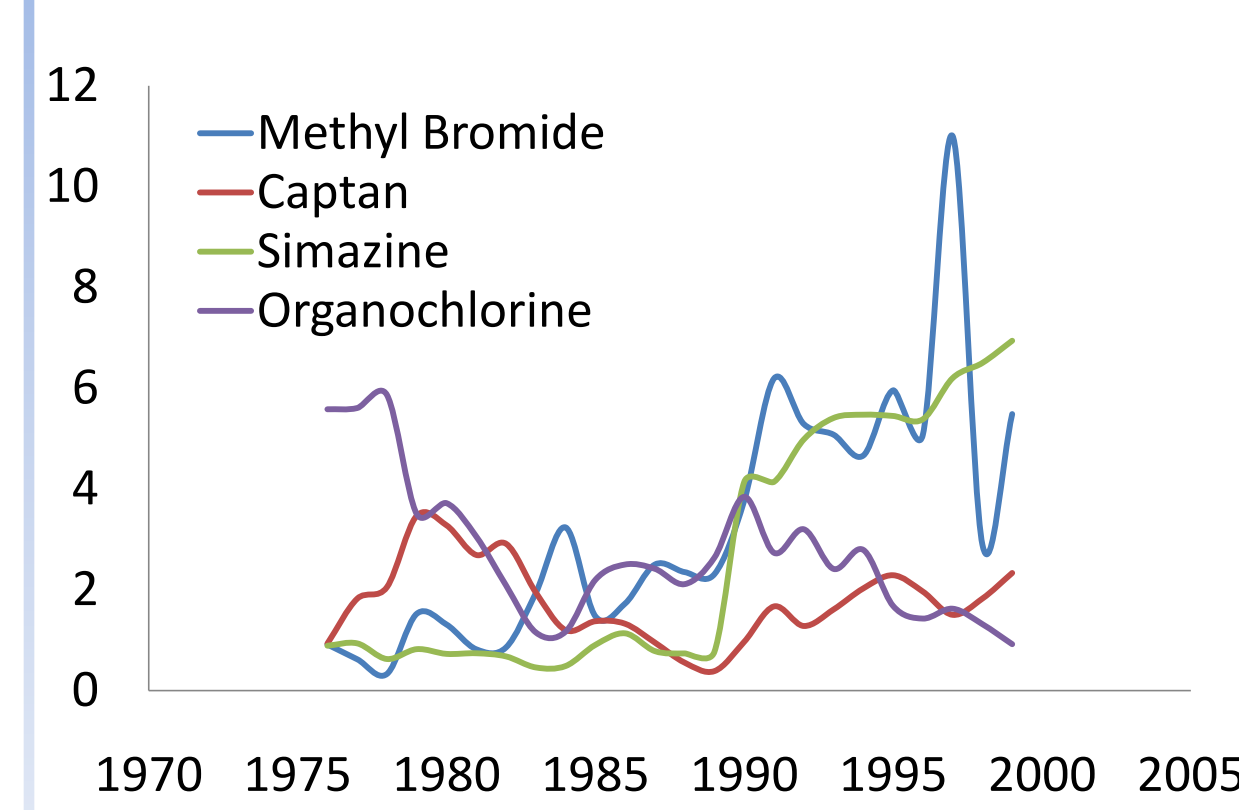


Organochlorine Group

- Group of chemicals.
- Including Aldrin, BHC, Chlordane, Dicofol, Dieldrin, Dieldrin, Endosulfan, Heptachlor, Lindane, Methoxychlor and Toxaphene.
- Most are applied through sprayers.
- Many have significant toxicity to animals including humans.
- In California, Aldrin, BHC and Lindane were officially banned for commercial application.



Secular trend of pesticide exposure within 500m buffer Estimated using GRPAES and 9228 points from registry



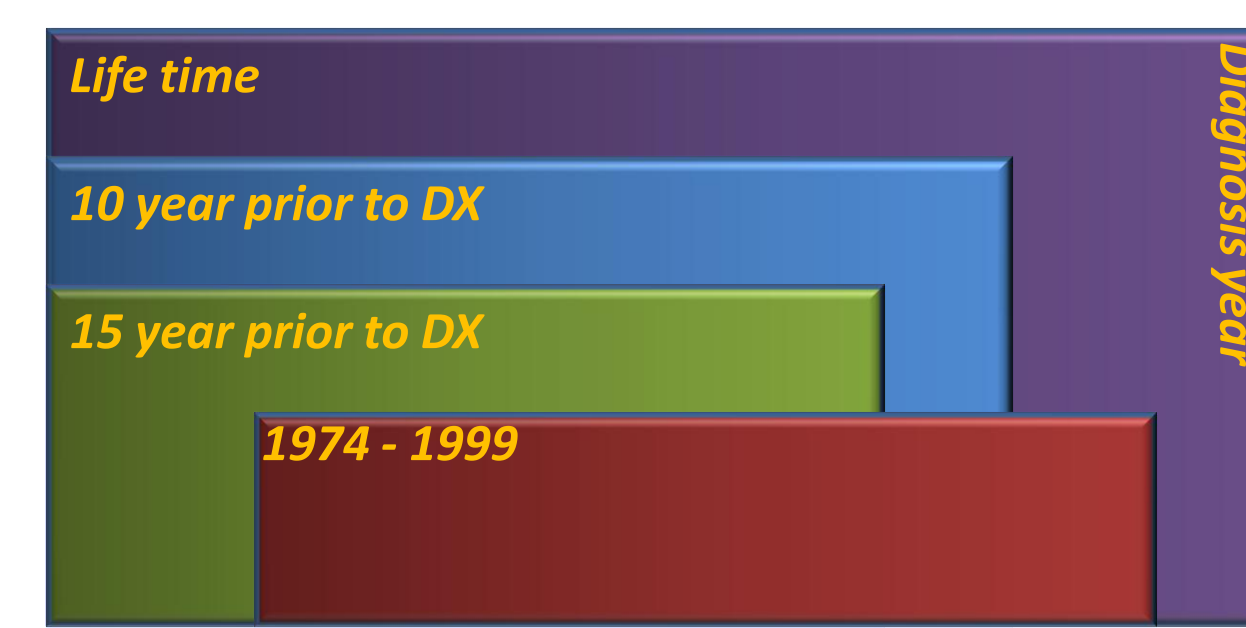
Statistical Analysis

The model

- The model we used is unconditional logistic regression.
- Adjusted for age, ethnicity and home pesticide use.
- Binary exposure and high-low exposure by median.

Five exposure summaries

- Diagnosis year only exposure.
- Life time annual average exposure.
- Annual average of 1974 – 1999.
- Annual average from birth to 10 years before diagnosis.
- Annual average from birth to 15 years before diagnosis.



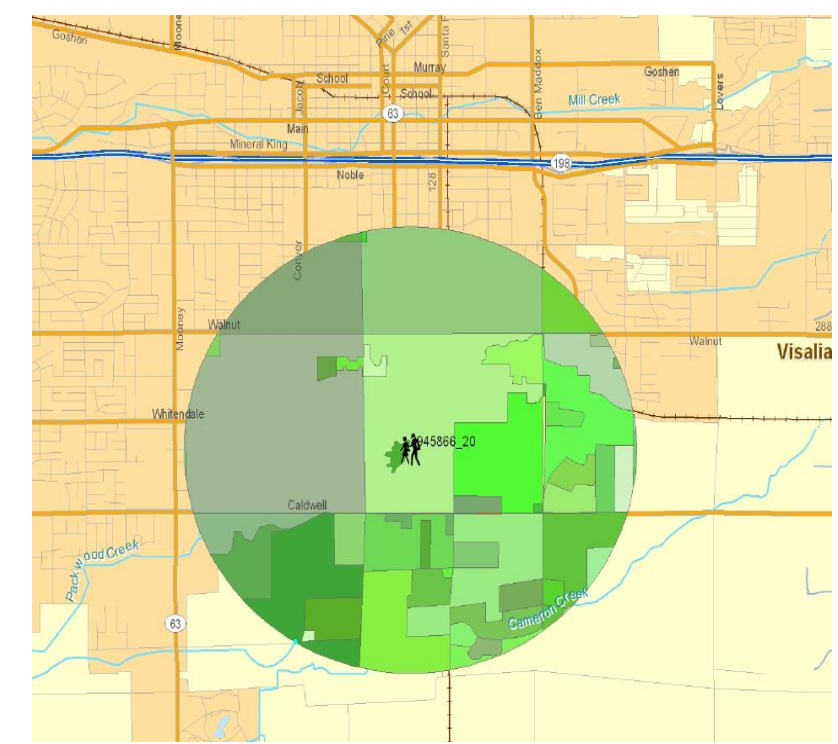
Missing data consideration

- The PUR data we have so far covers 1974 – 1999, for exposure outside this range, we used a semi-LOCF (last observation carried forward) method, i.e. use closest available PUR/LU data to estimate the exposure.
- There are missing years of exposure caused by unknown/unreported addresses. For this situation we used AVY (average valid year) method to obtain the annual average, i.e. calculate the average from those years where exposure estimates are available.

GIS-Based Pesticide Exposure Evaluation System

Highlights of GIS based method

- Based on the assumption that the actual ambient pesticide exposure is proportional to the amount of chemical applied within a 500 meter buffer around the individual's residence. The figure on the left illustrates the synthesized "area of activity" around the residence.
- Much more objective method, not subject to recall bias from self-report based study.
- The use of the combination of PUR and LU data further narrows down the actual area the application occurs, leaving less misspecification than PUR only methods.



How it works

- First calculate the density of the chemical applied in the PLSS section based on PUR records.
- Then use GIS tools to calculate the actual acreage of application within the 500m buffer based on Land-Use data.
- Finally multiply the density and the actual acreage to obtain the amount of exposure.

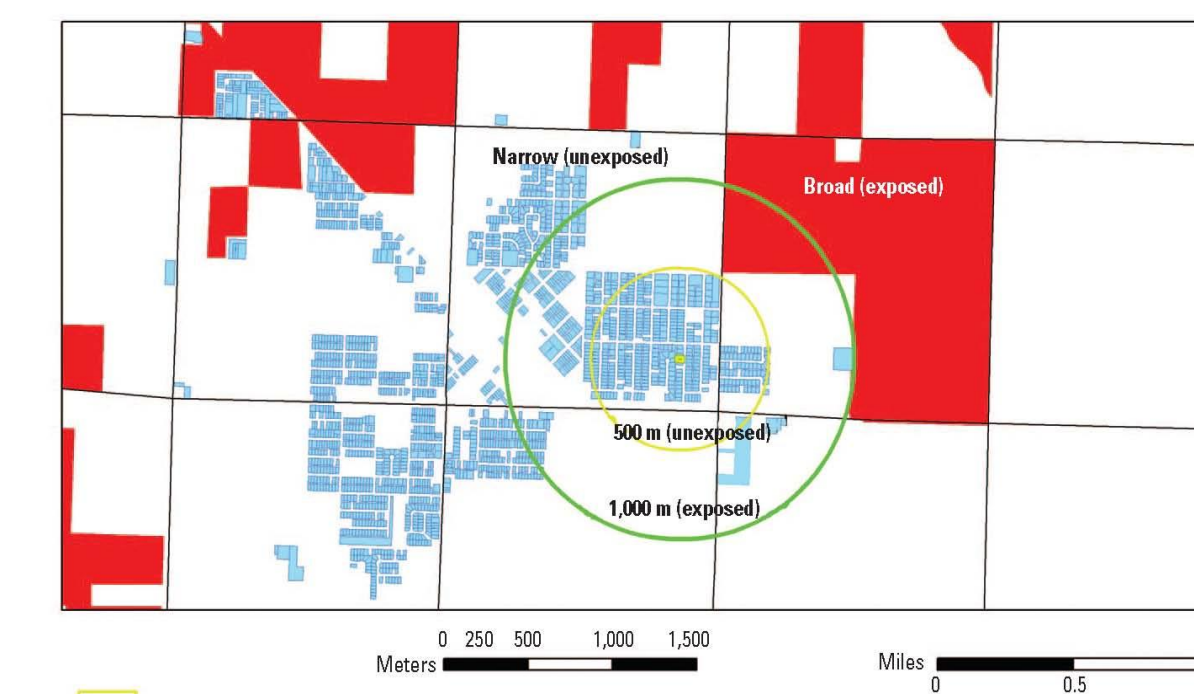


Figure 2. Example of exposure from residential proximity to parathion applications using the distance-based and narrow and broad zonal exposure definitions, 1988.

The Land Use Survey

The California Department of Water Resources performs countywide, large-scale surveys of land use and crop cover every 7-10 years. As an example, for 1988, the Kern County land-use survey closest in time was conducted in 1990 (left figure) and was readily available in digital format (i.e., ArcView GIS shapefile; ESRI, Redlands, CA). In the shapefile, fields, vineyards, orchards, and other land-use types exist as contiguous polygons that are individually linked to their respective attribute information (e.g., land use type, acreage) in a database table. The original land use data does not include PLSS boundary, the figure shows the results after integration.

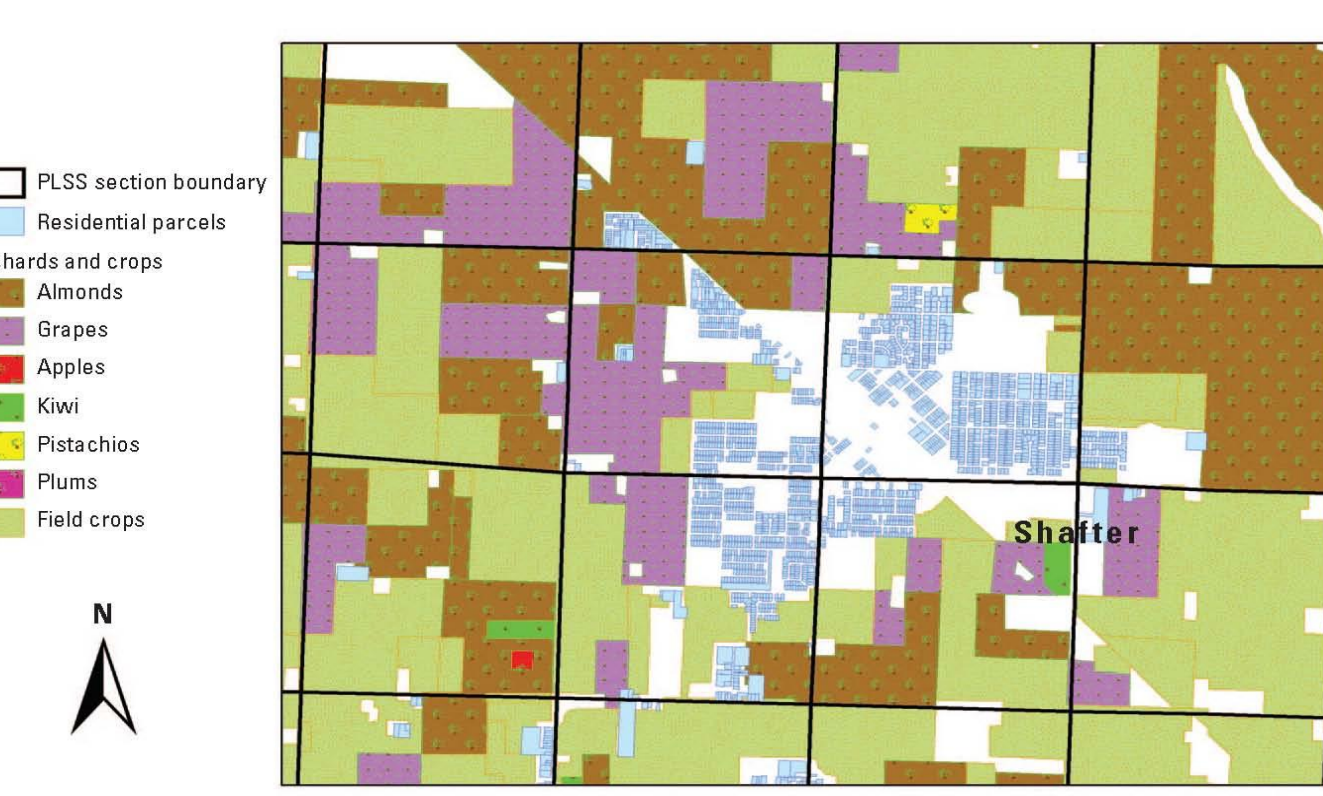


Figure 1. Agricultural land use, Shafter, Kern County, California, 1990.

The Pesticide Use Report

In 1972, reports for commercial applications of restricted-use pesticides was required by law in California. The law was later extended to cover all pesticides in 1990. The pesticide applications are reported according to the Public Land Survey System, which has a resolution of approx. 1 square mile. The data has been electronically available since 1974 from California Department of Pesticide Regulation.

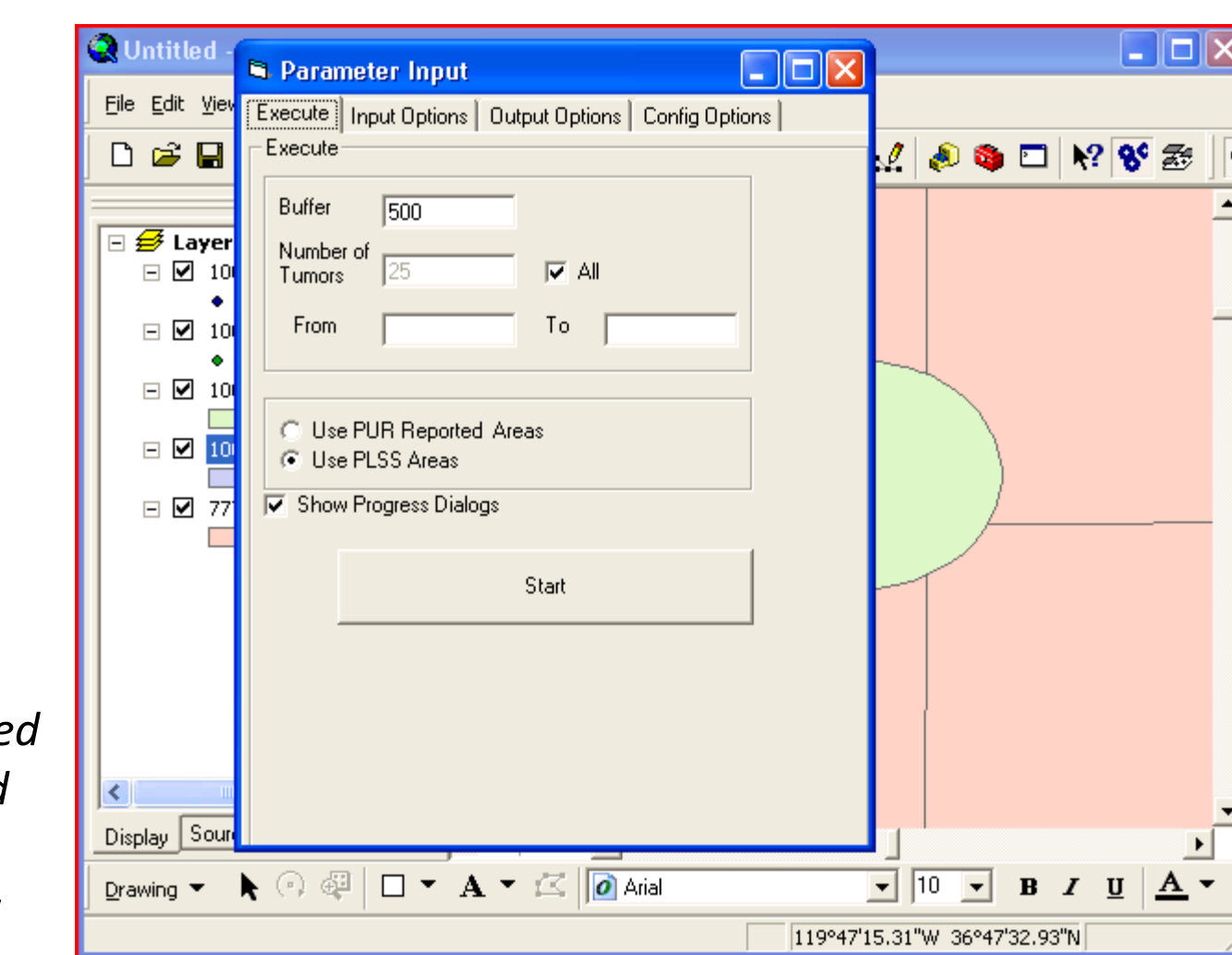
The original PUR data were converted to fit the study, including year, chemical names, crop types, areas and quantities applied inside the corresponding PLSS squares. The above table shows a small portion of the PUR data used in the study.

COUNTY	year	locate	METHOD	CHEMCODE	CHEMNAME	CROP	treated	pounds
10	1990	10M1SS20E03	G	105	CARBARYL	F	4	5.6
10	1995	10M1SS20E03	G	173	CRYOLITE	V	197	1052.16
10	1992	10M1SS20E03	G	198	DIAZINON	V	25	135
10	1991	10M1SS20E03	G	216	DIMETHOATE	V	40	80
10	1994	10M1SS20E03	G	231	DIURON	V	16	8.4
10	1990	10M1SS20E03	G	253	CHLORPYRIFOS	D12	30.5	40.1099
10	1995	10M1SS20E03	G	259	ENDOSULFAN	F	64	80
10	1994	10M1SS20E03	G	310	GIBBERELLINS	V	108	1.29
10	1990	10M1SS20E03	G	342	ISOPROPYL ALCOHOL	F	2	0.095
10	1975	10M1SS20E03	G	342	ISOPROPYL ALCOHOL	V	158	8.919075
10	1978	10M1SS20E03	G	369	MANEB	D12	18	79.8275
10	1990	10M1SS20E03	G	383	METHOMYL	F	10	7.32
10	1981	10M1SS20E03	G	383	METHOMYL	V	48	41.175
10	1990	10M1SS20E03	G	445	PROPARGITE	V	101	139.5
10	1999	10M1SS20E03	G	531	SIMAZINE	F	1.5	0.96
10	1995	10M1SS20E03	G	531	SIMAZINE	V	98	75.325

The GRAPES

The GIS based pesticide exposure evaluation method used in this study is fairly complicated. To make the exposure generation an automated process to benefit follow up studies, "GIS-based Residential Ambient Pesticide Exposure Software" (GRAPES) was developed. The software is a Visual Basic script running under ArcGIS environment.

Essentially, GRAPES is an automated factory that takes the pre-edited geo-coded residential history, combing both PUR and LU data to generate complete pesticide exposure history that can be used directly in final analysis. The right figure shows GRAPES in action.



Results and Conclusion

Methyl Bromide

When summarized as binary type exposure, the OR for diagnosis year exposure is 2.49 (1.05, 5.94, p = 0.04); the ORs for exposure summary based on residential history range from 1.42 to 1.82 with the OR for 1974-1999 period exposure being 1.82 (1.08, 2.83, p=0.07). Little Methyl Bromide, the low-high exposure scheme shows a clear trend with increasing Captan exposure: the OR for low exposure are close to 1 across the board, while the ORs for high exposure are higher than 2 showing a significant risk. For example, the OR for 1974-1999 period with high exposure is 2.29 (1.23, 4.28, overall p = 0.02).

Table 1a. Relative risk estimates for prostate cancer with exposure to Methyl Bromide in California's Central Valley 2005 - 2006

Exposure Type	Frequency	Control	Case	Crude		Adjusted	
				OR	95% CI	OR	95% CI
Diagnosis Year Exposure							
Missing	15	6	-	-	-	-	-
Unexposed	114	109	1.00	-	1.00	-	-
Exposed	8	22	2.90	1.24, 6.80	2.49	1.05, 5.94	0.04
Low (1)	3	3	1.06	0.21, 5.34	1.08	0.21, 5.70	0.08
High (1)	5	19	4.81	1.42, 11.12	3.31	1.17, 9.38	0.00
Life Time							
Missing	3	2	-	-	-	-	-
Unexposed	76	62	1.00	-	1.00	-	-
Exposed	50	72	1.52	0.98, 2.36	1.42	0.85, 2.34	0.17
Low	27	33	1.50	0.81, 2.76	1.49	0.80, 2.80	0.38
High	31	39	1.54	0.86, 2.75	1.36	0.74, 2.48	0.38
10 year prior DX							
Missing	8	16	-	-	-	-	-
Unexposed	79	58	1.00	-	1.00	-	-
Exposed	51	62	1.63	0.99, 2.70	1.55	0.92, 2.62	0.10
Low	33	34	1.39	0.77, 2.49	1.42	0.78, 2.50	0.22
High	18	28	2.09	1.06, 4.14	1.86	0.87, 3.71	0.07
15 year prior DX							
Missing	18	23	-	-	-	-	-
Unexposed	75	55	1.00	-	1.00	-	-
Exposed	48	57	1.73	1.09, 2.69	1.59	0.93, 2.64	0.09
Low	28	38	1.82	1.00, 3.31	1.71	0.93, 3.17	0.22
High	16	19	1.59	0.75, 3.37	1.11	0.53, 2.31	0.22

* Adjusted for age, ethnicity and home pesticide use
† Low exposure = 0 and 0.5 points, High exposure = 3.5 points

Captan

For history type exposure, the OR for diagnosis year exposure is 2.24 (0.88, 5.72, p = 0.09). The ORs for history type exposure are fairly close, range from 1.04 to 1.64 with the OR for 1974-1999 period exposure being 1.64 (0.96, 2.83, p=0.07). Little Methyl Bromide, the low-high exposure scheme shows a clear trend with increasing Captan exposure: the OR for low exposure are close to 1 across the board, while the ORs for high exposure are higher than 2 showing a significant risk. For example, the OR for 1974-1999 period with high exposure is 2.29 (1.23, 4.28, overall p = 0.02).

Table 1b. Relative risk estimates for prostate cancer with exposure to Captan in California's Central Valley 2005 - 2006

Exposure Type	Frequency	Control	Case	Crude		Adjusted	
				OR	95% CI	OR	95% CI
Diagnosis Year Exposure							
Missing	15	6	-	-	-	-	-
Unexposed	113	114	1.00	-	1.00	-	-
Exposed	7	16	2.30	0.91, 5.81	2.24	0.88, 5.72	0.09
Low (1)	0	2	-	-	-	-	-
High (1)	7	14	2.82	0.79, 9.19	1.85	0.70, 5.09	0.09
Life Time							
Missing	3	2	-	-	-	-	-
Unexposed	93	81	1.00	-	1.00	-	-
Exposed	41	53	1.48	0.90, 2.46	1.42	0.86, 2.40	0.19
Low	21	16	0.87	0.43, 1.79	0.83	0.40, 1.72	0.05
High	20	37	2.12	1.14, 3.95	2.09	1.09, 3.99	0.02
10 year prior DX							
Missing	8	16	-	-	-	-	-
Unexposed	98	72	1.00	-	1.00	-	-
Exposed	39	51	1.76	1.05, 2.97	1.64	0.96, 2.82	0.07
Low	17	11	0.87	0.38, 1.99	0.82	0.35, 1.89	0.09
High	22	40	2.45	1.34, 4.49	2.29	1.23, 4.28	0.02
15 year prior DX							
Missing	18	23	-	-	-	-	-
Unexposed	85	67	1.00	-	1.00	-	-
Exposed	24	48	1.72	1.09, 2.67	1.62	0.96, 2.63	0.10
Low	16	13	1.03	0.46, 2.29	0.94	0.44, 2.27	0.08
High	18	35	2.33	1.21, 4.49	2.16	1.08, 4.30	0.02

* Adjusted for age, ethnicity and home pesticide use
† Low exposure = 0 and 0.5 points, High exposure = 3.5 points

Simazine

For history type exposure, the OR for diagnosis year exposure is 1.90 (0.98, 3.68, p = 0.06). However, the ORs for history type exposure, ranging from 1.08 to 1.19, are very close to 1 showing almost no departure from the null (with p values greater than 0.5).

When low-high exposure summary is used, we can see a linear trend similar to Captan. For example the OR for low life time exposure is 0.82 (0.47, 1.43) and the OR for high life time exposure is 2.03 (0.95, 4.35).

Table 1c. Relative risk estimates for prostate cancer with exposure to Simazine in California's Central Valley 2005 - 2006

Exposure Type	Frequency	Control	Case	Crude		Adjusted	
				OR	95% CI	OR	95% CI
Diagnosis Year Exposure							
Missing	15	6	-	-	-	-	-
Unexposed	108	97	1.00	-	1.00	-	-
Exposed	17	33	2.10	1.10, 4.01	2.00	0.98, 3.68	0.06
Low (1)	7	10	1.55	0.57, 4.22	1.33	0.48, 3.73	0.12
High (1)	10	23	2.48	1.13, 5.49	2.30	1.03, 5.14	0.04
Life Time							
Missing	3	2	-	-	-	-	